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Rising consumption of anticoagulants in Central and Eastern European countries in the period 2007–2019

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Introduction and Aim: Due to the growing incidence of thromboembolic disease and atrial fibrillation, increasing trends in anticoagulants consumption can be expected. The aim of this study was to analyse the consumption of anticoagulants in the Czech Republic, Croatia, Hungary, Romania, and Slovakia between 2007 and 2019.

Methods: A retrospective analysis of anticoagulants comprising B01AA, B01AB, B01AE, B01AF and B01AX was performed using ATC/DDD methodology. The analysis was initiated in the year before the launch of the first non-vitamin K oral anticoagulant (NOAC). The consumption of each drug was assessed based on annual data and was expressed as DDD per 1,000 population per day (DDD/TID).

Results: The overall rates of anticoagulant consumption increased in all countries. Specifically, doubled in the Czech Republic, Croatia, and Slovakia, more than tripled in Hungary and more than quadrupled in Romania. Parenteral anticoagulant consumption remained stable or decreased, while the proportion of oral anticoagulants increased from an average of 61.41% in 2009 to 66.95% in 2019. The use of vitamin K antagonists declined, with the highest rate in the Czech Republic (11.16 DDD/TID in 2019). NOAC consumption showed substantial growth: from 0.002 to 8.33 DDD/TID in the Czech Republic, 0.001 to 6.73 in Croatia, 0.009 to 8.31 in Hungary, 0.0005 to 5.40 in Romania, and 0.03 to 10.77 in Slovakia. By 2019, rivaroxaban was the most commonly used NOAC in all countries, apart from Romania.

Conclusion: The study showed an overall increase in the anticoagulant consumption. However, specific characteristics of individual countries need to be further analysed to better understand the different factors influencing utilization patterns.

Key words: drug utilization analysis, Europe, oral anticoagulation, parenteral anticoagulation.

Rostoucí spotřeba antikoagulancií v zemích střední a východní Evropy v letech 2007–2019

Úvod a cíl: S rostoucí incidencí tromboembolických onemocnění a fibrilace síní lze předpokládat rostoucí trend ve spotřebě antikoagulancií. Cílem práce bylo analyzovat spotřeby antikoagulancií v České republice (ČR), Chorvatsku, Maďarsku, Rumunsku a na Slovensku v letech 2007–2019.

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Metodika: Retrospektivní analýza spotřeb antikoagulancií zahrnující B01AA, B01AB, B01AE, B01AF a B01AX pomocí metodologie ATC/DDD. Analýza byla zahájena v roce před uvedením prvního non-vitamin K dependentního perorálního antikoagulancia (NOAC) na trh. Spotřeba pro každou molekulu byla hodnocena za kalendářní rok a byla vyjádřena jako počet DDD na tisíc obyvatel a den (DDD/TID).
Výsledky: Ve všech zemích byl celkově zaznamenán nárůst spotřeb antikoagulancií, a to na dvojnásobek v ČR, Chorvatsku a na Slovensku, na více než trojnásobek v Maďarsku a na více než čtyřnásobek v Rumunsku. Spotřeba parenterálních antikoagulancií byla stabilní nebo klesala, zatímco podíl perorálních antikoagulancií vzrostl z 61,41 % v roce 2009 na 66,95 % v 2019. Spotřeba antagonistů vitaminu K ve všech zemích klesala, kdy největší spotřeba byla zaznamenána v ČR (11,16 DDD/TID v 2019). Spotřeba NOAC rostla, a to v ČR z 0,002 na 8,33 DDD/TID, v Chorvatsku z 0,001 na 6,73, v Maďarsku z 0,009 na 8,31, v Rumunsku z 0,0005 na 5,40 a na Slovensku z 0,03 na 10,77. V roce 2019 byl kromě Rumunska nejpoužívanějším NOAC rivaroxaban.
Závěr: Studie prokázala nárůst celkové spotřeby antikoagulancií, přesto jednotlivé země vykazují celou řadu národních specifik, která je třeba dále analyzovat, aby byly lépe pochopeny různé faktory ovlivňující spotřebu těchto léčiv.

Klíčová slova: analýza spotřeb léčiv, Evropa, parenterální antikoagulancia, perorální antikoagulancia.

Introduction

Anticoagulants are widely prescribed drugs, the most common indication for their administration is therapy and prophylaxis of venous thromboembolism including deep vein thrombosis and pulmonary embolism. Venous thromboembolism has a global incidence from 1.15 to 2.69 cases per 1,000 persons and is also associated with high morbidity and mortality (1). Prevention of stroke and systemic embolism in adult patients with atrial fibrillation is yet another important indication for the administration of anticoagulants. Incidence and prevalence rates for this disease have also been increasing in the past decades, showing an increase of more than 30% in both parameters over the last 20 years (2). Consequently, increasing trends in the consumption of anticoagulants can be expected, which has been demonstrated by studies conducted worldwide (3-6).

In the group of oral anticoagulants, warfarin is still the most prescribed drug. However, in recent years, there has been a shift away from the use of vitamin K antagonists (VKA) in favour of non-vitamin K oral anticoagulants (NOAC) representing an equally effective and safer treatment alternative compared to VKAs (7). Several studies have been published evaluating trends in consumption of oral anticoagulants in Europe (3-5,8-11), North America (5,6,12-14), China (15), and Qatar (16). These studies have shown an increasing trend in the overall consumption of oral anticoagulants and have also confirmed a preference for NOACs. Nevertheless, studies mapping the situation on anticoagulant consumption in the world do not provide sufficient data related to Central and Eastern Europe. The aim was therefore to analyse the consumption of anticoagulants in the Czech Republic, Croatia, Hungary, Romania, and Slovakia over a period of 13 years, from 2007 to 2019.

Methods

Study setting and data collection

A retrospective analysis of anticoagulant consumption was performed. Representatives of the Visegrad Group countries (Czech Republic, Hungary, Poland, Slovakia) and geographically and culturally related countries (Croatia, Romania) were addressed. Except for Poland, all the addressed countries participated in the project. All data were facilitated by national coordinators.

The ATC/DDD methodology was used for data collection according to the WHO Collaborating Centre for Drug Statistics Methodology (17). Drug consumption was assessed at the level of individual active substances (5th level of ATC classification) including B01AA (vitamin K antagonists), B01AB (heparins), B01AE (direct thrombin inhibitors), B01AF (direct factor Xa inhibitors), and B01AX (other anticoagulants, antithrombotics). The inclusion criteria were either (a) annual consumption data in the last 10 years or (b) consumption data at least one year before the first NOAC was launched in the particular country. Data were available in the period from 2007 to 2019 in the Czech Republic, from 2008 to 2019 in Croatia, from 2007 to 2019 in Hungary, from 2007 to 2019 in Romania, and from 2009 to 2019 in Slovakia.

All data on drug consumption in the Czech Republic were obtained from the State Institute for Drug Control (SÚKL) database, which provides data on the quantities of medicinal products supplied to pharmacies and other health care facilities by entities that are authorised to distribute medicinal products. Similarly, in Slovakia, data on drug consumption from 2009 to 2018 was derived from the State Institute for Drug Control (ŠÚKL) database, including wholesale reports of deliveries to pharmacies and other health care facilities as well as exports from Slovakia. In 2019, data was derived from the National Centre for Health Information comprising reports on dispensing of medicines in pharmacies. Data on consumption in Hungary were obtained from the Hungarian National Health Insurance Fund (NEAK) database, which is the only and mandatory health insurance provider in the country and contains data on prescribed and dispensed medicines that are reimbursed. Data on consumption in Romania were obtained through the IQVIA Sell-In Audit database, comprising data on sales of medicinal products through distributors to community and hospital pharmacies. Data was provided for the study period from 2007 to 2019, on May 25th, 2020. Data on anticoagulant consumption in Croatia were obtained from the Agency for Medicinal products and Medical Devices (HALMED) based on sales data of medicinal products in community and hospital pharmacies. In case when data from all the pharmacies in the given country were not available, extrapolation to 100% was performed. The

available data for Croatia ranged from 97% for 2008 to 99% for 2019 that was subsequently extrapolated to 100% values.

Data analysis

The consumption per calendar year was expressed in defined daily doses (DDD) for each individual drug, where the denominator was the population of a particular country in a particular year. DDD valid in particular year was used for calculation. To compare consumption between countries, anticoagulant consumption was expressed as DDD per 1,000 population per day (DDD/TID). Data were processed using descriptive statistics in Microsoft Office Excel 2007 (Microsoft Corp., USA). Time-series analysis was used to measure the relationship between groups of anticoagulants with a statistical significance set at $p<0.05$ using the software Wolfram Mathematica 12.0 (Wolfram Research Inc., USA).

Results

In the participating countries, increasing trends were observed in the consumption of anticoagulants during the study period (Figure 1). Consumption increased from 15.52 to 31.42 DDD/TID (2007–2019) in the Czech Republic, from 7.32 to 19.15 DDD/TID (2008–2019) in Croatia, from 9.27 to 25.26 DDD/TID (2007–2019) in Hungary, from 3.08 to 14.29 DDD/TID (2007–2019) in Romania, and from 10.89 to 28.64 DDD/TID (2009–2019) in Slovakia.

Parenteral anticoagulants

In 2009 (i.e., the first year with available data sufficient for comparison of consumption in all countries), the parenteral anticoagulants were 44.15% out of the total anticoagulant consumption in Slovakia, 40.16% in Croatia, 38.49% in Romania, 35.14% in the Czech Republic, and 35.02% in Hungary. Ten years later, in 2019, the consumption rate of parenteral anticoagulants was almost the same in the Czech Republic (34.78% of all anticoagulants), while decrease was observed in Croatia, Romania, and Slovakia (20.25%, 28.13%, and 42.51%, respectively). Only Hungary reported slightly higher consumption of parenteral anticoagulants (39.57%) compared to 2009.

The highest rates of parenteral anticoagulants were represented mainly by heparins, while fondaparinux consumption was negligible in all the participating countries (0–0.42% in 2009 and 0–0.27% in 2019). The consumption of low-molecular-weight heparins (LMWHs) was higher than unfractionated heparin. In the Czech Republic and Slovakia, nadroparin was the most used drug, followed by enoxaparin. In Hungary and Romania, the pattern was reversed. In Croatia, the most frequently used LMWH was enoxaparin followed by dalteparin (Figure 2).

Oral anticoagulants

The proportion of oral anticoagulants in the total consumption of anticoagulants in 2009 was 64.98% in Hungary, 64.86% in the Czech Republic, 61.51% in Romania, 59.85% in Croatia, and 55.85% in Slovakia. In 2019, the proportion of oral anticoagulants was the highest in Croatia (79.75%), and still high in Romania (71.88%). In Hungary, the Czech Republic, and Slovakia, the proportion of oral anticoagulants remained at similar levels as in 2009 (60.43%, 65.22%, and 57.49%, respectively) (Figure 3).

Vitamin K antagonists

Warfarin was the only representative of the VKAs utilized in the Czech Republic, Croatia, and Slovakia. Acenocoumarol was utilized in Romania only, while both VKAs were used in Hungary. The highest consumption of VKAs was in the Czech Republic (Figure 4). There was a slight annual increase in warfarin consumption (up to 11.70 DDD/TID in 2015). Thereafter, a slight decrease in consumption was observed (11.16 DDD/TID in 2019). In Croatia, there was an increase in warfarin consumption (from 2.78 in 2008 to 9.29 DDD/TID in 2016), however, a slight decrease was observed in the subsequent years (8.53 DDD/TID in 2019). Similarly, an increase of acenocoumarol consumption was observed in Romania

Fig. 1. *Consumption of anticoagulants in the Czech Republic, Croatia, Hungary, Romania, and Slovakia from 2007 to 2019*

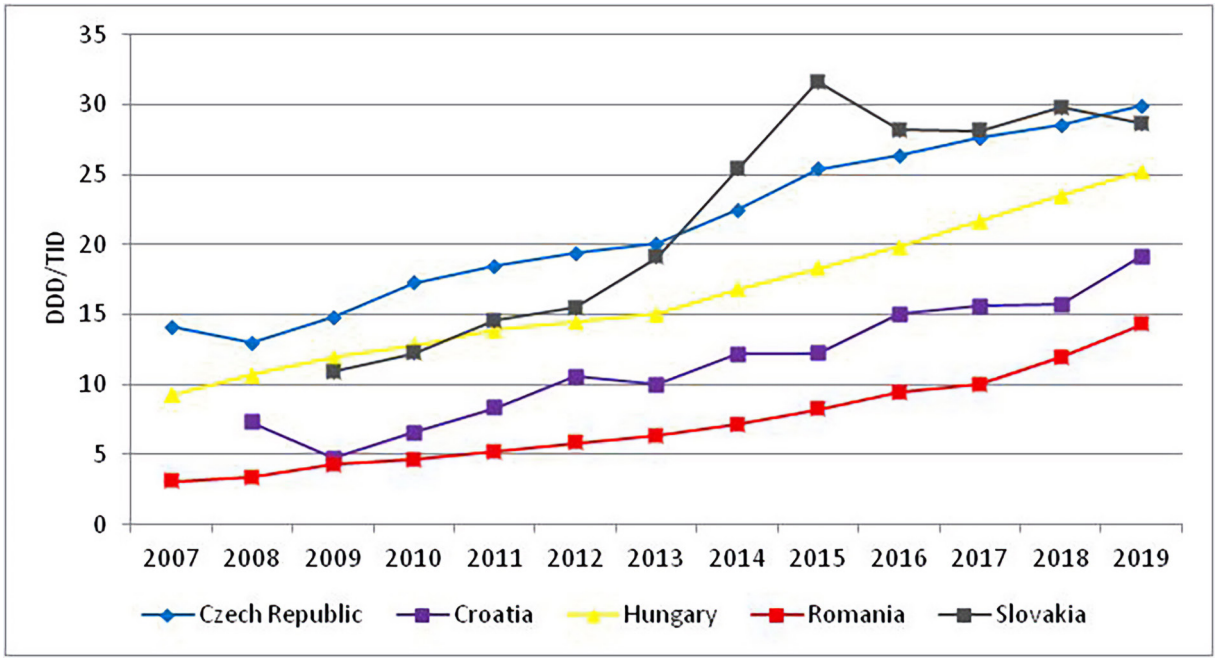


Fig. 2. *Proportion of heparins at three-year intervals, 2009, 2012, 2016 and 2019*

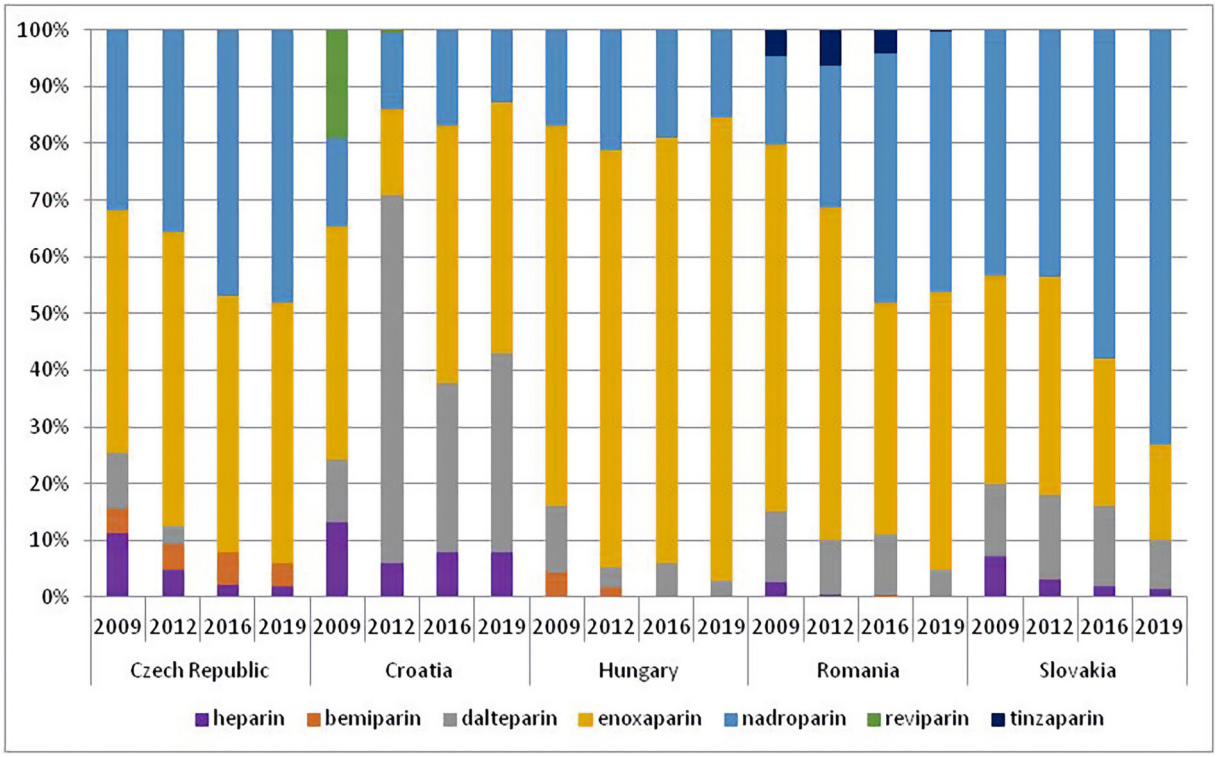
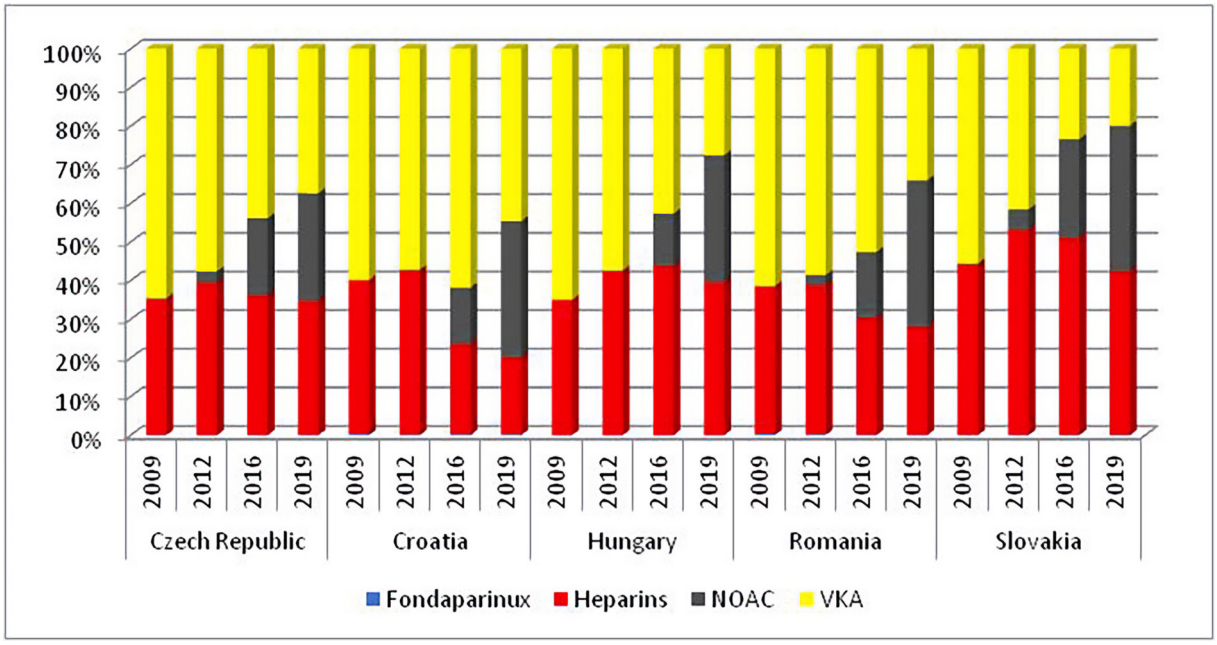


Fig. 3. *Proportion of oral and parenteral anticoagulants in total anticoagulant consumption at three-year intervals, 2009, 2012, 2016 and 2019*



(from 1.84 in 2007 to 4.97 DDD/TID in 2016), but rates reflecting slight decrease were recorded each year afterwards (4.87 DDD/TID in 2019). In Hungary, the highest consumption of VKAs was already in 2014 (8.76 DDD/TID), followed by a yearly decrease (6.93 DDD/TID in 2019). Also in Slovakia, the highest consumption of warfarin was already observed in 2013 (7.06 DDD/TID), followed by a yearly decrease (5.69 DDD/TID in 2019).

Non-vitamin K oral anticoagulants

The consumption of NOACs was observed to increase in all the participating countries (Figure 5), with rates ranging from 0.002 to 8.33 DDD/TID (2008–2019) in the Czech Republic, from 0.001 to 6.73 DDD/TID (2009–2019) in Croatia, from 0.009 to 8.31 DDD/TID (2010–2019) in Hungary, from 0.0005 to 5.40 DDD/TID (2008–2019) in Romania, and from 0.03 to 10.77 DDD/TID (2009–2019) in Slovakia. The increasing trend of NOACs halted the further increase of VKAs ($p<0.005$).

In the Czech Republic, the first marketed NOAC was dabigatran (launched in 2008), followed by rivaroxaban in 2009, apixaban in 2012 and edoxaban in 2017. In Croatia, dabigatran was launched in 2009, followed by rivaroxaban in 2010 and apixaban in 2015. No consumption of edoxaban was recorded in Croatia during the study period. Similar

Fig. 4. *Consumption of vitamin K antagonists in the Czech Republic, Croatia, Hungary, Romania, and Slovakia in the period 2007–2019*

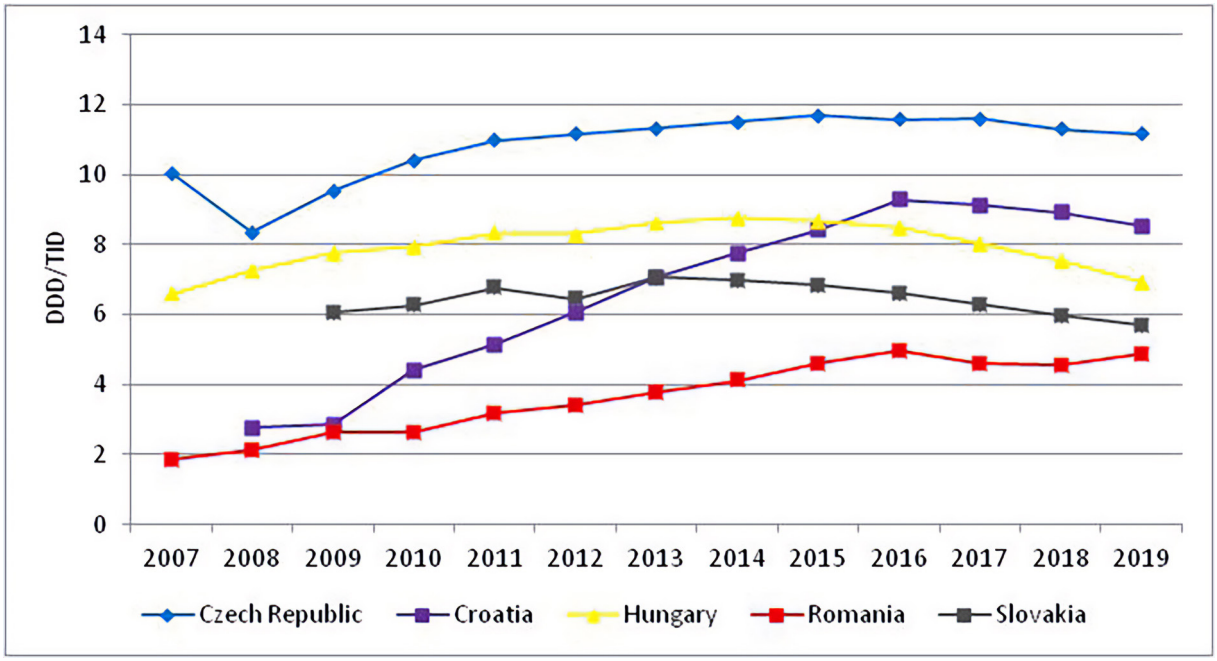
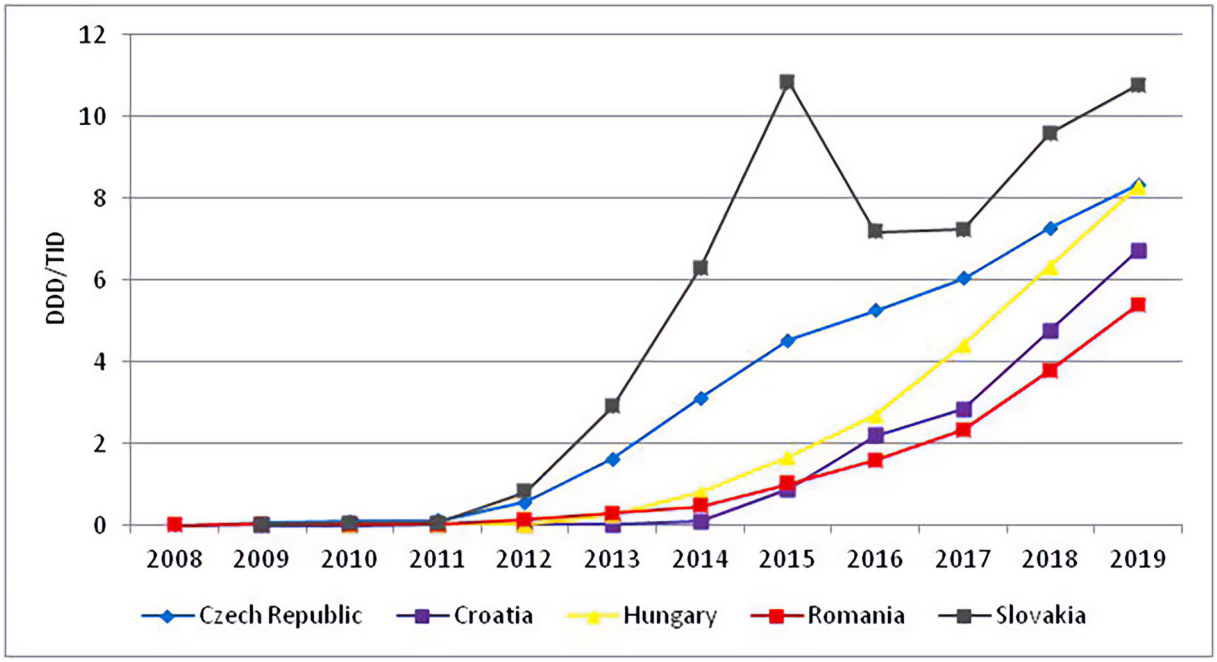


Fig. 5. *Consumption of non-vitamin K oral anticoagulants in the Czech Republic, Croatia, Hungary, Romania, and Slovakia in the period 2008–2019*



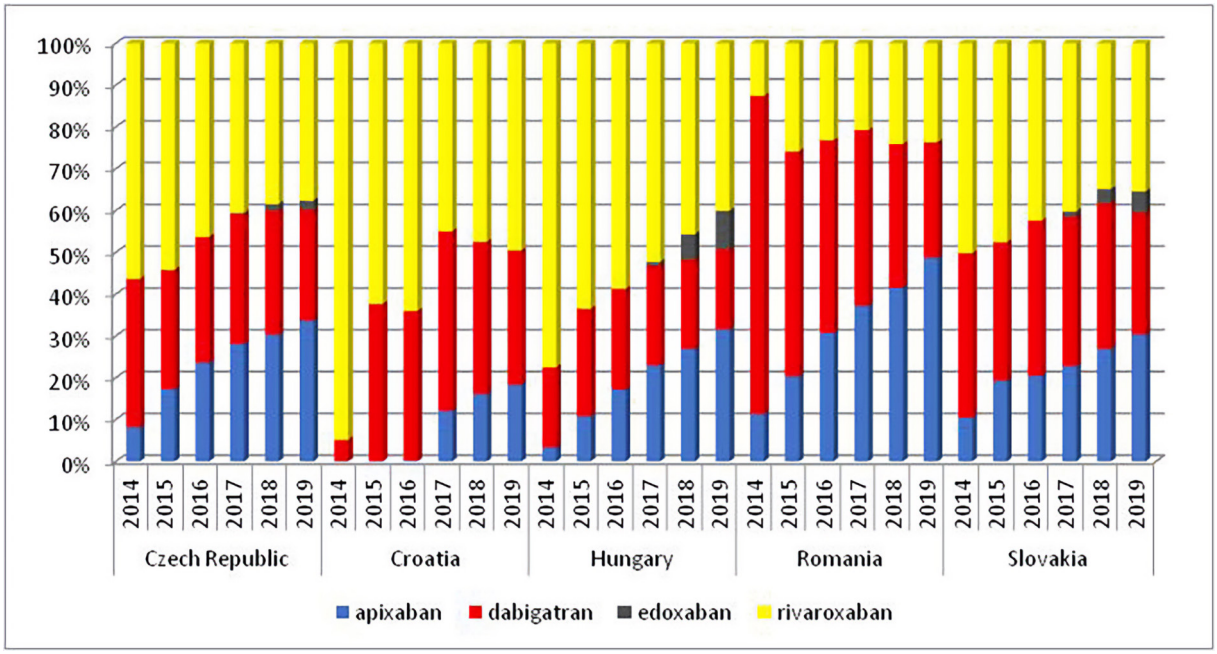
situation was observed in Romania with dabigatran launched in 2008, followed by rivaroxaban in 2009 and apixaban in 2013, whereas no consumption of edoxaban was recorded during the observation. In Hungary, both dabigatran and rivaroxaban were launched in 2010, followed by apixaban in 2014 and edoxaban in 2016. Similarly in Slovakia, dabigatran and rivaroxaban were launched in 2009, followed by apixaban in 2013 and edoxaban in 2017.

In 2019, rivaroxaban was the most utilized NOAC in the Czech Republic (3.14 DDD/TID), Croatia (3.33 DDD/TID), Hungary (3.33 DDD/TID), and Slovakia (3.81 DDD/TID), while the highest consumption of NOACs was related to apixaban in Romania (2.63 DDD/TID) (Figure 6).

Discussion

The study demonstrates the consumption of oral and parenteral anticoagulants in five countries in Central and Eastern Europe over a period of thirteen years. Therefore, it is unique in its temporal coverage as well as its scope because the drug utilization review was performed in several countries with similarities in their political, cultural, and geographical features. The study also reflects the marketing of individual NOACs and the trends in their consumption in each country. Moreover, the changes in consumption of parenteral anticoagulants were also addressed, which is a topic often neglected in the literature.

Fig. 6. *Proportions of non-vitamin K oral anticoagulants in period 2014–2019*



In all participating countries, an increase in the total consumption of anticoagulants was reported during the study period, and similar trends have been reported worldwide (3-5,8,9,11-16). The increase in consumption is particularly evident in the oral anticoagulant group, which may be due to several factors: firstly, an increase in the incidence of diseases for which anticoagulants are prescribed; secondly, the increase in the consumption of anticoagulants is influenced by the expansion of their indications, both in the adult and paediatric population (3,8). This is particularly related to NOACs as their consumption has increased annually in all the participating countries. The consumption of edoxaban was recorded only in the Czech Republic, Hungary, and Slovakia, which may be explained by its lower use in clinical practice, also due to its narrower indication spectrum.

The consumption of parenteral anticoagulants increased during the observation but accounted for less than half of the total consumption of all anticoagulants. However, except for a slight increase in Hungary, the proportion of parenteral anticoagulants in the total consumption was decreasing. Heparins predominated, while fondaparinux consumption was negligible in all the participating countries. Compared with LMWHs, fondaparinux has shown a lower incidence of thrombocytopenia, but its long biological half-life causes problems with dosing, especially in patients with renal insufficiency (18,19). The unavailability of all the licenced packages of fondaparinux with various strengths may also hinder its wider use in clinical practice. However, this fact would not fully explain the low rates of fondaparinux consumption. For example, in Romania, even though consumption of different packages of fondaparinux has been found, and yet consumption was recorded to be very low there too.

The increased heparins consumption rate is mainly due to the higher LMWH rates, such as observed in the Czech Republic, Hungary, and Romania. The consumption of heparins in Slovakia, interestingly, exceeded the same rates observed in the rest of the participating countries. One of the possible explanations is the re-export of LMWHs from Slovakia to other European countries, as the legal ban on the re-export of medicines came into effect as late as 2017 (20). In Croatia, the consumption of heparins fluctuated during the study period, which may be partly explained by the data collection methodology. In this case, data was obtained based on reports regarding medicinal products dispensing in community and hospital pharmacies; in certain cases, when data collection from the pharmacies was not viable, extrapolation to 100% was performed. In contrast, consumption of unfractionated heparin declined in the Czech Republic, Romania, and Slovakia, while its consumption remained virtually unchanged in Croatia and Hungary. Compared to LMWHs, it may be explained by the fact that LMWHs are safer and more effective, they can be administered subcutaneously 1-2 times daily, and do not usually require laboratory monitoring in routine clinical practice (21,22). Enoxaparin and nadroparin were found to be the most used LMWHs. The high consumption may be explained by marketing strategy of the manufacturers, adherence to professional guidelines, or drug policies in particular countries.

In all the participating countries, a gradual increase in VKA consumption was followed by its gradual decrease. Warfarin is generally used more frequently than acenocoumarol, as it is presented by more stable anticoagulation due to its longer biological half-life (36 hours) and to prevent factor VII fluctuations (biological half-life 10 hours). However, this assumption has not been confirmed by clinical studies (23,24). In the Czech Republic, there was a significant decrease in warfarin consumption between 2007 and 2008. A possible explanation may be found in the introduction of dabigatran into the Czech market. In the other countries, however, similar fluctuations have not been observed after introduction of NOACs into the market.

Conversely to VKAs, the consumption rates of NOACs have steadily increased since their introduction in each country and probably resulted in the lower utilization of VKAs in most of the participating countries. In

2019, their consumption was even higher than that of VKAs in Hungary, Romania, and Slovakia. A similar situation can be seen in the United Kingdom, Denmark, Italy, Norway and in the USA (5,25,26). The increase in consumption of NOACs can be explained by their numerous benefits over VKAs, e.g., rapid onset of the effect, no need to regularly monitor therapeutic effect, fewer clinically relevant interactions (27,28). Moreover, adherence to recommendations of professional societies play an important role (7,29).

Despite the steady increase in dabigatran consumption, an ongoing preference for factor Xa inhibitors has been observed. Except for Romania, rivaroxaban was the most used NOAC in all the participating countries in 2019 and similar results were published in studies on anticoagulant consumption from Qatar (16) or China (15). In contrast, apixaban was the most frequently utilized NOAC in France, United Kingdom, and in the USA (4,5,8). The once-daily dosing may also explain the high preference for rivaroxaban, even though it is not clearly proven whether medication adherence to this dosing regimen is higher (30). Unlike dabigatran, both rivaroxaban and apixaban can be indicated in patients with severe renal insufficiency or can be crushed in case of swallowing difficulties or when administration by nasogastric tube is necessary (31,32).

Generally, drug consumption is influenced by a variety of factors. The size of the market in the given country, the interests of individual drug manufacturers and their marketing strategies, affordability, adherence to guidelines provided by professional societies. For example, the role of health insurance companies and the impact of reimbursement on the increase in NOAC consumption were discussed in a study focusing on the consumption of oral anticoagulants between 2011 and 2015 in France (8). The increased rates in prescription of individual drugs always occurred soon after the reimbursement by health insurance companies was approved. Similar conclusions were drawn in a study conducted in Canada that analysed anticoagulant consumption between 2008 and 2014 and showed that the increase in NOAC prescription coincided with the introduction of health insurance reimbursement in each province (33). Regarding some national specifics in our study, there was a significant increase in NOAC consumption in 2015 in Slovakia, which may be at least partly explained by the re-exports to other European countries (34). The effects of the changes in the DDD were also considered, as until 2015 the DDD of dabigatran was 220 mg, apixaban 5 mg, and rivaroxaban 10 mg, whereas in 2016 the DDD of dabigatran was 300 mg, apixaban 10 mg, and rivaroxaban 20 mg. The calculation of the DDD was checked by the authors, but the results provided no explanation for the jump in NOAC consumption in Slovakia in 2015 either.

Strengths and Limitations

To our knowledge, this is the first ever published data on anticoagulant consumption from Croatia, Hungary, Romania, and Slovakia. Our study analysed data covering a period of over ten years, while other studies of anticoagulant consumption usually covered a significantly shorter time. Importantly, our study demonstrated national consumption data, not just a representative sample, as is the case with many published utilization studies (5,10,11,15,16). Furthermore, it should be emphasized that most of the published studies have focused on the analysis of oral anticoagulant consumption (4,5,8,9,12,14), whereas our study reviewed the consumption of both types of drugs, i. e., administered either orally or parenterally. Due to the calculating method of DDD/TID, the possibility of comparing the consumption in the analysed countries with each other was a great advantage. It is difficult to compare consumptions of different studies using different units, which usually means the number of prescriptions or the number of dispensing in a pharmacy.

The different sources of data in the participating countries admittedly are among the main limitations and caused the difficulties in determining more proper statistical analysis. Unlike the data obtained from insurance companies or pharmacy dispensing lists, data from wholesale distributors do not reflect the direct consumption by patients. For this reason, consumption may be overestimated in all countries, except from Hungary. In Slovakia, for example, it is strongly suspected that consumption in some years is significantly influenced by re-exports, with the proportion of re-exports not being quantifiable. Given the source data, a certain share of re-exports cannot be omitted in the Czech Republic and Romania as well. Furthermore, the ATC/DDD classification and the subsequent calculation of consumption in DDD/TID used in our study do not correspond to the daily dose for all indications of the analysed drugs. However, the same methodology enables to compare the consumption rates across the countries involved in our research. Another potential limitation is that the data collection period lasted until the end of 2019, therefore it was not possible to evaluate changes in the anticoagulant consumption during the COVID-19 pandemic, when a significant increase in consumption could be expected (35). The termination of data collection in 2019 was driven by the study protocol initiated in 2018, being also affected by the inclusion criteria and other operating issues in receiving new data. Therefore, further studies are needed to examine the utilization trend in NOAC consumption or whether consumption of NOACs will continue to increase at the expense of VKAs. Similarly, it would be very interesting to observe the trends in anticoagulant consumption during the COVID-19 pandemic, when the high number of hospitalized patients, the increased incidence of venous tromboembolism and new guidelines might have affected the consumption of parenteral anticoagulants (35). As for the future development, the upcoming launch of generic NOACs can also have a certain impact on the overall anticoagulant utilization.

Conclusion

The overall consumption of oral and parenteral anticoagulants increased in the Czech Republic, Croatia, Hungary, Romania, and Slovakia in the period 2007–2019, yet the individual countries show various national specificities that need to be further analysed to better understand the different factors influencing the consumption of these drugs.

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