ABSTRACT

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Doctoral Degree Program	Clinical and Social Pharmacy
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Title of Doctoral Thesis	The aspects influencing the therapeutic value of anticoagulants in the Czech Republic

Background and aim: Anticoagulants prevent the onset or maintaining of thromboembolic (TE) diseases. Both long-term used drugs, the disadvantages of which may limit treatment, and newer ones, the benefits of which may be limited by shorter clinical experience, are currently approved. Drug utilization may be an important indicator of trends in drug use, as well as pharmacovigilance surveillance and the benefits and risks assessment in clinical practice. Research related to the evaluation of the therapeutic value of anticoagulants and the factors influencing their use in clinical practice contribute to safer pharmacotherapy, therefore the aims of this thesis were: 1) to analyze the drug utilization of parenteral and oral anticoagulants (OACs) in the Czech Republic (CR) between the years 2007–2020; 2) to evaluate the numbers and characteristics of spontaneously reported suspected adverse drug reactions (ADRs) related to OACs in the CR between the years 2005–2017 with the intention to enhance knowledge about OACs safety and search for possible unknown ADRs.

Methods: 1) Data for this descriptive retrospective study were obtained from the State Institute for Drug Control (SUKL) database of obligatory reports from distributors on drug supplies. There were included: warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, unfractionated heparin (UFH), low molecular weight heparins (LMWHs) – dalteparin, enoxaparin, nadroparin, reviparin, bemiparin, and fondaparinux. The utilization of anticoagulants was calculated by relating the number of defined daily doses (DDD) per 1000 Czech inhabitants and per day (DDD/TID). Data was analyzed using descriptive statistics and cross-correlation. 2) A retrospective pharmacovigilance analysis of spontaneous reports of suspected ADRs related to OACs was performed. These reports were from the Central Database of ADRs Department of Pharmacovigilance of the SUKL. The only reports from healthcare professionals (HCPs) and patients related to warfarin, dabigatran, rivaroxaban, and apixaban were evaluated. The analysis of reports included evaluation of ADR (hemorrhagic, TE and others), ADRs seriousness and expectedness, the reported patient characteristics (age, gender) and the persons reporting the ADRs. Also, the analysis of interactions of drugs reported as concomitantly used with OACs, which could lead to an increased hemorrhagic risk was conducted using the Micromedex and UpToDate databases. The number of reports was related to the drug exposure unit, i. e. per million DDD (mDDD) as so called reporting rate (RR). Data were analyzed using descriptive statistics. The reporting odds ratio (ROR) with 99% confidence intervals (CI) were used to determine the association between warfarin and direct oral anticoagulants (DOACs). DOACs were compared using Pearson's Chi-square test ($\chi 2$).

Results: 1) During the study period, the total anticoagulants utilization increased from 14.1 DDD/TID to 31.54 DDD/TID. Out off all anticoagulants, warfarin accounted for 48.97%. The highest utilization within parenteral anticoagulants was found in association with enoxaparin (49.66 DDD/TID) and nadroparin (47.65 DDD/TID). The utilization of UFH gradually decreased from 0.65 to 0.20 DDD/TID and fondaparinux reached very low values (0.0167 DDD/TID in 2020).

Warfarin utilization gradually increased until 2015 (11.70 DDD/TID), between 2016–2020 fluctuated with a decreasing trend, especially in 2020 (10.65 DDD/TID). Drug utilization of all DOACs increased, with higher utilization of rivaroxaban since 2014 and apixaban since 2018, respectively. In 2007, warfarin represented 100% of OAC utilization and by 2020 for only 51%. The remaining 49% of OACs´ utilization was represented by DOACs (19% rivaroxaban, 16% apixaban, 13% dabigatran and 1% edoxaban). The growth of warfarin utilization was stopped by DOACs ($p < 0.05$). UFH and LMWH together with fondaparinux tended to compete with each other ($p < 0.05$). 2) During the study period, SUKL received 297 reports, which contained 672 ADRs. In 65% of OAC reports, ADRs were due to DOACs (41% for dabigatran, 15% rivaroxaban, 9% apixaban). ADRs were more frequently reported in relation to DOAC than to warfarin (ROR = 10.76; 99% CI 8.70–13.32; $p < 0.001$). Comparison of DOACs revealed the highest number of ADRs associated with dabigatran ($\chi2 = 193.28$; $p < 0.001$). For warfarin, the RR was almost negligible due to its higher utilization compared to DOACs. On the contrary, the RR for DOACs was high, especially after their approval. HCPs sent 269 reports, of which 85% were sent by physicians and 6% by pharmacists. The majority of reports (96%) contained serious ADRs. Fatal outcomes were included in 7% of reports (hemorrhagic ADR, TE event or coagulopathy), most of them associated with dabigatran. The most frequent interactions were found in relation to dabigatran and warfarin, which also potentially interacted with the broadest spectrum of different drugs.

Conclusion: 1) The total anticoagulants utilization almost doubled. The utilization of DOACs was observed to increase at the expense of warfarin. However, warfarin remains the main OAC used in the CR. LMWH (enoxaparin, nadroparin) predominated within parenteral anticoagulants compared to lower utilization of UFH and fondaparinux. 2) Most of the ADRs reported to OACs in the CR were serious. To date, no unknown recurrent serious ADRs have been detected, which is in line with the previously assessed safety profile of these drugs. Most reports were received in association with DOACs, mainly dabigatran. Due to the increasing anticoagulants utilization, it is necessary to perceive these drugs responsibly by HCPs in order to ensure effective and safe treatment or prevention of TE diseases.