

Influence of novel oral anticoagulants on anticoagulation care management

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Anticoagulation treatment was recently improved by the introduction of novel oral anticoagulants (NOACs). Using a combination of qualitative and quantitative methods, this study explores the effects of the introduction of NOACs on anticoagulation care in Slovenia. Face-to-face interviews with key stakeholders revealed evolvement and challenges of anticoagulation care from different perspectives. Obtained information was further explored through the analysis of nationwide data of drug prescriptions and realization of health care services. Simplified management of anticoagulation treatment with NOACs and their high penetration expanded the capacity of anticoagulation clinics, and consequentially the treated population increased by more than 50 % in the last 5 years. The main challenge concerned the expenditures for medicines, which increased approximately 10 times in just a few years. At the same time, the anticoagulation clinics and their core organisation were not affected, which is not expected to change, since they are vital in delivering high-quality care.

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Anticoagulation treatment is indicated for several conditions, including prevention of stroke in atrial fibrillation, and for the treatment and prevention of recurrent deep venous thrombosis and pulmonary embolism (1, 2). Incidence of atrial fibrillation, the disease that most frequently requires anticoagulation treatment, is approximately 1.5–2 % in the developed world, which is expected to double in the next 50 years (3). The most convenient route of administration for medicines is oral application. Until recently, oral anticoagulation (OAC) treatment was limited to only a few drugs, all from the same group of vitamin K antagonists (VKAs) (1). Effectiveness of VKAs has been consistently shown, but these drugs have some major disadvantages (4). Variable pharmacokinetics with many drug-drug interactions and a narrow therapeutic window are the main limitations for their use. Past developments in anticoagulation treatment were focused on improving the treatment

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with these drugs and comprised close monitoring through specialized anticoagulation clinics, self-monitoring and self-management (5, 6). However, in the last decade, new drugs, known as new (or non-vitamin K) oral anticoagulants (NOAC), with less complex management, were introduced as alternatives to VKAs (3). NOACs are administered in fixed doses and do not require frequent monitoring, but awareness before oversimplification of treatment with NOACs has been exposed (7, 8). Published cost-effectiveness studies have justified their steep price, mainly due to the complexity of current treatment with VKAs (9, 10). However, introduction of these pricey drugs in combination with many potential users could have a substantial impact on budgets. Therefore, health care authorities were looking for effective models to optimize their utilisation (11, 12). NOACs were also introduced in Slovenia, like in many other countries, but there are differences between countries in the approach, activities, and reimbursement restrictions (11, 13). Availability of NOACs is likely to have affected the traditional management of anticoagulation treatment and consequentially its organisation. NOACs are more suitable for patients as well as more convenient for health professionals. The purpose of this study was to explore the effects of the introduction of NOACs in Slovenia and to specify the expected challenges in the anticoagulation care management system.

EXPERIMENTAL

Evolution of anticoagulation care in Slovenia was explored by a combination of qualitative and quantitative methods. Semi-structured interviews with key stakeholders were conducted to identify challenges and obtain insights into major changes in anticoagulation care from different perspectives. The information provided was then objectivized and expanded with nationwide data on the usage and costs of medicines and health care services.

Interviews

Semi-structured interviews were selected because they enable focused and in-depth exploration of topics. To ensure suitable coverage of topics from different perspectives, we purposely recruited participants among leading experts, doctors, nurses, and clinical pharmacists involved in routine clinical practice, persons responsible for managing anticoagulation clinics, and representatives of public payers. We invited potential participants to obtain at least one opinion from each of the desired perspectives. The planned questions were open-ended and designed to permit interviewees to expand their answers, which could reveal new areas or ideas that were not anticipated. Six interviews with different respondents that consented to take part in the study were conducted on an individual basis at their respective workplaces. All interviews were conducted by one researcher (AJ) in July 2016. The interviews lasted approximately 30 minutes and were audio recorded. The transcripts were coded using standard thematic analysis techniques. The themes that emerged, highlighted from different perspectives, were classified into categories and additionally explored through analyses of health claims and health care services databases.

Databases

Data were extracted from two databases: the health claims data on prescription drugs and the data of realization of health care services. Both data sets were obtained from the

Health Insurance Institute of Slovenia (ZZZS), the public institute mandated to provide compulsory health insurance in Slovenia. The period from the introduction of the first NOAC to the latest available data, namely from 2009 to the end of 2015, was analysed.

The health claims database contains information on all outpatient medications dispensed in Slovenia at the individual prescription level. In addition to information on the kind of medications, their quantity, and when they were dispensed, the database also contains basic information about the patients, such as age, sex, place of residence and information about the prescribers. The database of the realization of health care services contains information about the number of visits, type and amount of services delivered, number of staff and the value of services provided at the health care provider level.

Health claims database

The health claims database was used to estimate the number of patients taking OACs, their basic characteristics, including concomitant treatments, the year they began anticoagulation therapy, and the brand of their first OAC, as well as the consumption of each individual drug for the analysis of volume and value. The selection of drugs was based on their anatomical therapeutic chemical (ATC) classification; the whole group of VKAs (ATC code: B01AA), dabigatran etexilate (B01AE07), rivaroxaban (B01AF01), and apixaban (B01AF02) were considered. To estimate the number of patients treated with OACs, including the number of initiating patients and the number starting the drugs each year, the criterion of the first dispensed OAC was applied for all years. Possible switches of therapy within a year were not considered for this purpose. For the volume and value analysis, the consumption of all dispensed medicines was included. Defined daily dose (DDD) was selected as the measure of volume consumption.

Provision of health care services

The database of the realization of health care services was used to evaluate the performance and patient load of anticoagulation clinics and to estimate the economic burden of anticoagulation care. The number of visits, number of staff teams and the value of services were extracted for each anticoagulation clinic at the primary level. The services of anticoagulation treatment at the secondary and tertiary levels were not recorded separately, but as a part of specialized cardiology clinics, which also performed other services not related to anticoagulation. The loads of these clinics were estimated according to the total number of patients on anticoagulation treatment (extracted from the first database) and the proportion of visits at the primary care level, estimated by experts. The absolute number of visits served to estimate the cost of anticoagulation treatment at the secondary and tertiary levels.

RESULTS AND DISCUSSION

Qualitative research exposed seven themes, which were classified into three categories: treated population, medicines, and organisation of anticoagulation care (Fig. 1). All except one (re-organisation of the work process) were also appropriate for the data analysis and objectification of respondents' observations.

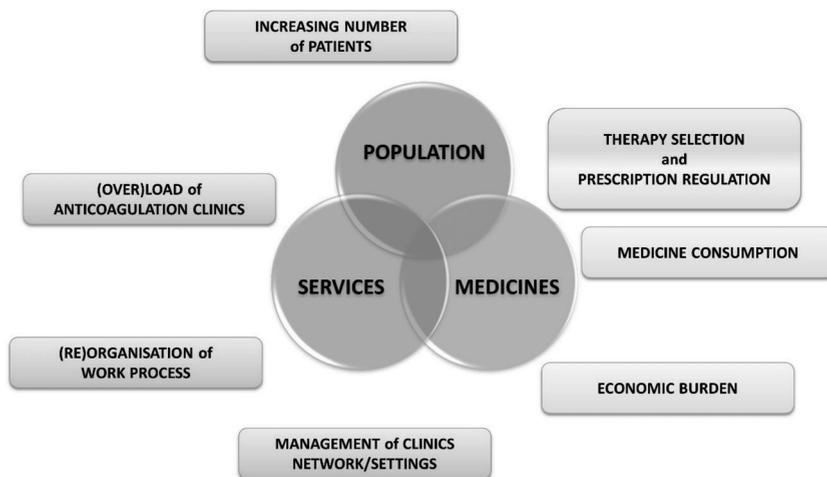


Fig 1. The themes identified in interviews and their categories.

Population

Many stakeholders anticipated the growth of treated population, but it seems that the extent of the increase was not expected. Moreover, respondents also expect that this trend will continue and will represent the main challenge in coming years, as more patients request an increase in the capacity of health care services, which, in combination with higher consumption of medicines, is reflected in expansion of the economic burden. Several reasons were noted, most often they were ageing of the population, a higher diagnostic rate, a more user-friendly therapy, and the different treatment approach, which also extends the eligibility of patients for anticoagulation treatment. As one respondent noted,

‘Some patients that should have been treated with oral anticoagulants were not treated in the past because of the challenges of VKA therapy, but now they can be treated with NOACs.’

Under-usage of oral anticoagulants in the pre- and early-NOAC era was also reported in other developed countries and availability of NOACs reduced the undertreated population (14, 15). Similar observations were also recorded in our study, as data analysis revealed that the treated population increased from an average of 7.4 % per year to almost 55.000 in 2015 (Table I). Based on the trends from 2012 to 2015, approximately 68,000 patients will be prescribed at least one OAC in 2018. Part of the reason for such increase could also be found in the broad policy of prescribing NOACs, which are available for naïve patients and patients with poor anticoagulation control on warfarin, but all patients should still be monitored at anticoagulation clinics. Simplified management of treatment with NOACs released the capacity of anticoagulation clinics, which are now able to treat more patients. A representative statement is the following:

‘Our wide policy of prescribing NOACs enabled more patients to be properly treated and probably fewer complications occur. Without the availability of NOACs we would not be able to treat so many more patients, since we were already overloaded.’

Table I. Characteristics of patients who received at least one oral anticoagulant

	2009	2010	2011	2012	2013	2014	2015
Number of patients (prevalence)	35,152	37,146	40,036	43,068	46,707	50,287	54,576
Average age (years)	72.5	72.6	72.7	73.1	73.4	73.8	74.0
Sex (% female)	51.3	51.4	51.4	51.5	51.3	51.6	51.4
Concomitant medicines (% of patients)							
Blood pressure modifying agents (ATCs: C03, C07, C08, C09)	90.6	90.2	89.7	90	89.9	90.1	89.8
Drugs used in diabetes (ATC: A10)	17.2	18.0	18.3	18.6	18.6	18.9	19.0
Acetylsalicylic acid, low dose (ATC: B01AC06)	15.8	16.7	17.3	18.3	17.9	17.4	16.9
Other oral antithrombotic agents ^a	1.5	1.6	1.7	1.8	1.8	1.9	2.0
Number of patients received							
VKA	34,618	35,675	37,715	39,722	38,664	37,199	35,812
NOAC	534	1,471	2,321	3,346	8,043	13,088	18,764
High dose ^b	0	0	0	359	2,659	5,526	8,571
Moderate dose ^b	230	360	547	962	3,185	5,453	7,778
Low dose ^b	304	1,111	1,774	2,025	2,199	2,109	2,415
Number of new patients (incidence)		8,423	9,371	9,904	10,695	11,377	12,308
% receive VKA as first OAC		83.3	77.4	70.4	42.1	34.6	26.4

VKA – vitamin K antagonist (warfarin, acenocoumarol), NOAC – non-vitamin K oral anticoagulant, OAC – oral anticoagulant

^a Clopidogrel (ATC: B01AC04), prasugrel (ATC: B01AC22), ticagrelor (ATC: B01AC24).

^b High dose: dabigatran 150 mg, rivaroxaban 20 mg, apixaban 5 mg; moderate dose: dabigatran 110 mg, rivaroxaban 15 mg, apixaban 2.5 mg; low dose: dabigatran 75 mg, rivaroxaban 10 mg.

The analysis of data showed that the majority of patients had already initiated anticoagulation treatment with NOAC (74 % in 2015). Many educational activities for practitioners were offered when NOACs were introduced. The respondents were confident that the majority of prescribers followed clinical guidelines and complied with prescription limitations. They perceived that the majority of patients with poor anticoagulation control were already translated to NOACs, and therefore, the number of patients on VKAs will probably remain stable, while the number of patients receiving NOACs will continue to rise. These observations were supported by data analysis, which revealed that the number of patients receiving VKAs increased up to 2012, and then declined by 3.4 % per year when NOACs became available for long-term treatment. At the same time, the number of patients receiving NOACs rapidly increased to almost 19,000 patients in 2015, accounting for 34 % of all patients receiving an OAC. High penetration of NOACs and their premium price raise the question of financial sustainability.

Medicines

Total expenditures for NOACs in 2015 were 8.2 million EUR, which is almost twice the entire budget for anticoagulation care before introduction of NOACs, including drug and monitoring costs. Compared to the traditional therapy, the volume consumption in 2015 was comparable between NOACs and VKAs (6.7 million *vs.* 6.6 million DDDs), while expenditures were approximately 10 times higher (Fig. 2). If the same trend should continue in the next 3 to 4 years, the economic burden of NOACs would probably exceed 15 million EUR. However, at the time of introduction some expected that expenditures for anticoagulation clinics would substantially decline, but in fact they did not change significantly. Most probably because the amount of work was not reduced, as new patients appeared. Most participants were aware that NOACs are much more expensive than warfarin and that consumption of these expensive drugs has risen rapidly, but they were not aware of the specifics at the national level. On the one hand, the practitioners said that they did not consider the economic aspect when deciding on an appropriate treatment; their decision was based solely on clinical criteria, taking into account reimbursement limitations. On the other hand, the same doctors also expressed concerns about potentially tighter prescription limitations due to high expenditures. However, public payers are convinced that expenditures for NOACs are manageable and current affordability can be maintained without imposing prescription limitations:

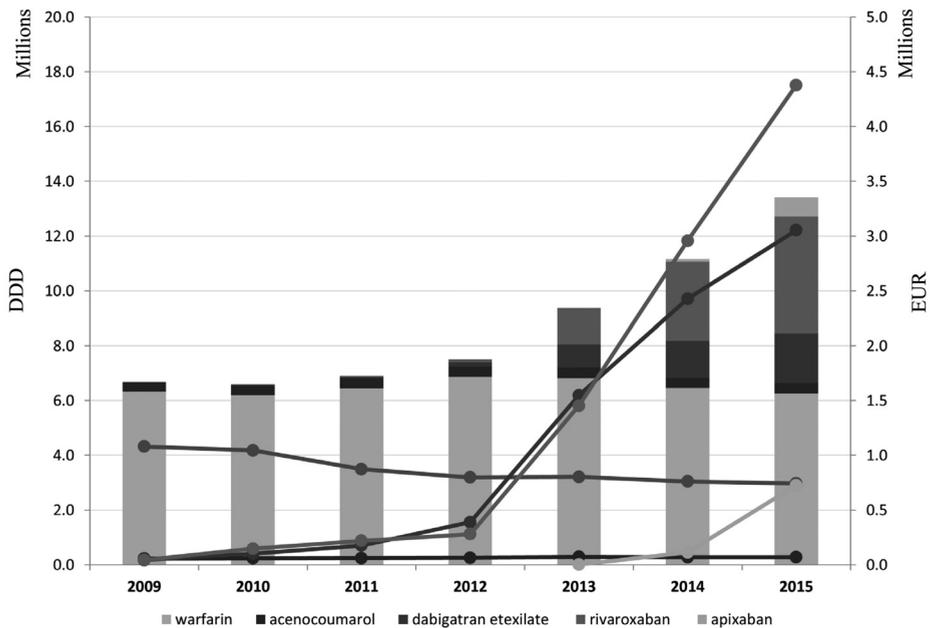


Fig. 2. Yearly consumption (bars) in defined daily doses (DDD) and expenses (lines) in EUR of oral anticoagulants.

'In this field we have complex agreements with ample protection against uncontrolled growth of expenditures with all manufacturers. If we are able to maintain these agreements, the expenditures will rise, but in a manageable range, and there would not be a need to interfere.'

The prescribers claim that they do not prefer any specific medicine because each medicine has its own characteristics. One medicine is sometimes suitable for one patient, sometimes for another. The nationwide data indicate a slightly higher growth of rivaroxaban compared to dabigatran etexilat, especially in later years. The underlying reason for this difference does not appear to be the price, since all NOACs have nearly the same daily cost. However, a difference between substances in the dispensed dosage was recorded. Most of rivaroxaban consumption was in a high dose (20 mg), while half of dabigatran etexilat consumption was in a moderate dose.

Services

Many interviewees expected that the introduction of NOACs would reduce the burden of already overloaded anticoagulation clinics. The practitioners have not observed the expected relief yet:

'You should know that our team manages 150 to 160 regular patients per day, and an additional up to 10 unplanned patients, who come to our clinic. Despite the fact that we try to refer a lot of patients to the primary level, the numbers are still enormous.'

Respondents also said that communication and collaboration between different levels were not as good as they should be. Some practitioners at the secondary level estimated that around 40 % of patients currently treated in their clinics could be managed at the primary level, but they cannot be transferred because of the insufficient capacity at the primary level. This was confirmed by data analysis (Table II). For example, in 2014 there were on average 24,169 visits per team at the primary level, which is 17 % more than the

Table II. Performance and expenditures of anticoagulation clinics at the primary level and estimations for the secondary/tertiary level of health care

Year	Primary level			Secondary/tertiary level (estimated)	
	Number of teams	Number of visits (in thousands)	Expenditures (in million EUR)	Number of visits (in thousands)	Expenditures (in million EUR)
2009	10	173	1.8	313–382	3.2–3.9
2010	10	212	1.9	292–363	2.6–3.3
2011	10	223	2.0	312–388	2.8–3.5
2012	11	245	2.1	322–401	2.8–3.5
2013	11	258	2.2	307–384	2.6–3.2
2014	11	264	2.2	296–371	2.5–3.1
2015	15	278	2.4	280–351	2.4–3.0

norm set in the calculation of service value, which predicts 20,735 visits per team per year. In Slovenia, specialized anticoagulation clinics were introduced approximately a decade ago, but the network at the primary level is still being built, therefore there are some differences between regions. This was also expressed by some interviewers:

'In 2015 we finally got some necessary anticoagulation clinics at the primary level in our region. Prior to that, we had only a few private practitioners, who provided anticoagulation treatment to a limited extent.'

'We do not expect that more patients will be referred to primary care unless something special, which is not expected, happens.'

Establishment of four anticoagulation clinics at the primary level, financed by ZZZS as early as in 2015, should reduce the overload and more patients could be managed at the primary level. However, the question of expediency of further expansion of specialized clinics in the environment with high usage of NOACs naturally arises. Furthermore, some authors suggest that the role of anticoagulation clinics should be redefined, including assisting patients and clinicians with selecting the appropriate anticoagulant and its dose, helping patients to minimize the bleeding risk, and potentially expanding their coverage to other higher risk medications (8). These activities will most probably be incorporated in the current work of anticoagulation clinics, but transferring current activities or only part of them to other facilities is not likely. This is mainly because stakeholders do not expect that this would have any important financial impact and they are aware that high quality of care can be maintained only through specialised anticoagulation clinics:

'Anticoagulation treatment is specific, requires special training and, most importantly, high frequency is necessary to ensure high-quality care.'

'From the financial point of view, I do not see any benefit of shutting down anticoagulation clinics and relocating patients to other facilities; the number of visits would probably remain the same, financed by the same payer at approximately the same price, so there would actually be no significant financial effect.'

Nevertheless, these facilities will still be required for proper management of patients receiving VKAs, as these medications remain an important alternative to NOACs. Approximately one third of patients with atrial fibrillation are not eligible for treatment with NOACs, based on experts' estimates confirmed by database analysis. Lower demand for warfarin could raise the price, but this should not substantially affect the economic burden of anticoagulation care, as the current price is approximately 30 times lower than NOACs.

The main strength of this study is that we combined epidemiologic data analysis with qualitative research. These two methods can complement each other. Qualitative research can provide the background or provide an additional perspective, justify reinterpretation of quantitative data, or serve as validating data. The major risk of the way we used these data arose from scarce or misleading information. We used high-quality databases but lacked data about the performance of clinics on the secondary and tertiary levels. Another limitation was that participants for interviews were purposely selected. Therefore, we cannot completely exclude bias in selection or the possibility that participants were not completely open with the researcher. Based on the attitude of respondents, however, we doubt that this problem occurred.

CONCLUSIONS

The introduction of NOACs into Slovenian medical practice enabled many more patients to be properly treated. First, patients that were not eligible for VKAs or management of therapy was too complex for them now have access to appropriate treatment and thus better health prospects. Second, simplified management of anticoagulation treatment with NOACs released some capacity of anticoagulation clinics, which was filled by new patients. This was reflected in the load of anticoagulation clinics, which did not diminish but slightly increased. Consequently, new anticoagulation clinics were established at the primary care level and strengthened their position in the health care system. In addition, the prevailing opinion is that such organisation assures high-quality care, including treatment with NOACs. The financial burden of anticoagulation treatment increased substantially, but seems to be in a manageable range. More importantly, increased expenditures predict better health outcomes for the population, since more patients are properly treated. This would be difficult to achieve without or with more limited access to NOACs, since there are limited resources for extension of the network of anticoagulation clinics.

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REFERENCES

1. W. Ageno, A. S. Gallus, A. Wittkowsky, M. Crowther, E. M. Hylek and G. Palareti, Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, *Chest* **141** (2012) e44S–88S; DOI: 10.1378/chest.11-2292.
2. A. Mavri and G. Tratar, Kakovost vodenja antikoagulacijskega zdravljenja v Sloveniji [Quality of the management of anticoagulant therapy in Slovenia], *ISIS* **16** (2007) 56–59.
3. A. J. Camm, G. Y. Lip, R. De Caterina, I. Savelieva, D. Atar, S. H. Hohnloser, G. Hindricks and P. Kirchhof, 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association, *Eur. Heart J.* **33** (2012) 2719–2747; DOI: 10.1093/eurheartj/ehs253.
4. R. G. Hart, L. A. Pearce and M. I. Aguilar, Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation, *Ann. Intern. Med.* **146** (2007) 857–867; DOI: 10.7326/0003-4819-146-12-200706190-00007.
5. S. J. Wilson, P. S. Wells, M. J. Kovacs, G. M. Lewis, J. Martin, E. Burton and D. R. Anderson, Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: a randomized controlled trial, *CMAJ* **169** (2003) 293–298.
6. C. J. Heneghan, J. M. Garcia-Alamino, E. A. Spencer, A. M. Ward, R. Perera, C. Bankhead, P. Alonso-Coello, D. Fitzmaurice, K. R. Mahtani and I. J. Onakpoya, Self-monitoring and self-management of oral anticoagulation, *Cochrane Database Syst. Rev.* **7** (2016) CD003839; DOI: 10.1002/14651858.CD003839.pub3.
7. S. Testa, O. Paoletti, A. Zimmermann, L. Bassi, S. Zambelli and E. Cancellieri, The role of anticoagulation clinics in the era of new oral anticoagulants, *Thrombosis* **2012** (2012) Article ID 835356, 6 pages; DOI: 10.1155/2012/835356.

8. G. D. Barnes, B. K. Nallamothu, A. E. Sales and J. B. Froehlich, Reimagining anticoagulation clinics in the era of direct oral anticoagulants, *Circ. Cardiovasc. Qual. Outcomes* 9 (2016) 182–185; DOI: 10.1161/Circoutcomes.115.002366.
9. A. Janzic and M. Kos, Cost effectiveness of novel oral anticoagulants for stroke prevention in atrial fibrillation depending on the quality of warfarin anticoagulation control, *Pharmacoeconomics* 33 (2015) 395–408; DOI: 10.1007/s40273-014-0246-7.
10. N. L. Liberato and M. Marchetti, Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for stroke prevention in non-valvular atrial fibrillation: a systematic and qualitative review, *Expert Rev. Pharmacoecon. Outcomes Res.* 16 (2016) 221–235; DOI: 10.1586/14737167.2016.1147351.
11. R. E. Malmstrom, B. B. Godman, E. Diogene, C. Baumgartel, M. Bennie, I. Bishop, A. Brzezinska, A. Bucsecs, S. Campbell, A. Ferrario, A. E. Finlayson, J. Furst, K. Garuoliene, M. Gomes, I. Gutierrez-Ibarluzea, A. Haycox, K. Hviding, H. Herholz, M. Hoffmann, S. Jan, J. Jones, R. Joppi, M. Kalaba, C. Kvalheim, O. Laius, I. Langner, J. Lonsdale, S. A. Loov, K. Malinowska, L. McCullagh, K. Paterson, V. Markovic-Pekovic, A. Martin, J. Piessnegger, G. Selke, C. Sermet, S. Simoens, C. Tulunay, D. Tomek, L. Voncina, V. Vlahovic-Palcevski, J. Wale, M. Wilcock, M. Wladysiuk, M. van Woerkom, C. Zara and L. L. Gustafsson, Dabigatran – a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs, *Front. Pharmacol.* 4 (2013) Article ID 39; DOI: 10.3389/fphar.2013.00039.
12. B. Godman, R. E. Malmstrom, E. Diogene, A. Gray, S. Jayathissa, A. Timoney, F. Acurcio, A. Alkan, A. Brzezinska, A. Bucsecs, S. M. Campbell, J. Czczot, W. de Bruyn, I. Eriksson, F. A. Yusof, A. E. Finlayson, J. Furst, K. Garuoliene, A. Guerra Junior, J. Gulbinovic, S. Jan, R. Joppi, M. Kalaba, E. Magnisson, L. McCullagh, K. Miikkulainen, G. Ofierska-Sujkowska, H. B. Pedersen, G. Selke, C. Sermet, S. Spillane, A. Supian, I. Truter, V. Vlahovic-Palcevski, L. E. Vien, E. H. Vural, J. Wale, M. Wladysiuk, W. Zeng and L. L. Gustafsson, Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?, *Expert. Rev. Clin. Pharmacol.* 8 (2015) 77–94; DOI: 10.1586/17512433.2015.990380.
13. B. Godman, R. E. Malmstrom, E. Diogene, S. Jayathissa, S. McTaggart, T. Cars, S. Alvarez-Madrado, C. Baumgartel, A. Brzezinska, A. Bucsecs, S. Campbell, I. Eriksson, A. Finlayson, J. Furst, K. Garuoliene, I. Gutierrez-Ibarluzea, K. Hviding, H. Herholz, R. Joppi, M. Kalaba, O. Laius, K. Malinowska, H. B. Pedersen, V. Markovic-Pekovic, J. Piessnegger, G. Selke, C. Sermet, S. Spillane, D. Tomek, L. Voncina, V. Vlahovic-Palcevski, J. Wale, M. Wladysiuk, M. van Woerkom, C. Zara and L. L. Gustafsson, Dabigatran – a continuing exemplar case history demonstrating the need for comprehensive models to optimize the utilization of new drugs, *Front. Pharmacol.* 5 (2014) Article ID 109; DOI: 10.3389/fphar.2014.00109.
14. T. Wilke, A. Groth, S. Mueller, M. Pfannkuche, F. Verheyen, R. Linder, U. Maywald, T. Kohlmann, Y. S. Feng, G. Breithardt and R. Bauersachs, Oral anticoagulation use by patients with atrial fibrillation in Germany. Adherence to guidelines, causes of anticoagulation under-use and its clinical outcomes, based on claims-data of 183,448 patients, *Thromb. Haemost.* 107 (2012) 1053–1065; DOI: 10.1160/TH11-11-0768.
15. T. C. Sarich, J. H. Seltzer, S. D. Berkowitz, J. Costin, J. T. Curnutte, C. M. Gibson, M. Hoffman, E. Kaminskas, M. W. Krucoff, J. H. Levy, P. D. Mintz, P. A. Reilly, P. T. Sager, D. E. Singer, N. Stockbridge, J. I. Weitz and P. R. Kowey, Novel oral anticoagulants and reversal agents: Considerations for clinical development, *Am. Heart J.* 169 (2015) 751–757; DOI: 10.1016/j.ahj.2015.03.010.