Apixaban or rivaroxaban in the treatment of acute venous thromboembolism?

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Venous thromboembolism (VTE) may affects all parts of the venous circulation, but frequently manifests as deep vein thrombosis or pulmonary embolism. Annually, around 10 million cases are diagnosed worldwide, and VTE constitutes a growing global health burden with increasing incidence and prevalence (1,2). VTE is associated with substantial morbidity and mortality, and about 30% of all patients with VTE experience a recurrent event within 10 years (3). Traditionally, vitamin K antagonists (VKA) have been the cornerstone in the treatment of patients with VTE, but the emergence of direct oral anticoagulants (DOAC; dabigatran, rivaroxaban, apixaban, and edoxaban) has led to a substantial shift in the pharmacological management of VTE during recent years (4). All four DOACs are non-inferior to VKA in the prevention of recurrent VTE event and superior to VKA with regard to bleeding events (5). Therefore, international guidelines recommend DOAC therapy over VKA therapy following acute VTE (6).

Dabigatran and edoxaban are initiated in a "VKA-like approach" with a low-molecular weight heparin run-in, while rivaroxaban and apixaban can be initiated immediately following VTE. This convenience benefit for patients as well as for physicians likely explains why rivaroxaban and apixaban are the most frequently used DOACs in the treatment of VTE (4,7,8). Based on data from clinical trials, the efficacy and safety of rivaroxaban and apixaban in the treatment of acute VTE have been compared indirectly in network meta-analyses (9,10). While the two DOACs provided comparable prevention against VTE in these analyses, apixaban appeared to confer a lower risk of bleeding than rivaroxaban. Although rivaroxaban and apixaban are the drugs of choice in the treatment of acute VTE, very little is known about the head-to-head effectiveness and safety of these drugs in clinical practice. Recently, a study by Dawwas *et al.* published in *Lancet Haematology* provided further evidence on this important clinical topic (11). Based on data from the Truven Health MarketScan commercial and Medicare Supplement claims database in the United States during 2014–2016, Dawwas and colleagues performed a propensity-score matched cohort study comparing the effectiveness and safety of apixaban *vs.* rivaroxaban in patients with newly diagnosed VTE. Sampled from an overall cohort of 38,630 VTE patients initiating either apixaban or rivaroxaban (3,387 and 35,243 patients, respectively), 3,091 apixaban initiators were matched 1:4 to 12,163 rivaroxaban initiators. During a mean follow-up time of 99 days following apixaban or rivaroxaban initiation, recurrent VTE as well as major bleeding occurred more frequently in the rivaroxaban

group than in the apixaban group corresponding to hazard ratios (HRs) after propensity score matching of 0.37 [95% confidence interval (CI): 0.24–0.55] and 0.54 (95% CI: 0.37–0.82), respectively. Results were consistent across a broad range of subgroup analyses including patients with active cancer, chronic kidney disease, and a specific type of VTE event (e.g., pulmonary embolism). Accordingly, the authors concluded that in patients with VTE, apixaban appeared to be more effective than rivaroxaban to prevent recurrent VTE events while posing a lower risk of major bleeding.

The paper by Dawwas *et al.* adds to the current literature on potential differences in the safety and effectiveness of rivaroxaban and apixaban in the treatment of VTE. In a Danish cohort study, Sindet-Pedersen *et al.* (12) found no difference between treatment with apixaban (n=1,504) and rivaroxaban (n=6,683) regarding the risk of recurrent VTE and hospitalization for bleeding following acute VTE (HRs of 1.03, 95% CI: 0.69–1.51 and 1.09, 95% CI: 0.72–1.64, respectively). However, the two studies differ on several important aspects and are, therefore, not directly comparable. Compared to the Danish study, the population in the Dawwas *et al.* study was younger, and the proportion of patients with pulmonary embolism as the index event was lower. Further, the study by Sindet-Pedersen *et al.* applied an "intention-to-treat"-like approach when assessing exposure, whereas Dawwas *et al.* used an "as-treated"-approach. Finally, propensity-score matching was only employed in the study by Dawwas *et al.*

The study by Dawwas *et al.* is indeed well-conducted and their results consistent in a range of relevant sensitivity analyses. They used a new-user active-comparator design which has the theoretical advantage of minimizing confounding by indication, healthy user and frailty already in the design phase, seeking to emulate a randomized controlled trial. This design is regarded the standard for pharmacoepidemiology studies assessing the real-world effectiveness and safety of drugs (13). In a new-user active-comparator design, the ability of the active comparator to mitigate confounding depends, among other factors, on the prescribing behavior in the source population in the context of the studied treatment indication (13). Ideally, the choice of whether to treat with the drug of interest or with the active comparator drug occurs randomly. If so, this would be reflected by comparability of frequency of use and drug user characteristics across the exposure groups. However, similar to what have been found in other populations (4,8,14,15), rivaroxaban was chosen 10-times more frequently than apixaban when treating acute VTE in the source population for the study by Dawwas *et al.*. While this indicates a strong preference for rivaroxaban in this population, it also suggests that when apixaban is chosen, this is likely an active treatment choice based on the physician's considerations regarding the individual patient. In other words, patients prescribed with apixaban may likely be specifically selected to receive this treatment, or to not receive rivaroxaban, making them different from patients given the "*comparator* treatment", i.e., rivaroxaban. So even though the authors performed a propensity-score matched analysis, the comparability of rivaroxaban users and apixaban users may be questioned, and the study could be susceptible to confounding. Importantly, an effect of selective DOAC prescribing on the results of an observational study, is not specific to the study by Dawwas *et al.*, but would pertain to any observational study based on a population where the preference of one DOAC over another seems as strong as in this particular study population.

The choice of study period, i.e., January 2014–December 2016, may also have had an impact on the comparability of the two treatment groups in the study by Dawwas *et al.* Rivaroxaban and apixaban were approved by the U.S. Food and Drug Administration for treatment of VTE in November 2012 and August 2014, respectively (16). Thus, rivaroxaban had already been available for the VTE indication for more than one year at study initiation, whereas apixaban became available for VTE during the study period. The utilization of a drug during the very first period of availability will differ from the utilization of drugs already available for a treatment indication. This include differences in the characteristics of both patients prescribed with the drugs and physicians prescribing the drugs (17). Thus, a comparison of a newly introduced drug with an already available drug will be associated with a risk of confounding. This could have been addressed if the authors had chosen a later study period (e.g., January 2015 as in Sindet-Pedersen *et al.*), performed stratified analyses to investigate potential cohort effects, and/or included calendar time in their propensity score model, which we surmise would have been an important discriminating factor in the study.

Further emphasizing that the results of the study by Dawwas *et al.* should be interpreted with caution, is the remarkably high frequency of study participants (72% in both groups) who received anticoagulant therapy of short duration only (<3 months), i.e., shorter than the minimum duration recommended in treatment guidelines (6,18).

Right censoring may have occurred and therefore the results do not necessarily apply to patients receiving DOAC treatment of longer duration.

So, should the results of the study by Dawwas *et al.* lead to a change in treatment guidelines? The answer is not easy. On one hand, the study Dawwas *et al.* suffered some methodological limitations and was observational of nature. However, their findings are indeed interesting, suggesting that apixaban could be a better treatment option than rivaroxaban for patients with acute VTE with regard to both effectiveness and safety. Supporting the latter inference, the seemingly superior safety of apixaban compared to rivaroxaban in clinical practice has also been reported in observational studies of patients with atrial fibrillation (19). The comparative efficacy and safety of rivaroxaban and apixaban is currently the subject of the CANVAS (NCT02744092) and COBRRA (NCT03266783) trials, which will hopefully provide an unconfounded answer of this important clinical question within few years. Meanwhile, based on the currently available evidence, we encourage that rivaroxaban and apixaban should still be considered as equal treatment options following acute VTE.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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