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Therapeutic quality control in a regional thrombosis center: The effect of changing the target intensity of anticoagulation with vitamin K antagonists

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ABSTRACT

Background: The target ranges (TR) for anticoagulation with vitamin K antagonists (VKA) in the Netherlands were changed in 2016 from INR 2.0–3.5 ('low intensity') and INR 2.5–4.0 ('high intensity') to INR 2.0–3.0 and INR 2.5–3.5, respectively.
Aim: To assess the effect of the TR change on therapeutic quality control (TQC) in a Dutch regional thrombosis center taking care of approximately 3600–5500 patients annually.
Methods: TQC of chronically treated patients was assessed as the average time in therapeutic range (TTR). Evaluations were performed for non-self-management (NSM), as well as self-management patients. INR percentiles were assessed from all INR determinations in all patients, i.e. including those of induction episodes and patients treated for a short-term.
Results: The number of NSM patients treated chronically decreased gradually, while their average age increased, with a marginal but significant gradual increase in bleeding complications. In the period 2011–2015, i.e. before the TR change, there was a gradual increase of the TTR in NSM patients from 77.5% to 88.9% (low intensity) and from 75.3% to 84.1% (high intensity). In the same period, the median INR of all patients in the low and high intensity ranges decreased from 2.9 to 2.7, and from 3.3 to 3.2, respectively. The TTR in self-management patients remained virtually constant. After TR changes from 2016 on, the TTR of all NSM patients in the low and high intensity groups decreased to 77% and 70%, respectively, and median INRs decreased to 2.6 and 3.0, respectively.
Conclusions: Introduction of internationally harmonized target ranges in 2016 resulted in further lowering of median INR values in both target ranges. As expected, TTR was reduced slightly. These findings, together with a slight increase in average age and concomitant bleeding complications, suggest that the patients on long-term VKA treatment will require intensified monitoring and treatment.

1. Introduction

In the Netherlands, ambulant patients receiving treatment with vitamin K antagonists (VKA) are managed and controlled by regional thrombosis centers or anticoagulant clinics [1]. Until 2016, two different therapeutic target ranges (TR) have been applied in the Netherlands, i.e. INR 2.0–3.5 (low intensity) and INR 2.5–4.0 (high intensity) [2]. Beginning 2016, the two TR were changed for all patients in the Netherlands: the low intensity range was changed to INR 2.0–3.0, and the high intensity range to INR 2.5–3.5. The main reason for the nationwide change was to achieve TR harmonization in agreement with international guidelines. The low intensity range of INR 2.0–3.0 has been described as "moderate intensity" in ACCP guidelines [3]. The purpose of the present study was to assess the effect of the change on therapeutic quality control in a Dutch regional thrombosis center, i.e. the Thrombosis Center "Neder-Veluwe" (abbreviated in this paper as TCNV), Ede, the Netherlands. Two methods were used to assess therapeutic quality control: a) time in therapeutic range by linear interpolation (TTR); b) percentiles describing the distribution of all measured INRs.

Obviously, the TTR depends on the width of the therapeutic range. By narrowing the therapeutic range, the TTR is expected to be reduced.

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The purpose of our retrospective study was to assess the magnitude of the TTR reduction due to the change of the TR. TTR depends on the selection of patients, e.g. long-term patients have higher TTR than during induction and short-term treated patients. Consensus regarding the minimum acceptable level of TTR of all patients under treatment has been achieved by the Netherlands Federation of Thrombosis Services [4]. In the present retrospective, observational study, the results obtained by TCNV are compared to those of other centers and to Dutch consensus values.

2. Methods

2.1. Setting and logistics

The following neighbouring towns and villages formed the working area of the TCNV: Amerongen, Bennekom, Ede, Ederveen, Elst (Utrecht), Harskamp, Heelsum, De Klomp, Leersum, Lunteren, Otterloo, Renkum, Rhenen, Veenendaal, Wageningen, and Wekerom. The total number of inhabitants in the working area was approximately 260,000 (in year 2020). The staff of the TCNV performed standardized visits at approximately 30 service points where patients were seen by appointment and venous blood samples were drawn. In addition, the staff of the TCNV also performed home visits for frail and disabled patients. Blood samples were transported by car to a central laboratory for INR determination within 6 h after venipuncture. The central laboratory used the reagents Dade Innovin and Thromborel-S (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). The central laboratory participated in an external quality assessment program [6]. Part of the patients performed self-testing or self-management using finger prick blood with a portable device for PT/INR determination at home. The following portable devices were used: Alere INRatio (Alere San Diego, Inc., San Diego, California) until the end of 2016, and CoaguChek XS (Roche Diagnostics, Mannheim, Germany) until today. Before patients were admitted to self-testing or self-management, they received a training course provided by the TCNV. For quality control, each self-testing patient was requested to come to the center every 6 months and to perform the self-test using the patient's own portable device in front of TCNV staff. Immediately after the self-test, the patient was pricked by the staff and the blood sample was tested using the center's device (same type as the patient's). The results obtained by the patient's self-test were compared to the results of the test performed by the staff. The performance of the center's device was evaluated regularly in an external quality assessment program [7,8].

2.2. Patient management

Patients are seen by the center's nurses, on average every three weeks. The nurses collect venous blood samples according to a standardized technique for laboratory INR determination and interview the patients in a standardized fashion regarding any untoward bleeding or thrombotic event. Self-measuring and self-management patients who report INR to the center using a digital interface, must provide the same information in this process. All patients are instructed to report actively any bleeding or thromboembolism. Hospitals are instructed to provide information to the thrombosis center in the event of hospital admission. Reports on potential adverse events by patients, physicians and hospitals are actively followed up and validated by two physicians employed by the TCNV. Major bleedings were defined as intracranial bleeding, intraarticular bleeding, fatal bleeding, bleeding leading to blood transfusion, hospital admission for treatment of bleeding, or surgical intervention for treatment of bleeding. Thromboembolic complications were defined as ischemic cerebrovascular accident, systemic embolism, pulmonary embolism, and deep venous thrombosis. Transient ischemic attack was not considered as thromboembolism in the present study. For the management of anticoagulant therapy, all potentially relevant information was recorded digitally in a web-based electronic patient file (Portavita B.V., Amsterdam, the Netherlands). Determination of dosage was done with the aid of computer-assisted dosing algorithms and, if necessary, subsequent professional optimization.

2.3. Statistical methods

Time in therapeutic range (TTR) was calculated by linear interpolation [5]. Until 2018 TTR was calculated for long-term patients only. From then on TTR was calculated for all patients including starting and short-term patients. The distribution of INRs was assessed visually using a histogram. Normality of the INR distribution was assessed with the Kolmogorov-Smirnov test. In addition, skewness and kurtosis of the INR distribution were determined. INR Percentiles were calculated for all INR assessments, for each calendar year. Percentiles were calculated for all INRs in each TR group annually.

Correlation between adverse event rate and calendar year of reporting was tested with Spearman's nonparametric test. $P < 0.05$ was defined as indicating statistical significance. All statistics were performed using SPSS Statistics version 25.0 (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Indications for treatment

Table 1 shows the main indications for treatment of patients controlled by TCNV, i.e. venous thromboembolism, atrial fibrillation, and mechanical heart valve prostheses. Other indications were coronary syndromes, heart failure, cardiomyopathy, cerebral vascular disease, and vascular surgery. In the past decade there was a slight increase in the percentage of patients with atrial fibrillation. The majority of patients were treated with either acenocoumarol or phenprocoumon. The percentage of patients treated with phenprocoumon increased from 17.5 to 24. The number of patients controlled by TCNV increased to 5506 on December 31, 2014 and then decreased to 3643 on December 31 of 2019.

3.2. Time in therapeutic range

Table 2 shows the TTR for long-term non-self-management (NSM) patients, i.e. patients who are managed by professionals of TCNV, and for self-management patients. The TTR for the regular low-intensity patients increased from 77.5% in 2011 to 88.9% in 2015. Similarly, the TTR for the regular high-intensity patients increased from 75.3% in 2011 to 84.1% in 2015. The TTR for self-management patients showed more stability and was generally greater than the TTR of the regular (NSM) patients. The TTR for high-intensity patients was always lower than the TTR for low-intensity patients in the same period. After the therapeutic target intensity was changed in 2016, there was a drop in the TTR of both regular and self-management patients. The Federation of Netherlands Thrombosis Services defined minimum acceptable TTR values to be achieved by individual member centers in 2019, i.e. 67.2% and 57.3% for all low-intensity and all high-intensity patients, respectively [4]. As can be seen in Table 2, the minimum acceptable TTR values defined by the Federation were achieved by TCNV.

3.3. INR percentiles

Table 3 shows the percentiles of all INR determinations in each calendar year. There was a gradual decrease of the median INR (i.e. percentile 50) over the years 2011–2015. When the target ranges were changed in 2016, an additional drop in the INR percentiles was observed. Over the years 2011–2019, there was a narrowing of the INR distribution (Fig. 1). Visual inspection of the INR histograms showed that INRs were not normally distributed. In addition, using the Kolmogorov-Smirnov test the hypothesis of a normal distribution was rejected ($P < 0.001$).

Table 1
Indications for treatment with vitamin K antagonists in patients controlled by Thrombosis Center "Neder-Veluwe".

Year	Total number of patients[a]	Number of self-management patients[a]	Indication				Vitamin K antagonist	
			Venous thromboembolism (%)	Atrial fibrillation (%)	Mechanical heart valve prosthesis (%)	Other (%)	Acenocoumarol (%)	Phenprocoumon (%)
2011	4902	409	19.7	60.3	6.0	14.0	82.5	17.5
2012	4933	507	18.4	63.1	5.6	12.9	81.4	18.6
2013	5028	557	18.4	64.3	5.5	11.8	80.9	19.1
2014	5506	595	18.6	64.4	5.5	11.5	80.0	20.0
2015	5318	576	18.8	64.6	5.5	11.1	80.0	20.0
2016	5037	582	16.3	65.9	6.8	11.0	79.0	21.0
2017	4673	615	16.7	65.5	6.2	11.6	77.0	23.0
2018	4103	575	16.6	62.9	5.8	14.7	76.0	24.0
2019	3643	548	16.7	62.5	6.3	14.5	76.0	24.0

[a] On December 31 of each calendar year.

Table 2
Time in therapeutic range for patients controlled by the Thrombosis Center "Neder-Veluwe".

Year	Patient category	Time in therapeutic range by linear interpolation method (%)			
		Non-self-management patients (NSM)		Self-management patients	
		TR: 2.0–3.5 INR	TR: 2.5–4.0 INR	TR: 2.0–3.5 INR	TR: 2.5–4.0 INR
2011	Long-term	77.5	75.3	83.5	80.6
2012	Long-term	81.2	77.3	86.2	82.9
2013	Long-term	82.6	76.6	85.9	82.6
2014	Long-term	86.0	79.7	82.5	81.7
2015	Long-term	88.9	84.1	85.4	80.6
		TR: 2.0–3.0 INR	TR: 2.5–3.5 INR	TR: 2.0–3.0 INR	TR: 2.5–3.5 INR
2016	Long-term	76.5	69.6	77.9	71.6
2017	Long-term	74.4	66.7	81.2	73.3
2018	All	72.7	64.2	79.2	71.4
2019	All	73.5	66.2	81.7	75.0

3.4. Adverse events

Table 4 shows the incidence of major bleeding, intracranial bleeding, fatal bleeding, and thromboembolism. The incidence of major bleeding and intracranial bleeding increased slightly and gradually from 2011 to 2019 ($P < 0.05$ Spearman's test). There was no obvious trend in the incidence of fatal bleeding. Thromboembolism was reported only from 2014 onwards. There was no obvious trend in the incidence of thromboembolism. The mean age of the patients increased from 72.35 years in 2011 to 75.23 years in 2019. For comparison we show the range and median incidence of adverse events reported by members of the Federation of Netherlands Thrombosis Centers (FNT). In 2011 there were 61 Dutch thrombosis centers, of which 51 were reporting adverse events. In 2019 there were 45 Dutch thrombosis centers, all reporting adverse events [4].

4. Discussion

Therapeutic control of anticoagulant therapy is meaningful only if the prothrombin time test procedure for laboratory control has been standardized and the results are expressed as INR. External quality assessment (EQA) of the prothrombin time and INR is an important component of quality assurance of anticoagulant therapy. In the Netherlands, a national PT-INR EQA scheme has been carried out by the Federation of Netherlands Thrombosis Services [6–8]. TCNV has participated in the national PT-INR EQA scheme throughout and TNCV results satisfied EQA requirements (data on file).

The purpose of our study was to evaluate the effect of the changes in therapeutic ranges effective from January 1, 2016. In the low-intensity NSM group TTR diminished from 88.9% to 76.5% (Table 2), as could be expected from a narrower therapeutic range. Similar effects were observed in the high-intensity NSM group and in the self-management patient groups. Before the change of the therapeutic range, there had been a gradual decrease of the median INR in both intensity groups, accompanied by a gradual increase of the TTR (see Tables 2 and 3), suggesting quality improvement in medical dosage schemes. It is interesting to compare our results with those of other studies. For example, in a meta-analysis to assess the quality of INR control in VTE patients, it was reported that these patients spent a weighted average 61% of the time in the target range of 2.0 to 3.0 [9]. The meta-analysis identified a number of factors that influenced TTR, suggesting TTR to be higher in patients having their VKA dosed in an anticoagulation clinic compared to patients in a community setting [9]. In a Swiss study of self-management patients in everyday practice the median time within the intended therapeutic range was 80%, which is similar to the TTR of self-management patients in the present study [10].

Over the years 2011–2019, there was a slight increase in the incidence of major bleeding, intracranial bleeding and fatal bleeding (Table 4). This trend may seem paradoxical because the median INR

Table 3
INR percentiles in low and high target intensity groups.

Year	Low target intensity				High target intensity			
	Number of INRs	INR			Number of INRs	INR		
		25th percentile	50th percentile	75th percentile		25th percentile	50th percentile	75th percentile
2011	74,424	2.4	2.9	3.6	16,488	2.7	3.3	4.0
2012	77,598	2.3	2.8	3.4	15,964	2.6	3.2	3.9
2013	81,619	2.2	2.7	3.4	15,840	2.6	3.1	3.8
2014	83,720	2.3	2.7	3.3	14,795	2.6	3.1	3.7
2015	84,916	2.3	2.7	3.2	14,109	2.7	3.2	3.8
2016	90,214	2.2	2.6	3.1	15,170	2.5	3.0	3.5
2017	85,602	2.1	2.6	3.1	16,176	2.5	3.0	3.6
2018	75,718	2.1	2.6	3.1	14,263	2.5	3.0	3.6
2019	61,116	2.2	2.6	3.1	12,449	2.5	3.0	3.6

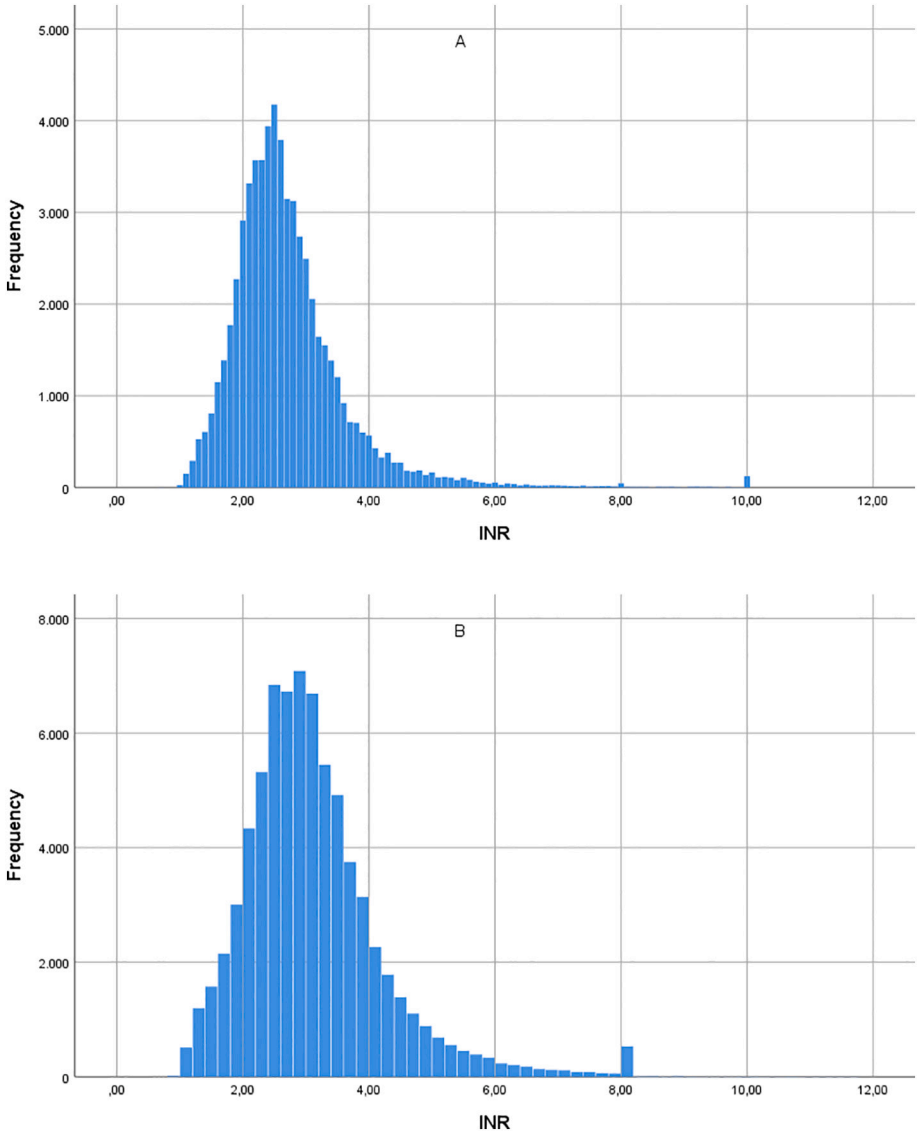

Fig. 1. Histograms of all INRs assessed in all patients in the low-intensity VKA treatment group. Panel A: Time period January 1, 2019–December 31, 2019; Number of observations: 61116; median INR: 2.6; interquartile range: 0.9; skewness: 2.52 (standard error: 0.010); kurtosis: 12.400 (standard error: 0.020). Panel B: Time period January 1, 2011–December 31, 2011; Number of observations: 74424; median INR: 2.9; interquartile range: 1.2; skewness: 1.575 (standard error: 0.009); kurtosis: 5.014 (standard error: 0.018).

Table 4
Incidence of adverse events reported by Thrombosis Center Neder-Veluwe (TCNV) and other Dutch centers.

Year	Mean age of TCNV patients (years)	Incidence (% per patient-year)							
		All major bleeding		Intracranial bleeding		Fatal bleeding		Thromboembolism	
		TCNV	FNT[a]	TCNV	FNT[a]	TCNV	FNT[a]	TCNV	FNT[a]
2011	72.35	1.30	1.1 (0.2–3.1)	0.30	0.3 (0–0.8)	0.13	0.2 (0–0.5)	–	–
2012	72.76	1.70	1.1 (0–3.0)	0.31	0.2 (0–1.0)	0.20	0.1 (0–0.6)	–	–
2013	73.08	1.30	1.2 (0.3–5.7)	0.30	0.2 (0–0.8)	0.28	0.1 (0–0.6)	–	–
2014	73.48	1.84	1.2 (0.1–2.6)	0.33	0.3 (0–0.7)	0.17	0.2 (0–0.4)	0.75	–
2015	73.87	2.67	1.3 (0.1–3.3)	0.73	0.3 (0–0.8)	0.49	0.1 (0–0.8)	0.58	0.3 (0–1.7)
2016	74.33	1.70	1.4 (0.1–5.6)	0.46	0.2 (0–0.9)	0.14	0.1 (0–0.5)	0.75	0.5 (0–1.6)
2017	74.88	2.34	1.3 (0.2–3.8)	0.62	0.3 (0–1.2)	0.29	0.2 (0–2.0)	0.68	0.6 (0–1.5)
2018	75.33	2.41	1.2 (0.4–3.3)	0.59	0.3 (0–0.6)	0.38	0.2 (0–0.5)	0.70	0.5 (0.1–1.3)
2019	75.23	3.02	1.4 (0.5–3.9)	0.75	0.3 (0–1.0)	0.41	0.2 (0–0.6)	0.85	0.5 (0–1.3)

[a] Median (range) of incidences reported by members of the Federation of Netherlands Thrombosis Centers (FNT).

decreased in the same period. It cannot be excluded that the low numbers in 2011 were due to under-reporting. Awareness of the importance of reporting adverse events has increased in subsequent years. Due to more strict quality assessment from the year 2014 onward, the practice of detecting and recording events has been improved to the current rigorous level. A plausible contributing factor to the increase of major bleeding is a gradual change of the TCNV patient population. In recent years an increasing number of patients without complex conditions were treated with direct oral anticoagulant drugs (DOACs) rather than with VKA, leading to a negative selection of more complex and older patients remaining on VKA treatment, and, as a plausible consequence, increased bleeding risk.

The incidences of adverse events reported by TCNV are similar to values reported by 45 other Dutch Thrombosis Centers in 2019: major bleeding ranged from 0.5–3.9 (median: 1.4) % per patient year, and the incidence of thromboembolism ranged from 0 to 1.3 (median: 0.5) % per patient year [4]. The incidence of bleeding and thrombotic complications in our study is also similar to those in a recent study of Italian patients who had 1.38% major bleeding per patient-year and 0.53% thrombotic events per patient-year [11]. Differences in reported incidences between centers may result from differences in patient characteristics, discrepancies in classification of adverse events or underreporting [12]. Warfarin is the preferred VKA in Italy, whereas in the Netherlands the use of acenocoumarol or phenprocoumon is standard. At TCNV there was a slight increase in the use of phenprocoumon from 2011 to 2019 (Table 1). Use of acenocoumarol resulted in fewer bleeds than use of phenprocoumon [13]. A Danish study of self-management patients compared safety of warfarin with phenprocoumon [14]. The investigators found that the risk of bleeding was higher in patients treated with phenprocoumon than with warfarin, despite the TTR of the patients on phenprocoumon being higher than the TTR of patients on warfarin [14]. An important risk factor is age. The incidence of both bleeding and thromboembolic events increases sharply with advanced age [15]. Advanced age may account for the increase of bleeding events observed in the TCNV patients. Implementation of lower target intensities for VKA therapy was reported to decrease the complication risk [16]. We did not observe this in our study. The advancing age and increased complexity of patients in the TCNV population may have neutralized this effect.

5. Conclusions

Adoption of internationally harmonized target ranges for anticoagulation with vitamin K antagonists by TCNV in 2016 resulted in a small but acceptable (according to Dutch requirements) loss of average time in therapeutic range in both low and high intensity long-term treated patients. Median INR values decreased further after a gradual decrease in the years preceding 2016. The average age of patients on long-term treatment increased gradually over time concomitant with a slight but significant increase in bleeding complications, but we cannot provide evidence for a causal relationship between these observations. With more patients being treated with direct oral anticoagulants (DOAC), the patients remaining on vitamin K antagonists may constitute a vulnerable group with complex pathology demanding intensified monitoring and guidance by a thrombosis center.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] W.G. Breukink-Engbers, Monitoring therapy with anticoagulants in the Netherlands, Semin. Thromb. Hemost. 25 (1999) 37–42.
[2] J.H.H. Van Geest-Daalderop, A. Sturk, M. Levi, H.J. Adriaansen, Extent and quality of anti-coagulation treatment with coumarin derivatives by the Dutch thrombosis services, Ned. Tijdschr. Geneeskd. 148 (2004) 730–735.
[3] W. Ageno, A.S. Gallus, A. Wittkowsky, M. Crowther, E.M. Hylek, 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 (Suppl) (2012) 44S–e88S.
[4] Netherlands Federation of Thrombosis Services. Summary medical annual reports 2019. Available at https://www.fnt.nl/algemeen/jaarverslagen.
[5] F.R. Rosendaal, S.C. Cannegieter, F.J.M. van der Meer, E. Briët, A method to determine the optimal intensity of oral anticoagulation therapy, Thromb. Haemost. 39 (1993) 236–239.
[6] A.M.H.P. Van den Besselaar, A.C.E. Moor, Photodynamic treatment of pooled coumarin plasma for external quality assessment of the prothrombin time, J. Clin. Pathol. 53 (2000) 470–475.
[7] A. Stavelin, P. Meijer, D. Kitchen, S. Sandberg, External quality assessment of point-of-care international normalized ratio (INR) testing in Europe, Clin. Chem. Lab. Med. 50 (2011) 81–88.
[8] A.M.H.P. Van den Besselaar, C.F. Abdoel, D. Ardanary, G. van de Kamp, F.A. C. Versluijs, Preparation of control blood for external quality assessment of point-of-care international normalized ratio testing in the Netherlands, Am. J. Clin. Pathol. 141 (2014) 878–883.
[9] E.S. Mearns, C.G. Kohn, J.S. Song, J. Hawthorne, J. Meng, C.M. White, et al., Meta-analysis to assess the quality of international normalized ratio control and associated outcomes in venous thromboembolism patients, Thromb. Res. 134 (2014) 310–319.
[10] M. Nagler, L.M. Bachmann, P. Schmid, P.R. Müller, W.A. Wuillemin, Patient self-management of oral anticoagulation with vitamin K antagonists in everyday practice: efficacy and safety in a nationwide long-term prospective cohort study, PLoS One 9 (2014), e95761. 24748062.
[11] G. Palareti, E. Antonucci, L. Migliaccio, N. Erba, F. Marongiu, V. Pengo, et al., Vitamin K antagonist therapy: changes in the treated populations and in management results in Italian anticoagulation clinics compared to those recorded 20 years ago, Intern. Emerg. Med. 12 (2017) 1109–1119.
[12] S. Schulman, C. Kearon, on behalf of the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Commitee of the International Society on Thrombosis and Hemostasis, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients, J. Thromb. Haemost. 3 (2005) 692–694.
[13] F.J.M. Van der Meer, F.R. Rosendaal, J.P. Vandenbroucke, E. Briët, Bleeding complications in oral anticoagulant therapy. An analysis of risk factors, Arch. Intern. Med. 153 (1993) 1557–1562.
[14] C.F. Jensen, T.D. Christensen, M. Maegaard, J.M. Hasenkam, Quality of oral anticoagulant therapy in patients who perform self management: warfarin versus phenprocoumon, J. Thromb. Thrombolysis 28 (2009) 276–281.
[15] M. Torn, W.L.E.M. Bollen, F.J.M. van der Meer, E.E. van der Wall, F.R. Rosendaal, Risks of oral anticoagulant therapy with increasing age, Arch. Intern. Med. 165 (2005) 1527–1532.
[16] M. Torn, F.J.M. van der Meer, F.R. Rosendaal, Lowering the intensity of oral anticoagulant therapy. Effects on the risk of hemorrhage and thromboembolism, Arch. Intern. Med. 164 (2004) 668–673.