

## Who could benefit most from treatment of acute pulmonary embolism with rivaroxaban? Commentary to the article: “Acute pulmonary embolism treatment with rivaroxaban results in a shorter duration of hospitalisation compared to standard therapy: an academic centre experience”

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Meta-analyses of phase III trials have compellingly demonstrated that non-vitamin K oral anticoagulants (NOACs), including rivaroxaban and apixaban alone and dabigatran as well as edoxaban, after parenteral anticoagulant induction, are as effective as, and probably safer than, standard treatment with heparin/warfarin of acute venous thromboembolism (VTE). The relative efficacy and safety of the NOACs seem consistent across a wide range of patients [1]. Moreover, the NOACs significantly simplify VTE treatment because they are administered at fixed doses without any dietary restrictions along with limited interactions with other drugs, and, notably, no routine anticoagulation monitoring is required [2]. Despite growing evidence for the favourable risk-benefit profile of NOACs compared to warfarin, few studies have assessed the impact of NOACs used for treatment of acute VTE in real life. The present study by Paczyńska et al. [3] could be of particular interest for Polish cardiologists by providing such data from a well-known Warsaw centre following an investigation involving 215 consecutive acute pulmonary embolism (PE) patients hospitalised in the years 2013–2014. The study shows that patients treated with rivaroxaban (following a maximum of three days' heparin administration) compared with those receiving vitamin K antagonists (VKA) stayed in hospital for a shorter period of time both when they had simplified PE severity index (sPESI) = 0 and sPESI  $\geq$  1 [3]. To explain this observation, comparative analysis of demographic and clinical characteristics for the PE patients on rivaroxaban and those on the standard therapy is needed. One might expect that the choice of rivaroxaban over the standard treatment in this cohort is driven by lower age of patients, fewer comorbidities, absence of dual antiplatelet agents, and normal renal function. Danish nationwide data from 2011 to 2013 published recently documented the pattern of use of currently available NOAC and warfarin in patients with atrial fibrillation (AF) and demonstrated that for this indication, NOAC are more commonly

used in female subjects at older age and in those with prior stroke, and less commonly in subjects with a history of chronic kidney disease, myocardial infarction, and heart failure [4]. Even if the current cohort was younger (median, 65 years) than most AF populations treated with NOACs [2], but higher than the average age of patients in each clinical trial on NOACs in VTE (55–60 years) [5], most associations reported in AF could be applicable to the VTE patients, although prolonged use of low-molecular-weight heparins, not only when strongly indicated, i.e. in cancer- or pregnancy-associated PE, is relatively common in Poland. From my experience, in 2015 NOACs are preferred over warfarin in patients of both sexes with low- and intermediate-risk acute PE at ages below 65 years in whom renal function is normal or slightly reduced and a history of gastrointestinal bleeding is negative (A. Undas, unpublished data). It would be extremely interesting to show which factors influenced the Warsaw doctors' decisions to use rivaroxaban or the standard therapy, apart from high-risk PE in which preferentially heparins followed by VKA antivitamin K were most likely to be used. This issue is unclear after having read the paper by Paczyńska et al. [3]. Another issue that deserves comment is a temporal prescription pattern of rivaroxaban compared with warfarin or acenocoumarol throughout the two-year study period.

Current European Society of Cardiology guidelines on acute PE management do not endorse NOACs over warfarin. There is a consensus that the choice of anticoagulation regimen should be personalised based on the relative efficacy and safety of different agents across subgroups stratified by thrombotic and bleeding risk, as well as on other clinical factors, e.g. drug interactions or compliance. I encourage the authors to continue their study and extend follow-up to provide much-needed data on the outcomes of rivaroxaban versus standard therapy of PE in Poland. To optimise treatment for acute PE in the real-world setting, further research

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is warranted to identify PE patients who may preferentially be managed with rivaroxaban or other NOACs in order to ease the burden of this potentially lethal disease.

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## LIST DO REDAKCJI / LETTER TO THE EDITOR

### Response to the letter concerning the article “Acute pulmonary embolism treatment with rivaroxaban results in a shorter duration of hospitalisation compared to standard therapy: an academic centre experience”

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We have read with great interest the Letter to the Editor by Prof. Anetta Undas with comments to our study [1]. Non-vitamin K oral anticoagulants (NOACs) are free from many of the limitations of vitamin K antagonists (VKA) and represent a valuable alternative for the treatment of patients with acute pulmonary embolism (APE). According to the recent European Society of Cardiology guidelines on the diagnosis and management of APE, rivaroxaban and apixaban alone and dabigatran as well as edoxaban, after short-term parenteral anticoagulant, achieved class I level of evidence B recommendation in acute phase treatment and rivaroxaban, dabigatran, apixaban, class IIa, level B for extended anticoagulation [2]. Numerous favourable factors associated with the use of NOAC and increasingly affordable price result in increasing use of these drugs in a population of patients with APE. The aim of our study was to evaluate the frequency and characteristics of patients with APE treated with rivaroxaban in an academic referral centre and to assess the possibility of shortening hospitalisation time of patients treated with NOAC compared with those treated with VKA. We included 215 consecutive APE patients: 110 female, 105 male, median age 65.0 (range 19.5–91.9) years. High-risk APE was diagnosed in seven (3.3%) patients, intermediate in 157 (73%), and low

risk in 51 (24%). At discharge 30.5% of patients received VKA, 39.0% of subjects were prescribed rivaroxaban, while in the remaining 30.5% of patients low molecular weight heparin (LMWH) was used. An interesting finding of our analysis was the fact that patients who were treated and discharged with rivaroxaban were hospitalised for significantly shorter periods of time than were patients who received VKA (6 [2–22] vs. 8 [2–17] days,  $p = 0.0005$ ).

We stratified the severity of APE in normotensive patients according to simplified pulmonary embolism severity index (sPESI) score, and we found that those patients with sPESI = 0 points and also in subjects with sPESI  $\geq 1$  points, who were treated with rivaroxaban, were hospitalised for significantly shorter periods of time than were others, treated with VKA [1]. We did not find any differences in age between patients treated with rivaroxaban vs. VKA and rivaroxaban vs. LMWH (63.7 [19.8–90.6] vs. 63.2 [19.5–90.5] and 63.7 [19.8–90.6] vs. 67.0 [26.6–91.9], respectively,  $p = \text{NS}$ ) and also in mean glomerular filtration rate (GFR) values ( $78.8 \pm 27.2$  vs.  $79.0 \pm 33.4$  and  $78.8 \pm 27.2$  vs.  $72.1 \pm 29.9$  mL/min/1.73 m<sup>2</sup>, respectively,  $p = \text{NS}$ ). However, we noticed that in the rivaroxaban group median sPESI score was significantly lower than in LMWH

patients (0 vs. 1 point,  $p = 0.002$ ). Similarly, median sPESI score was significantly lower in the VKA group than in the LMWH group (0 vs. 1 point,  $p = 0.002$ ). The reason was probably the fact that patients treated with LMWH had higher levels of active cancer than those in the rivaroxaban or VKA groups (39% vs. 1.2%,  $p < 0.001$ ; 39% vs. 3.1%,  $p < 0.001$ , respectively).

We would like to emphasise that we proposed rivaroxaban as a long-term phase therapy for all normotensive APE patients without contraindications for this drug. However, for some patients (e.g. those with  $eGFR < 30 \text{ mL/min/1.73 m}^2$  or with active cancer) first-choice drugs were VKA or LMWH. As we have mentioned above, 82 (39%) of all our patients were discharged home on rivaroxaban. However, about 60% of “rivaroxaban eligible patients” received this medication. It seems to us that the frequency of use of NOAC for patients with APE will steadily increase due to the numerous advantages of this class of drugs. Definitely, for our patients, the economic factor was the most important argument for VKA

selection in the “rivaroxaban-eligible group”. We analysed our two years’ experience with rivaroxaban in APE patients. As expected, in the beginning of this period, due to our limited experience, we were more careful while using rivaroxaban; however, after only a few months NOAC was much more frequently prescribed. We believe that significant shortening of the hospitalisation period in the rivaroxaban group, independently of the sPESI value, is an argument to start discussion on the optimal organisation of healthcare systems.

**Conflict of interest:** none declared

### References

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