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Oral Anticoagulant Therapy and Bleeding Events with Vitamin K Antagonists in Patients with Atrial Fibrillation in a Hungarian County Hospital

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Background: Vitamin K antagonists, despite their tight therapeutic spectrum and the fear of bleeding complications, were long the most important drugs used in anticoagulant therapy. The aim of this study was to evaluate the quality of anticoagulant therapy and its relation with bleedings in everyday clinical practice.

Material/Methods: We analyzed the data of 272 patients with non-valvular atrial fibrillation treated in our county hospital using retrospective data collection of the last 1008±384 days. The INR (International Normalized Ratio) values and the time in therapeutic range (TTR) were analyzed. We asked patients about bleeding complications and searched the medical records.

Results: The TTR proved to be 64% and there was no statistically significant difference between that of 252 (92.7%) patients taking acenocoumarol and 20 (7.3%) on warfarin. Analyzing various factors leading to TTR under 70%, we found that none of them have a significant impact. Significantly more bleeding events occurred in the first 3 months after the initiation of anticoagulant therapy and in patients with TTR under 70%, but the latter was not significant after adjustment for factors influencing bleeding (OR 1.607, CI 0.571–4.522, p=0.392).

Conclusions: Although the present study's TTR values were similar to those found in the warfarin branch of various large-scale international trials and in real-life settings, further improvement of vitamin K antagonist therapy are necessary. As the possibilities for this are limited, we believe that the new type anticoagulant agents have a place in everyday clinical practice.

MeSH Keywords: Anticoagulants • Atrial Fibrillation • Warfarin

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Background

Atrial fibrillation (AF) is the most common arrhythmia of high clinical importance, which can often cause systemic thromboembolic events. The loss of mechanical function of the left atrium (which normally fills the left chamber) and its enlargement make patients more susceptible to developing thrombus, which in the presence of other thrombotic risk factors results in a significant risk for (predominantly) ischemic stroke. In the general population AF is present in 1–2%, its incidence increases with age, and in the 80–90 years age group its incidence is 23.5%. It is responsible for 20% of ischemic stroke [1,2]. According to Tomcsányi et al., the Hungarian prevalence of the AF is 2.37–2.67% [3].

Antithrombotic treatment in patients with AF is an established method for primary and secondary prevention of stroke and systemic embolism. Until recently, vitamin K antagonists were considered the traditional and generally accepted therapy, and they are included in European and American guidelines as well [2,4,5]. Oral anticoagulant therapy (OACT) has been used for years due to concern about bleeding complications and recurrent thrombotic events in case of under-dosage. Due to this concern about adverse effects, predominantly significant bleeding events, the introduction of appropriate anticoagulant therapy is often missed. Effective and target INR value-based vitamin K antagonist therapy is made more difficult by the narrow therapeutic spectrum and interactions with food and other drugs [1,6]. Thus, INR value is in the therapeutic range in less than two-thirds of patients on OACT [7], and only half of patients needing and being eligible for this therapy receive it [8].

Connolly et al., in the ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) study, analyzed the data of more than 3300 patients taking warfarin. They investigated the time in therapeutic range (TTR) and they concluded that in case of TTR values over the median, the decrease in vascular event number was double the median TTR values. To benefit from OACT, the achievement rate of TTR should be over 58% [9]. Although there is no clear consensus, in different publications and guidelines a threshold of 70% is suggested [10–13].

Now that novel anticoagulants have been introduced and wide use can be expected, it may be useful to assess the quality of traditional OAC treatment based on former guidelines, ie, the precision of antithrombotic treatment and the incidence of bleeding, which is the most feared complication. Therefore, we investigated the parameters of anticoagulant therapy in a well-defined indication, in patients with non-valvular atrial fibrillation.

Material and Methods

We investigated data of patients receiving OACT due to non-valvular atrial fibrillation and presenting for regular INR (international normalized ratio) check between November 2012 and March 2013 at the outpatient departments of Pandy Kalman Bekes County Hospital in Gyula, Hungary (125 patients controlled at the Outpatient Department of Cardiology, 147 at other units). Data collection was performed by retrospective method and questioning patients. The patients gave their consent to participate and the study was conducted in accordance with the Declaration of Helsinki and ICH-GCP (International Conference on Harmonization – Good Clinical Practice). In the 272 patients the occurrence of bleeding complications was reviewed and the risk scores of thromboembolic events and bleedings ($CHADS_2$, CHA_2DS_2-VASC and HAS-BLED score) were calculated [2,5,14]. In $CHADS_2$ 1 point is given for congestive heart failure, hypertension, age (≥75 years), and diabetes mellitus, and 2 points for stroke or transient ischemic attack (TIA). In CHA_2DS_2-VASC scoring, congestive heart failure counts for 1 point, age over 75 years 2 points, diabetes mellitus 1 point, stroke or TIA 2 points, vascular disease 1 point, age between 65–74 1 point, female sex 1 point [4,15].

The bleeding risk was determined by HAS-BLED score [H – Hypertension (1 point), A – Abnormal renal or liver function (1-1 point), S – Stroke (1 point), B – Bleeding in history (1 point), L – Labile INR (1 point), E – Elderly (age over 65 years) (1 point), and D – Drug or alcohol dependence (1-1 point)] [Pisters]. The observed bleeding complications were classified according to the Bleeding Academic Research Consortium (BARC) definitions (Type 0: no bleeding; Type 1: Bleeding that is not actionable and does not cause the patient to seek treatment; Type 2: Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional; Type 3: overt bleeding plus hemoglobin drop more than 3 g/dL, requiring transfusion, surgical intervention or IV vasoactive agents; intracranial hemorrhage; intraocular bleed compromising vision; Type 4: CABG-related bleeding within 48 hours; Type 5: probable or definite fatal bleeding) [16].

Patients on OAC treatment for at least 12 weeks were enrolled in the study. Target INR value was defined as between 2.0 and 3.0. The occurrence of bleeding complications was investigated by questioning the patients and reviewing the database from the beginning of the OACT.

The quality of treatment was determined by 2 methods. The first was the occurrence of therapeutic INR value during the investigated period, ie, the percent incidence of INR between 2 and 3. The second was determining the time in therapeutic range (TTR) by Roosendaal method [17].

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All statistical analyses were performed by SPSS 16.0 for Windows (SPSS, Chicago, IL, USA). Categorical variables are reported as absolute numbers and percentages, all continuous variables with normal distribution are described as mean and standard deviation, and in case of continuous variables with abnormal distribution the median and interquartile ranges are presented. Categorical data were analyzed by Pearson chi-square or Fisher's exact test; continuous variables and categorical data were compared using non-parametric Mann-Whitney U test. Pearson's test was used to test the correlation of parametric variables, and Spearman's test was used to test the nonparametric variables. Logistic regression analysis was used to assess the predictors of appropriate TTR. Results are given as odds ratio (OR) and confidence interval (CI). All p values are 2-tailed and p value <0.05 was considered significant.

Results

Two hundred seventy-two patients receiving OACT due to nonvalvular atrial fibrillation took part in the survey – 134 men (49.3%) and 138 women (50.7%). Mean age was 71.5±8.6 (70.6±8.9 in men, 72.4±8.2 in women). The patients' characteristics, $CHADS_2$, CHA_2DS_2-VASC and HAS-BLED scores are presented in Table 1.

There were 252 patients (92.7%) who received acenocoumarol and 20 (7.3%) were on warfarin. Mean duration of OACT was 49 months; the extreme values were 3 and 128 months. Sixteen patients (5.9%) had been receiving OACT for 3–6 months, 26 (9.5%) for 6–12 months, 78 (28.7%) for 1–2 years, 98 (36.0%) for 2–5 years, and 54 patients (19.9%) for more than 5 years. The investigated period for determining TTR was 1008±384 days.

Table 2 shows TTR data and ratio of therapeutic INR value broken down by all patients, men, women, acenocoumarol, and warfarin therapy. No statistically significant difference can be found in the data of patients taking acenocoumarol and warfarin (p=0.06).

The relationship between various parameters and inappropriate anticoagulation level based on correlation analysis is presented in Table 1. Inadequate anticoagulation was defined as a TTR value below 70% [10–13]. The effects of patient sex and presence of malignancy, as well as treatment supervision by cardiology or other outpatient department of the hospital on achieving TTR value, were also investigated but no statistically significant difference was found with any parameter.

TTR values plotted against $CHADS_2$, CHA_2DS_2-VASC, and HAS-BLED scores are shown in Figure 1. No correlation was identified between CHA_2DS_2-VASC or HAS-BLED score and the precision of anticoagulant treatment. In our patient population, no patient had a HAS-BLED score of 6 or higher.

During the investigated period bleeding complications developed in 68 patients (25%). Out of these patients, 10 had been receiving OACT for more than 10 years, 27 for 5–10 years, 20 for 1–5 years, and 11 for less than 1 year. Figure 2 presents the occurrence of bleedings according to the BARC classification [16]. Type 1 bleeding was observed in 36, type 2 in 15, and type 3 in 16 patients. The most bleedings (14 cases) occurred within the 3 months after the initiation of oral anticoagulant therapy (Figure 3).

A statistically significant difference was found in TTR values of patients with or without bleeding event during the therapy (23 out of 120 correctly treated patients *vs.* 45 out of 152 incorrectly treated patients, OR: 1.615, CI: 1.029–2,533, p=0.032). After the adjustment for the factors included in HAS-BLED score, the significance disappeared (OR: 1.607, CI: 0.571–4.522, p=0.392) (Table 1). In case of appropriate anticoagulation (TTR >70%), bleeding complications tend to develop less frequently, but in multiple regression model the difference was not significant.

Discussion

The conventional oral anticoagulation treatment of patients with atrial fibrillation is carried out with Vitamin K antagonists (VKA). Due to the narrow therapeutic spectrum and the fear of bleeding complications, there are a significant number of patients in whom the necessary thromboembolic prophylaxis is not started at all, although it would be recommended based on the guidelines. This is especially true for older frail patients whose regular INR check is difficult to perform. On the other hand, it is well-known that in elderly patients the thromboembolic and bleeding risks are also higher. To determine the thromboembolic risk, $CHADS_2$ and the more precise CHA_2DS_2-VASC score are used (Table 1) [4,15]. However, we should always determine the patients' bleeding risk, for which the HAS-BLED score is mainly used (Table 1) [14]. Based on the regular use of these 2 (thromboembolic and bleeding) score systems, our task is to find those patients with atrial fibrillation for whom the otherwise justified anticoagulant prophylaxis against stroke and systemic embolism is not advised.

The other difficulty with VKA drugs is that the INR value is often not in the therapeutic range of 2–3. This is related to either the lack of patient cooperation [18] or eating habits, and in addition to drug interactions, genetic causes may have a role as well but their background is only partly understood [19,20].

Our study assessed the quality of VKA therapy performed using the same methods and principles in a county hospital. The patients' INR value was in the therapeutic range in 58% and TTR was 64%. Based on clinical experiences, we believe that appropriate treatment reduces the frequency of bleeding complications. In our study, bleedings were significantly more common in patients

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Table 1. Characteristics of 272 patients.

		Number of patients	Frequency (%)	TTR%	O.R	C.I.
All patients		272		64.0±16.1		
Sex	Female	138	50.7	65.2±16.6	Reference	
	Male	134	49.3	62.7±19.1	1.030	0.834–1.272
Age (years, mean ±SD)	71.4±8.5					
	Age 65	54	19.9	63.3±17.0	Reference	
	66-74	114	41.9	66.0±17.9	1.142	0.869–1.501
	74	104	38.2	61.9±17.9	1.246	0.638–2.436
Follow-up (days, mean ±SD)	1008±384					
	Cardiology	128	47.1	62.7±18.8	Reference	
	Non-cardiology	144	52.9	65.0±16.8	1.154	0.890–1.495
Anticoagulant	Acenocoumarol	252	92.3	63.8±18.1	Reference	
	Warfarin	20		67.4±14.9	1.060	1.000–1.151
Medical history	Diabetes	68	24.6	62.9±19.0	1.000	0.661–1.514
	Hypertension	219	81.4	64.7±17.9	0.889	0.793–0.997 p=0.049
	Stroke/TIA	106	38.1	62.7±19.7	1.030	0.763–1.391
	CHF	39	13.9	62.0±18.0	1.135	0.628–2.050
	Malignant disease	16	5.9	60.0±18.7	2.368	0.784–7.158
$CHADS_2$ Score	1	4	1.5	52.3±8.2	–	–
	2	157	57.7	63.9±19.2	Reference	
	3	61	22.4	65.6±18.6	0.812	0.530–1.243
	4	37	13.6	64.7±13.0	1.067	0.594–1.917
	5	13	4.8	59.3±10.4	8.816	1.173–66.273 p=0.08
CHA_2DS_2-VASc Score	1	0	–	–	–	–
	2	68	25.0	61.8±18.2	Reference	
	3	86	31.6	64.7±19.7	0.720	0.545–0.952 p=0.022
	4	45	16.5	66.0±18.9	0.657	0.420–1.028
	5	25	9.2	70.3±14.2	0.461	0.232–0.914
	6	38	14.0	61.5±14.6	1.068	0.615–1.854
	7	6	2.2	60.5±12.1	1.683	0.376–7.521
	8	4	1.5	54.4±3.7	1.923	0.227–16.325
	9	0				
	10	0				
HAS-BLED Score	1	57	21.0	62.7±18.3	Reference	
	2	108	39.7	64.9±20.0	0.727	0.581–0.909 p=0.05
	3	72	26.5	63.7±14.5	0.871	0.640–1.185
	4	29	10.7	67.3±16.9	0.581	0.324–1.043
	5	6	2.2	48.1±5.0	–	–

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Table 2. The occurrence of TTR and therapeutic INR values in all patients, in males and females and in acenocumarol or warfarin treated groups.

	Number of patients	Therapeutic INR value (% ±SD)	TTR (% ±SD)
All patients	272	57.2±16.3	64.0±16.1
Males	134	56.4±16.9	62.8±19.1
Females	138	58.2±18.4	65.3±16.6
Acenocumarol	252	56.9±17.8	63.8±18.1
Warfarin	20	62.1±15.0	67.4±14.9

Table 3. The relationship between inappropriate anticoagulation level (TTR under 70%) and type of bleedings according to BARC classification.

	unadjusted OR	CI	P value	Adjusted OR	CI	P value
Type 1	1.015	0.65–2.20	0.34	0.900	0.441–1.840	0.371
Type 2	2.171	0.709–6.648	0.163	1.154	0.946–1.407	0.221
Type3	5.921	1.381–25.391	0.005	4.286	0.543–33.852	0.117
All bleedings	1.615	1.029–2.533	0.032	1.607	0.571–4.522	0.392

with TTR values under 70%, but after the adjustment for factors influencing the bleeding, ie, the factors included in HAS-BLED score, the difference was not significant (Table 3). This suggests that the occurrence of bleeding is better determined by its risk factors, not by the quality of anticoagulation. Another explanation may be that patients with uncontrolled VKA treatment may more often be below the intended INR therapeutic range than above. No correlation between TTR and bleedings was found in other studies [13,21]. Naruse et al. found no difference between the TTR values of patients with or without major bleeding complications receiving triple antithrombotic therapy [22].

The fact that in our study bleedings were more common in the first 3 months after the initiation of OAC therapy shows that in the first period more attention has to be put to the control examinations. Garcia et al. reported the highest risk of bleeding was when OAC treatment was initiated [23].

Our TTR values are comparable to those of the warfarin branch of large international randomized controlled studies (ACTIVE, RE-LY – Randomized Evaluation of Long-Term Anticoagulation Therapy, ROCKET AF – Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, ARISTOTLE – Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) in which the protocols were designed with enhanced attention to the appropriate OAC treatment (Figure 4) [24–27]. Our 64% TTR value is similar to that reported by Gallagher et al. in more than 27 000 warfarin-treated patients [10] and is more favorable than the 52.6% TTR in a multicenter study from Kuwait [28]. TTR values above 70% [10–13] offer sufficient protection against thromboembolic events, but it cannot be forgotten that the patients' INR values were outside of the therapeutic target range for about one-third of treatment period [29].

A major problem of the TTR method is that it makes no difference whether the non-suitable INR is in the low or in the high range. Lind et al. studied more than 19 000 patients and compared the prognostic power of INR and TTR values on bleeding, stroke, hospitalization, and mortality, and the INR proved to be a better predictor [30]. Based on observational data of another 27 000 patients with atrial fibrillation, TTR was not a better indicator of the complications either [31]. The emergence of novel types of anticoagulants may resolve the dilemma of using INR or TTR in our practice.

Our data were obtained in our everyday clinical practice, and the TTR values are similar to that from the warfarin branch of large randomized multicenter trials and to that from a large database published by Gallagher (Figure 4) [10,24–27]. Taking all of these factors into consideration, we believe that routinely and carefully conducted OAC treatment may have its limit at this level, whereas in more than one-third of cases and time, either using INR or TTR values for assessing the quality of anticoagulation, the results are poor and the reason for this lies in the method. In addition to patients receiving inadequate antithrombotic therapy, we should also take into consideration

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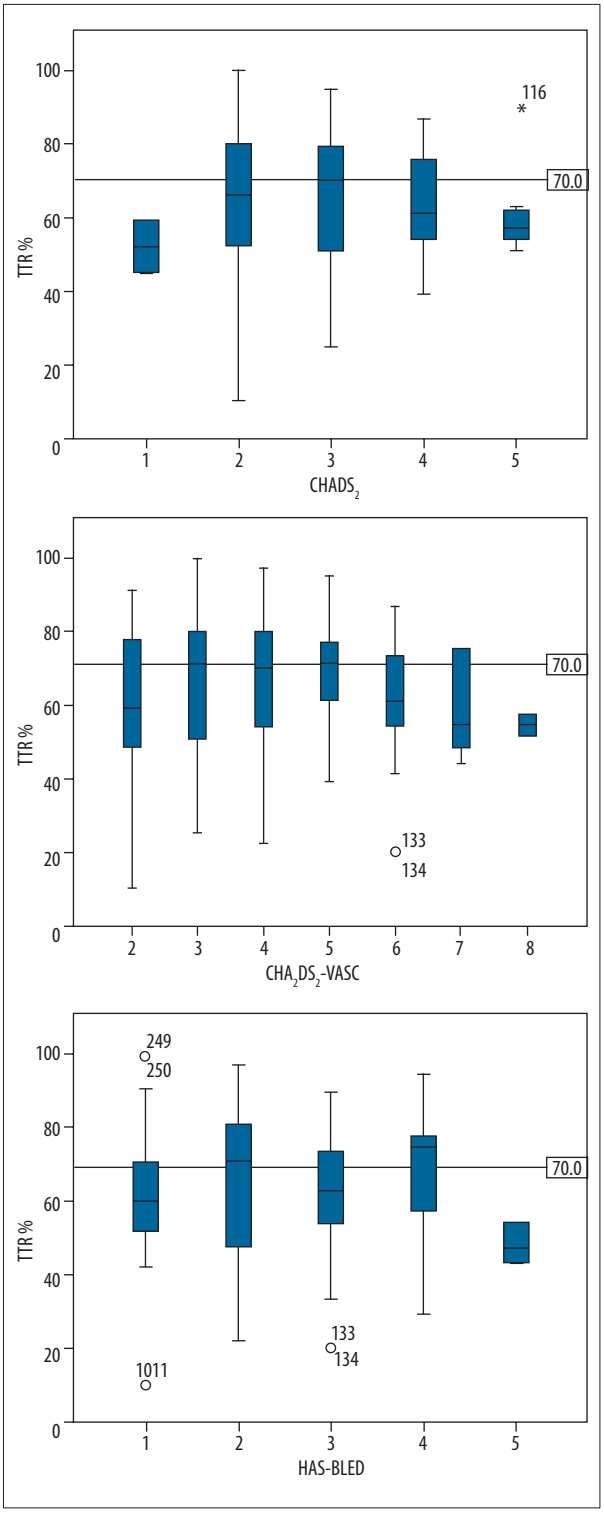

Figure 1. The relationship of TTR values with $CHADS_2$, CHA_2DS_2-VASC, and HAS-BLED score points.

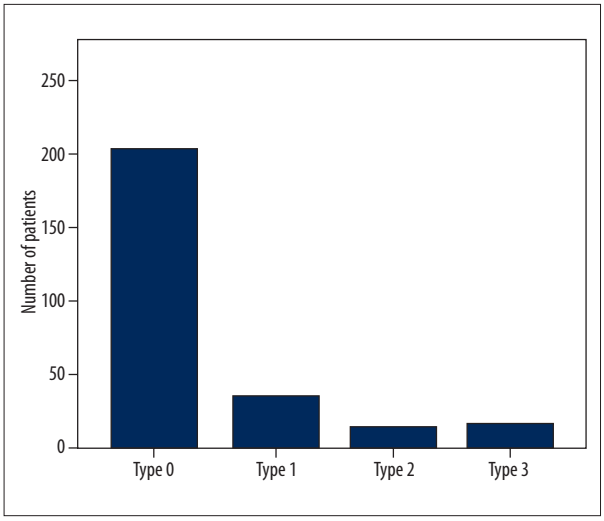

Figure 2. The occurrence of bleeding events according to the BARC classification.

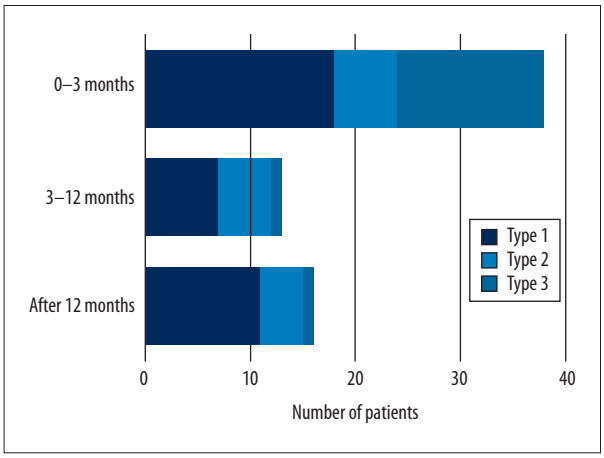

Figure 3. The occurrence of bleeding complications depending on the time elapsed after initiation of oral anticoagulant therapy.

those in whom the required treatment is not started at all. Out of patients needing and being eligible for this therapy, only half of them receive it [8]. In spite of these, we believe that the administration of novel oral anticoagulants has and will have an important role in better management of anticoagulation in patients with atrial fibrillation. According to data from large clinical trials, the novel oral anticoagulant drugs have similar preventive effect on thromboembolic events like VKA drugs (non-inferiority) and are also less likely lead to bleeding complications. Comfort and economic considerations may also gain importance as no INR checks are required. However, patients treated with novel anticoagulants need regular controls as well (e.g., periodic monitoring of kidney function, maintaining good therapeutic collaboration, identifying tasks around surgeries/procedures).

Our study had several limitations. Firstly, it has retrospective. Although the data were collected directly from the patients and hospital's database, the loss of some data could occur and we did not investigate the data of dead patients having AF. Secondly,

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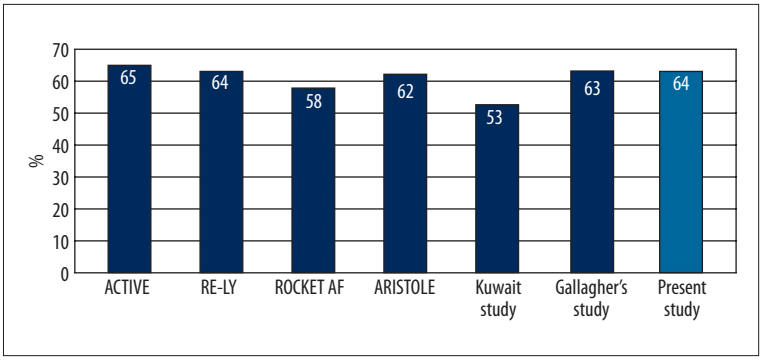

Figure 4. The comparison of TTR values (%) in the warfarin branch of large international randomized controlled studies, with 2 real-life studies and the present analysis.

the number of patients is low, but this is compensated for by the fact that all the patients were treated in 1 hospital with similar approach and in this way the sample is appropriate for the quality analysis. Because of the low number of patients, we did not investigate the incidence of stroke. Thirdly, we did not study dietary characteristics affecting the metabolism of vitamin K antagonists, the concomitant diseases, or medications.

Conclusions

Our analysis based on the comparison of TTR values showed that the quality of conventional OAC therapy in our hospital is comparable to that reported from other papers [10,24–27]. Analyzing the various factors, no single factor was found to significantly influence TTR values over 70%. Further improvement in vitamin K antagonist therapy is necessary, but, since the possibilities for that are limited, we believe that there is no real chance of such improvement. Therefore, novel anticoagulant agents are needed in everyday clinical practice. Similar to other reports [23], bleeding events were more common in the first 3 months after initiation of anticoagulant therapy. This suggests that appropriate controls after the beginning of treatment deserve more attention.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding this work and they have no financial and personal relationships with other people or organizations that could inappropriately influence their work.

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