PROFESE ONLINE
recenzovaný časopis pro nelékařské zdravotnické obory

ISSN 1803-4330
DOI: 10.5507/pol.2018.001
volume 11 / 1 • June 2018

Patients using new oral anticoagulants – results of an epidemiological study

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ABSTRACT

Background: New oral anticoagulants are undoubtedly a big step forward. Their use is safer than warfarin, and there is no need for monitoring, which provides a great deal of relief especially for less-moving patients. In spite of their great advantages, especially for the optimization of treatment, the group of patients and their basics should be monitored.

Aim: The aim of the study was to find out the basic characteristics of patients, including comorbidities and other important parameters.

Methods: The data was obtained from the Benedor cardiac database in Ostrava. The selection criterion was the use of DOACs (Direct Oral Anticoagulants), i.e. the use of dabigatran, rivaroxaban or apixaban. The EpiData program was used for data processing. Data was also exported and processed in Excel, Stata and OpenEpi. The total number of respondents was 334 patients**.**

Results: The most prominent feature of patients was overweight and obese 55.8%. Normal weight was maintained by only 11.3% of patients. Most patients suffered from three other diseases (most often hypertension and ischemic heart disease).

Conclusion: In general, a group of patients may be characterized as polymorbid, overweight or obese. It would be appropriate to lead patients to a healthy lifestyle and thus improve their health.

KEY WORDS

New peroral anticoagulants, dabigatran, rivaroxaban, apixaban, darexaban

INTRODUCTION

For 60 years, warfarin was the only oral anticoagulant. However, despite its undoubted clinical efficacy, particularly in preventing stroke and reducing the risk of death in patients with atrial fibrillation, warfarin has numerous adverse effects. Therefore, and for other reasons, new direct oral anticoagulants (DOACs) were developed and introduced; these are as effective and safe as, but easier to administer than, warfarin. Today, two groups of agents are available, oral direct thrombin inhibitors (gatrans) and oral direct factor Xa inhibitors (xabans). Based on large clinical trials, the following drugs to prevent stroke and other systemic embolic events in patients with atrial fibrillation have been approved so far (in the order as listed): dabigatran (Pradaxa®), rivaroxaban (Xarelto®) apixaban (Eliquis®) and edoxaban (Lixiana®) (1, 2, 3, 4).

DOACs have only been used for several years. Therefore, experiences with them will only gradually accumulate. Nevertheless, DOACs add to the anticoagulation treatment options, are undoubtedly beneficial in terms of treatment safety and efficacy and, last but not least, contribute to better patient comfort. Due to their older age and frequent comorbidities, patients using DOACs may be encountered at most centers providing care in various specialties and at various levels of healthcare (1).

The present epidemiological study of new anticoagulants was concerned with a group of patients taking DOACs. It is desirable to gain as much information on these patients as possible to ensure maximum treatment optimization and health benefit for patients. If a specialist and health workers have sufficient information on a particular patient, for example their comorbidities and other medications, or if an individual's nutritional status is found to be a potential risk factor, the patient may receive better care based on this valuable information. Namely, the patient's subjective and objective health status may be improved, for example, through educating them on a healthy lifestyle such as smoking cessation, alcohol abstinence or weight reduction. Moreover, the study also analyzed the adverse effects of DOACs; these data, however, are not included in this paper.

OBJECTIVE

The study aimed at determining basic characteristics of patients, including comorbidities and other significant parameters. The survey was conducted in outpatient cardiology centers in the towns of Ostrava and Opava, Czech Republic.

METHODS

Data were collected from a database of Benedor, a network of outpatient cardiology centers in Ostrava and Opava. The inclusion criterion was the use of DOACs, that is, dabigatran, rivaroxaban or apixaban. The data were processed using the EpiData software. Subsequently, the data were exported and analyzed using MS Excel, Stata and OpenEpi. The statistical significance was set at a level of 5%. Sensitive information was anonymize to adhere to the personal data protection act. The data were collected from fall 2016 until the end of 2017. Data were obtained from a total of 334 patients.

RESULTS

The sample comprised a total of 334 patients, of whom 185 were males (55.4%) and 149 were females (44.6%). Their mean age was 72.3 years (range, 34-93 years).

In all patients, height and weight were also ascertained to calculate their body mass index (BMI). Based on their BMI, the patients were distributed into six groups, in accordance with the WHO. The distribution of patients into groups is shown in Table 1.

Table 1 shows that as few as 11.3% of patients had normal weight while 32.7% were overweight. A total of 55.8% of patients were obese, suffering from various degrees of obesity. Only 0.2% of patients (two out of 334) were malnourished, or underweight. Overweight or obesity was noted in 110 females and 158 males, that is 32.9% and 47.3% of all participating females and males, respectively.

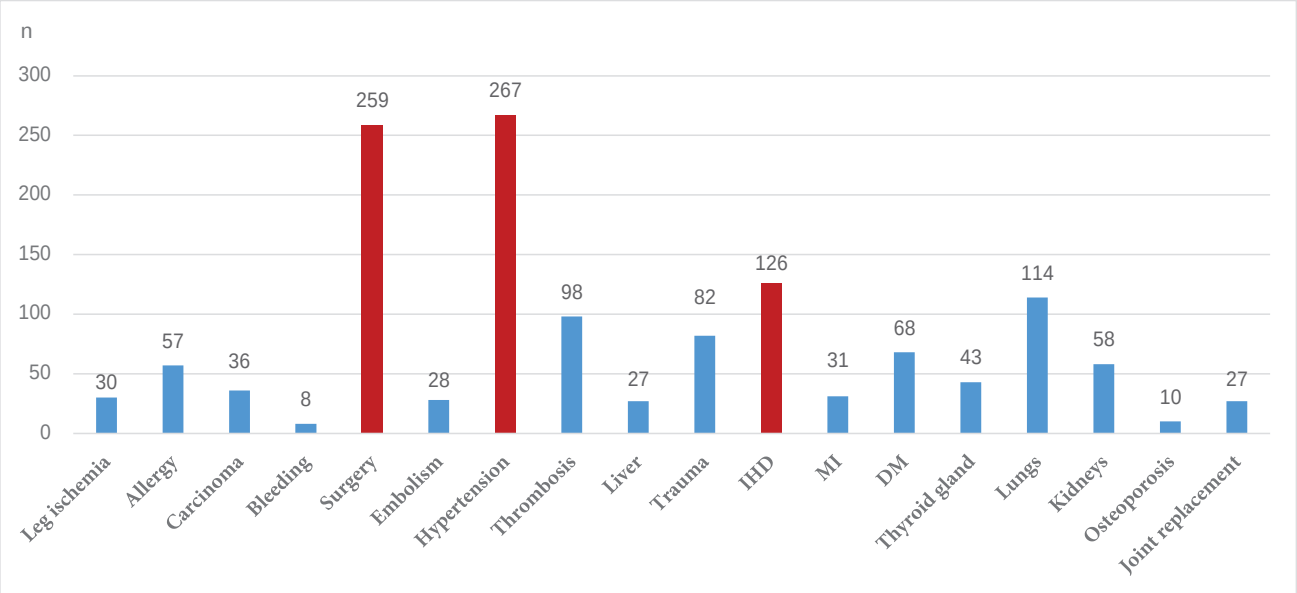
Table 1 Distribution of patients into groups based on their BMI (according to the WHO)

Weight status	BMI category	BMI	n	%
Underweight	1	< 18.5	2	0.2
Normal (ideal) weight	2	18.5 – 24.9	64	11.3
Overweight (pre-obesity)	3	25.0 – 29.9	123	32.7
Mild obesity	4	30.0 – 34.9	104	36.8
Moderate obesity	5	35.0 – 39.9	32	14.2
Severe (morbid) obesity	6	> 40.0	9	4.8

Notes: n – number of individuals, BMI – body mass index, % – relative frequency

The study also determined patients' basic selected comorbidities. All comorbidities and their absolute numbers are shown in Figure 1. Three groups of comorbidities most frequently affecting the patients are marked red. Specifically, these included hypertension in 79.9% of patients (267 individuals); at the same time, 77.5% of patients underwent some type of surgery (259 individuals) and 37.7% of patients suffered from ischemic heart disease (126 individuals). Other comorbidities were lung disease, thrombosis, trauma, type 2 diabetes mellitus, etc. The number of comorbidities in a single patient was also ascertained. Most frequently, patients had three or four comorbidities (21.26% and 20.66%, respectively). Only 1.2% of patients (4 individuals) had no comorbidities. The highest number of comorbidities, six, was noted in 0.9% of patients (three cases).

Figure 1 Presence of comorbidities



Legend: IHD – ischemic heart disease, MI – myocardial infarction DM – diabetes mellitus

Additionally, the study analyzed the patients' actual blood pressure during their use of DOACs. Systolic and diastolic values were recorded separately. The normal range of systolic pressure was noted in 50.3% of patients. However, 49.1% of patients suffered from elevated systolic pressure. The remaining less than one percent, by contrast, had systolic hypotension (two males). The mean systolic pressure was 139 mmHg; the minimum and maximum values were 97 mmHg and 200 mmHg, respectively. The facts about diastolic pressure were as follows. As many as 69.8% of patients had their diastolic pressure in the normal range. Hypertension and hypotension were observed in 29.6% and only 0.6% of patients, respectively. The mean diastolic pressure was 82.11 mmHg, ranging from a minimum of 46 mmHg to a maximum of 117 mmHg.

The most frequent initial diagnosis for which DOACs were prescribed was atrial fibrillation in 68% of patients (223 individuals), followed by deep vein thrombosis (21%; 69 patients), pulmonary embolism (4%; 12 patients) and atrial flutter (3%); the other diagnoses included stroke and ischemic heart disease. Atrial fibrillation was more commonly seen in males (55.4%) than in females (44.6%); and so was deep vein thrombosis (55.1% vs 44.9%).

Further, rivaroxaban was found to be most commonly used (44.91%), followed by apixaban (27.85%) and dabigatran (27.24%). The majority of DOAC users were males (55.39%). Similarly, males prevailed over females as users of individual drugs, as seen from Table 2.

Table 2 Use of individual agents by gender

	Dabigatran		Rivaroxaban		Apixaban		All DOACs	
Gender	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Male	47	14.07	85	25.45	53	15.87	185	55.39
Female	44	13.17	65	19.46	40	11.98	149	44.61
Total	91	27.24	150	44.91	93	27.85	334	100.00

Notes: n – number of individuals, DOACs – direct oral anticoagulants, % – relative frequency

As for the duration of therapy with individual DOACs, a long-term use was significantly more common than a short-term use (94% vs 6%).

Table 3 lists the prescribed doses of dabigatran, rivaroxaban and apixaban. In case of dabigatran, the user groups were nearly identical (13.8% using 150 mg and 13.2% using 110 mg). A 30 mg dose of rivaroxaban was used by 39.2% of all patients, as compared with 6% using a lower dose of 15 mg. Similarly, apixaban at a dose of 5 mg was used by 23.4% of all patients, compared to 4.5% of patients using half that dose. In other words, rivaroxaban and apixaban were mostly administered at higher doses.

Table 3 Doses of individual oral anticoagulants

Dabigatran			Rivaroxaban			Apixaban		
Dose (mg)	**n**	**%**	**Dose (mg)**	**n**	**%**	**Dose (mg)**	**n**	**%**
150 (twice day)	47	13.8	**20 (once a day)**	130	39.2	**5 (twice a day)**	78	23.4
110 (twice a day)	44	13.2	**15 (once a day)**	20	6	**2.5 (twice a day)**	15	4.5

Notes: n – number of individuals, % – relative frequency

To obtain a complete picture of patients using DOACs, the study analyzed some selected lifestyle factors that could be retrieved from patients' medical records. Apart from the aforementioned overweight and obesity, those were mainly smoking status, alcohol use and coffee intake.

Among DOAC users, non-smokers accounted for 68.9% (230 individuals), ex-smokers for 11.4% and smokers for 12.3% of all patients. Also interesting are data on smokers. There were significantly more male smokers than female smokers (75% vs 25%). A similar trend was observed in the ex-smoking group. Males ceased smoking more frequently than females (81.6% vs 18.4%).

The data on coffee and alcohol intake were as follows. Alcohol was used by 55.39% of patients while 36.23% reported themselves as abstainers. No data on alcohol use were available for the remaining 28 patients (8.38%). There were 71.26% of coffee drinkers; once again, no data were available for 28 individuals (8.38%).

Other lifestyle factors could not be ascertained from the database, or medical records.

DISCUSSION

The epidemiological study of DOACs was carried out from fall 2016 until the end of 2017. Data for the study were obtained from a cardiology database in the towns of Ostrava and Opava. The data were anonymized to adhere to Act No. 101/2000 Coll., on the Protection of Personal Data and on Amendment to Some Acts.

The present study analyzed data on 334 patients, of whom 185 were males (55.4%) and 149 were females (44.6%). Their mean age was 72.3 years (range, 34-93 years). Since over half of the participants (68%) had atrial fibrillation as the initial diagnosis warranting DOAC therapy, the obtained data basically could be compared with those in Profile of Czech AF, a large epidemiological study aimed to provide a comprehensive view of patients with nonvalvular atrial fibrillation in the Czech Republic which involved 197 Czech physicians – internists and cardiologists. It assessed data on 982 patients with a mean age of 69.9 ± 10.04 years. The mean age of patients in the present study was 72.3 years. In the earlier study, there was a slight preponderance of males (n = 543; 55.3%), particularly in a group of patients younger than 65 years of age. Similarly, males were more prevalent (55.4%) (5).

In the present study, the most frequent initial diagnosis for which DOACs were prescribed was atrial fibrillation (68%; 233 patients). Atrial fibrillation is one of the most common cardiac arrhythmias in the population; its prevalence increases with age. Apart from age, the most frequent risk factors are hypertension, male gender, ischemic heart disease and chronic cardiac failure. In these patients, other factors potentially causing atrial fibrillation have been documented. The most discussed risk factors include obesity, together with metabolic syndrome, obstructive sleep apnea and inflammatory response, together with oxidative stress and subclinical atherosclerosis. It is noted in approximately one quarter of inpatients staying in internal medicine wards; its prevalence increases with age, particularly in the seventh decade of life. This age distribution has been confirmed by the present study on DOACs. In more than half of the patients, atrial fibrillation was the primary diagnosis for which DOACs were administered. Further, atrial fibrillation is associated with the male gender, both in patients with cardiac disease and in those with no structural heart disease, as seen from numerous epidemiological studies where the ratio of males to females with atrial fibrillation ranges from 3:1 to 4:1. In the present epidemiological study, more males than females suffered from atrial fibrillation (55.4% vs 44.6%), confirming the general tendency towards male preponderance but not the male-to-female ratio. In the present study, the ratio was 1.2:1 (55.4% vs 44.6%). This, of course, may be explained by several factors. The participants, selected for their use of dabigatran, rivaroxaban and apixaban, were patients of Benedor, a network of outpatient cardiology centers in Ostrava and Opava, that is, in a small geographical area. Therefore, it cannot be representative of the entire Czech Republic as each region is specific, having different risk factors (6).

The second most frequent initial diagnosis requiring prescription of DOACs was deep vein thrombosis (21% of patients). A study on the impact of deep vein thromboembolism in European countries found that the total number of symptomatic cases in the European Union is more than 1.5 million, of which over

500,000 are fatal. This is more than all deaths caused by breast cancer, car accidents and AIDS together over one year. The remaining non-fatal cases are acute deep vein thrombosis (approx. two thirds) and pulmonary embolism (approx. one third). In the present study, 21% suffered from deep vein thrombosis and 4% had pulmonary embolism, that is, the ration changed to 5.25:1. In other words, more patients had deep vein thrombosis than pulmonary embolism. Once again, this may be due to the small geographic area, with specific living or working conditions and risk factors in the Moravian-Silesian Region where the study was set. Despite the changed ratio, however, the preponderance of patients with deep vein thrombosis remained (7).

Hypertension, as a comorbidity, was identified in 79.9% of patients in the present study (267 individuals). Other comorbidities were also noted, such as ischemic heart disease, lung disease, thrombosis, trauma and type 2 diabetes. Most frequently, the participants had three or four comorbidities. Only 1.2% of patients (4 individuals) had no comorbidities. The Profile of Czech AF epidemiological study results clearly showed that patients with atrial fibrillation were often elderly, polymorbid and high-risk individuals; these findings were fully consistent with the present study, as confirmed by available data (5).

The present study determined current values of the participants' systolic and diastolic blood pressure. Elevated systolic pressure was noted 49.1% of patients. The mean value was 139 mmHg. Age-related elevation of blood pressure cannot be considered a normal and benign manifestation of ageing. Hypertension means systolic blood pressure higher than 140 mmHg or diastolic blood pressure higher than 90 mmHg. The prevalence of hypertension increases with age; about two thirds of the population over 65 years of age suffer from hypertension. In the present study, it was more than three quarters of the participants. While the mean systolic blood pressure steadily increases with age in the population, diastolic blood pressure tends to increase until approximately 55 years of age and then decreases. Once again, these facts were confirmed by the DOACs epidemiological study, with systolic blood pressure over 140 mmHg being present in nearly 50% of patients but diastolic blood pressure above the normal range being noted in less than 30% (8).

Further, rivaroxaban was found to be most commonly used (44.91%), followed by apixaban (27.85%) and dabigatran (27.24%). The majority of DOAC users were males (55.39%). Similarly, males prevailed over females as users of individual drugs, with the gender distribution being almost balanced in case of dabigatran. For numerous conditions, physicians may choose any of the anticoagulants; in other cases, one drug is preferred for better efficacy and higher safety; and sometimes, the selection is limited to a single agent. For example, any anticoagulant may be used to prevent stroke in otherwise noncompromised patients. High-dose dabigatran is likely to be preferred if there is a high risk of thromboembolic stroke. But if the glomerular filtration rate is moderately to severely reduced, dabigatran cannot be used and xabans need to be selected. Similarly, dabigatran is not suitable for patients with coronary artery disease or those at a high risk of acute coronary syndrome. Patients at a high risk of bleeding, in particular gastrointestinal, however, should be given apixaban. If there is a high risk of both stroke and gastrointestinal bleeding, apixaban is, once again, most beneficial. For other indications, such as to prevent thromboembolic events in patients undergoing large weight-bearing joint surgery, rivaroxaban or apixaban are preferred. In a situation when an anticoagulant to treat acute deep vein thrombosis is selected, it is necessary to consider whether the strategy is to administer a single drug from the beginning; in that case, rivaroxaban or apixaban is the option. Therefore, DOAC treatment options should be individually considered for each patient. That is, therapy with one DOAC should be preferred based on knowing both the patient and the pros and cons of the particular drug. In the present study on DOACs, the most frequently used DOAC was rivaroxaban. However, the data cannot be generalized as they come from only one network of outpatient cardiology centers in Ostrava and Opava (9).

As for the duration of therapy with individual DOACs, a long-term use was significantly more common (94%) than a short-term use. This was because most to be treated with DOACs are chronic or need long-term prophylaxis with DOACs. They are used in prevention in case of surgeries such as joint replacement, but mostly for a short time (10, 11, 12).

The study also analyzed doses of dabigatran, rivaroxaban and apixaban. In individual patients, the doses should reflect their health condition and should be beneficial for their health. The physician should have a detailed knowledge of the summaries of product characteristics for the drugs, including their adverse effects and interactions with other drugs. Patients should always be educated about the proper use of the DOAC selected by their physician, including all potential adverse effects (10, 11, 12).

To obtain a complete picture of patients using DOACs, the study analyzed some selected lifestyle factors that could be retrieved from patients' medical records. Those were mainly overweight and obesity, smoking status, alcohol use and coffee intake.

As few as 11.3% of patients had normal weight while 32.7% were overweight. A total of 55.8% of patients were obese, suffering from various degrees of obesity. Overweight or obesity was noted in 32.9% and 47.3% of all participating females and males, respectively. The 2014 European Health Examination Survey (EHES) defined pre-obesity and obesity as BMI 25.0–29.9 kg/m^2 and BMI ≥ 30.0 kg/m^2, respectively. In the present study, the mean BMI values were higher in males than in females and the mean BMI was in the overweight range. Overweight or obesity was found in more males than females and in more than half of the participants, consistently with the EHES findings (13). Both obesity and overweight are associated with a risk of death from cardiovascular diseases. There is a positive linear correlation between BMI and overall mortality. The overall mortality is lowest if BMI is 20–25 kg/m^2. Further weight reduction cannot be considered protective against the development of cardiovascular diseases. The potential adverse effects of increased body weight on the cardiovascular system are increased insulin resistance (impaired glucose tolerance, type 2 diabetes), elevated blood pressure, increased signs of systemic inflammation and a prothrombotic state, albuminuria, dyslipidemia and irregularities in the cardiovascular and cerebrovascular systems (endothelial dysfunction, cardiac failure, ischemic heart disease, atrial fibrillation, stroke, abnormal left ventricular geometry, systolic and diastolic dysfunction, increased sympathetic activity). Therefore, it is necessary to educate patients on healthy lifestyle and obesity or overweight reduction (14).

The present study found that among DOAC users, non-smokers accounted for 68.9% (230 individuals), ex-smokers for 11.4% and smokers for 12.3% of all patients. There were significantly more male smokers than female smokers (75% vs 25%). However, a similar trend was observed in the ex-smoking group. As a widely spread habit, smoking is one of the most serious health risks associated with chronic diseases of affluence. These are mainly cardiovascular diseases (including most conditions for which DOACs are prescribed or comorbidities in patients using DOACs); however, there is also an association with numerous cancers, particularly lung cancer. Therefore, smoking cessation is essential to improvement of cardiovascular health (14, 15).

Alcohol and coffee were used by 55.39% and 71.26% of patients, respectively. No data on alcohol or coffee use were available for 28 patients (8.38%). Excessive alcohol intake inevitably leads to irreversible damage of many organ systems including the cardiovascular system. A long-term use results in the development of hypertension; ethanol is assumed to have an effect on the renin-angiotensin-aldosterone system and interact with brain stem receptors. Alcohol users more frequently suffer from supraventricular arrhythmias including atrial fibrillation. Recent studies have shown an association with the development of arrhythmia in both long-term heavy drinkers and binge drinkers. Also caffeine, another frequently used stimulant, is thought to be linked to various dysrhythmias. Caffeine is a methylxanthine derivative. Its central and, possibly, peripheral effects are caused by adenosine receptor blockade. After caffeine is ingested, blood pressure rapidly increases by 10 mmHg; the heart rate is slowed first and then accelerates for approximately two to three hours. At present, however, there is no absolutely convincing evidence about the impact of caffeine on the development of atrial fibrillation. Moreover, it must be borne in mind that coffee, as the main source of caffeine, contains more than 3000 substances (6).

Other lifestyle factors could not be retrieved from patients' medical records. Therefore, potential future research should be focus on these factors, proposing a suitable method for more effective collection of valid data.

LIMITATIONS

As is the case with any study, there are certain limitations of this study. One limitation is definitely the large number of persons entering data on patients into their medical documentation. Each person has their own way of entering the information, resulting in ambiguities with respect to some variables.

It was difficult to ascertain more detailed information on lifestyle as the health professionals only concentrate on basic information with no additional data.

Further, the participant came from the Ostrava -Opava area so the data cannot be generalized to the entire population.

The study analyzed data on 334 patients and thus cannot be compared to large clinical studies such as ARISTOTLE, ROCKET AF or RE-LY. However, it provides a good insight into the issue and the group of DOAC users.

CONCLUSION

New oral anticoagulants are undoubtedly a major advance in anticoagulation therapy. The present study found that apixaban and dabigatran had the fewest and the most adverse effects, respectively. A typical participant in the study may be characterized as a male with a mean age of 72 years, suffering from obesity or overweight, with hypertension, using a mean of four drugs. These DOAC users need to be followed up so

that (based on data from other epidemiological studies), after careful assessment of individual or general risk factors, the most optimal treatment option may be proposed for a particular patient.

Moreover, given the fact that numerous comorbidities and obesity or overweight were frequently identified, patients should be educated on lifestyle issues. Weight reduction, a healthier diet and other steps should be recommended, leading to better health of patients, including those with significant conditions such as type 2 diabetes mellitus.

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