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ORIGINAL RESEARCH

The Clinical Impact of Different Coagulometers on Patient Outcomes

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ABSTRACT

Introduction: Long-term anticoagulation therapy using vitamin K antagonists (VKA) is used in millions of patients worldwide to reduce the risk of thrombotic or thromboembolic events. Control and monitoring of VKA therapy is improved by the regular self-measurement of international normalized ratio (INR) using a home monitoring device. This retrospective analysis of a large cohort of patients in the Netherlands seeks to determine whether the choice of INR monitor could have a clinical impact on patient outcomes.

Methods: The National Thrombosis Service provides medical supervision, training and support to anticoagulant patients eligible for home-monitoring of INR in the Netherlands. Two INR monitors (CoaguChek XS and INRatio2) have been distributed at random to patients since June 2011, and patient self-testing data (INR measurements and other clinical parameters) have been recorded to measure and improve treatment outcomes. The data have been retrospectively analyzed to determine any effect of the choice of monitor. Univariate and multivariate statistical tests are used to assess any differences between groups in terms of efficacy and safety parameters.

Results: Data from 4,326 patients were collated, and 156,507 INR values were included in the analysis. Over half the patients (54.3%) were being treated for atrial fibrillation, and 77.6% were prescribed acenocoumarol. There were few differences between the patient populations using the two different monitors. Anticoagulant control overall was good, with high percentage of time (87.9%) in the appropriate INR range and low incidence of excessively high or low INR values (0.085/month). Minor clinical events related to safety

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were low (0.78 per patient-year) and showed few differences between monitors. Mortality rates were similar [hazard ratio (HR) 1.05, 95% confidence interval (CI) 0.65–1.70].

Conclusion: Self-testing data from a large cohort of patients in the Netherlands suggest that there is no clinically relevant effect of the choice of coagulation monitor (CoaguChek XS or INRatio2) on the time in therapeutic range (TTR), minor or fatal outcomes of long-term anticoagulation management.

Keywords: Anticoagulation; CoaguChek XS; INRatio2; International normalized ratio (INR); Patient self-monitoring (PSM); Patient self-testing (PST); Point of care (POC) test (POCT); Time in therapeutic range (TTR); Time in target range; Vitamin K antagonist (VKA)

INTRODUCTION

Anticoagulation is a widespread therapeutic intervention as secondary prevention after various venous or arterial thrombotic or thromboembolic events, or as primary prophylaxis, especially of stroke or systemic embolism in patients with atrial fibrillation. More than 6 million people in Europe have atrial fibrillation [1], with prevalence estimated from 1–2% [1] to 2.9% or more in adults [2], and increasing with age. Long-term risk reduction of thrombotic or thromboembolic events can be achieved using vitamin K antagonists (VKA) and in Europe the most commonly used are acenocoumarol, phenprocoumon and warfarin. Treatment with these types of anticoagulants is very effective in reducing the risk of an ischemic stroke while maintaining a low risk of bleeding [3].

The effectiveness of anticoagulant therapy with VKA is however crucially dependent on maintenance of the coagulation status within a specific range. The international normalized ratio (INR) is the established and generally accepted method to guide treatment of patients on long-term anticoagulation treatment with VKA [1]. Time within INR therapeutic range >70% is associated with significantly improved outcomes [4]. Patients whose INR strays too far from the optimal level of anticoagulation are at increased risk of experiencing a hemorrhagic or thromboembolic event [5], with significantly higher incidence of thromboembolism [relative risk 4.5 for INR <2.0, 95% confidence interval (CI) 3.1–6.6, $P < 0.001$] or major bleeding (relative risk 6.4 for INR >5.0, 2.5–16.1, $P < 0.001$) compared with INR 2.0–3.0 [6].

Maintenance of INR within the therapeutic range with VKA is challenging for many patients. More frequent measurement of INR, which improves control of anticoagulant therapy, can be better achieved by the patient using a home-based INR monitoring device compared to outpatient visits to a laboratory or clinic [7, 8]. Two options of self-care are available to the patient: patient self-testing (PST), where the INR test is executed by the patient and the INR value is communicated with the patient's clinic, which responds with a new dosage schedule; and patient self-management (PSM), where the patients are trained to monitor and interpret the INR themselves, and adjust the anticoagulant dose accordingly. Systematic reviews have shown PST and PSM to be superior to standard monitoring, with fewer thromboembolic events, decreased overall mortality and reduced bleeding events [7, 9–12]. PST/PSM is therefore recommended in anticoagulant guidelines for suitable patients [13, 14].

Effective PST or PSM requires not only able and motivated patients, a user-friendly,

intelligent Electronic Patient Record and a suitable algorithm for management of dose adjustment, but also depends on reliable and accurate point of care testing devices. While the benefits of PST/PSM have been established, there has been no large scale comparison of the effect of different INR monitors on clinical outcomes. The current analysis seeks to address this question by retrospectively examining the large database of the National Thrombosis Service (NTS), TK Ede, the Netherlands, which records relevant parameters for patients' measurements and clinical outcomes, allowing for identification of trends and correlations.

Time in therapeutic range (TTR) is widely accepted as a valid surrogate parameter for the clinical effectiveness and safety of VKA anticoagulant treatment [4, 15–18]. The level of INR variation and the number of critical INR values (INR <1.5 or >5.0) have also been discussed as surrogate parameters specifically addressing the risk of adverse events [8, 19, 20]. The current analysis aims to observe the clinical impact of the different INR measurement devices on the coagulation control parameters as well as on the overall clinical outcomes.

METHODS

Description of the NTS

The NTS was established in 2006 and has developed an extensive patient support service, comprised of e-learning, user-friendly, intelligent software, one-on-one instruction and education, 24/7 medical service desk, 6-weekly newsletters and various reminder services to optimally motivate, support and develop 'good patientship'.

Potential users of NTS self-care establish contact with the NTS through the internet, and NTS staff follow up within 24 h through telephone contact. The goal is to make sure that the patients have purposefully made contact with the NTS and then to establish their eligibility for INR self-testing at home. Patient eligibility is based on the patient's level of understanding, motivation to self-care, ability and willingness to perform the blood test itself and available technology (computer/mobile device with internet access), with no influence of age or disease severity. Eligible patients are then provided with access to and support for a number of e-learning modules about thrombosis, anticoagulation, INR measurement, the advantages and the responsibilities of self-care, the practical and technical implications of self-care and (voluntary) self-dosing. Those who pass a mandatory certification go on to execute a practice test, at home or at work, in the presence of a qualified NTS nurse, using the monitor to measure their INR and practising the use of the Electronic Patient Record. Patients who pass the practice test are accepted for self-testing by the NTS. Patients who express the interest to become fully self-managing will first gather 3 months of experience in the PST model before entering into the advanced program for PSM. Patients who do not meet the requirements will not be accepted; approximately 53% of all patients who make contact via the NTS website go on to home-monitor (33% drop out during first telephone contact, 10% are unwilling or unable to complete e-learning, 4% drop out during the intake process or the first 4 weeks). Of the patients on home-monitoring in this analysis, 80% were on PST and 20% were willing and able to perform PSM.

Patients then start to measure their INR and record the measurement result on the system, and answer questions regarding their clinical

status. NTS staff access this information to check and (if relevant) respond to any mention of thrombotic or bleeding events, adverse effects, changes in concomitant medication and other events. Dose adjustments are provided or, in self-dosing patients, checked and approved or adapted as required. Frequency of testing depends on the level of INR stability, with the appropriate dosing schedule provided by NTS medical staff for PST patients, and determined by PSM patients themselves, supervised by medical staff. Further education, motivational support and—if necessary—reminders are provided on a regular basis. Round-the-clock medical support is also offered to NTS patients.

Minor clinical events are regularly self-reported by all patients at the time of the INR measurements. Deaths are required to be pro-actively reported to the Dutch healthcare authorities, and details of serious but non-fatal events may also be requested retrospectively by the authorities. Therefore the NTS captures and retains records of death and serious events that could potentially lead to death which could be related to the therapy, such as hemorrhages or strokes. This has been done in a structured, uniform way since February 2012. While the number of deaths can be reliably captured by the NTS, the actual event or reason for death cannot always be audited reliably. Similarly, serious non-fatal events are not independently audited. Only the verified data regarding number of deaths have therefore been included in this analysis.

The therapeutic ranges for INR in anticoagulation therapy with VKAs are individually set by the admitting physician, and follow the Federation of Dutch Thrombosis Services guidelines for INR ranges for different indications [21]. The guidelines specify a low (2.0–3.0) and high (2.5–3.5) intensity anticoagulant range, and recommend an additional 0.5 INR units be considered acceptable in order to avoid low INR values, leading to therapeutic ranges of 2.0–3.5 and 2.5–4.0. In comparison to 'target range' used as a standard term internationally, these correspond to INR ranges of 2.0–3.0 and 2.5–3.5. As the TTR is typically used in the Netherlands and the processes of the NTS are laid out accordingly, the TTR was primarily used in the subsequent analysis in this paper. The wider ranges mean that values reported here for TTR and number/proportion of values in therapeutic range are higher than those in many studies in the literature using target ranges 1 INR unit wide [22].

The use of two different point of care coagulometers (CoaguChek® XS, Roche Diagnostics, Basel, Switzerland; INRatio®2, Alere Inc., San Diego, USA) with identical protocols within the NTS system allows direct comparison of their impact on patient outcomes.

Statistical Analysis

All patients entering the NTS from June 2011 and fatal events starting 2012 onwards were included in the analysis. The reason for this start date was that from then onwards the NTS worked with both devices, CoaguChek XS and INRatio2. Monitors were distributed to patients based on device availability within the NTS purchasing system at the time, and with no consideration of patient characteristics except for those in residential care settings ($\sim$5%), where the choice was determined by the existing point of care monitors used by the care home.

The first 90 days after treatment start were excluded from the observation period to allow for familiarization with the system (consistent with the analytical approach used elsewhere

[8, 23]), and to be able to assess any differences between devices during the more stable phase associated with better INR control after the first 3 months [23].

Main endpoints in the statistical analysis are TTR values. TTR values were computed by the Rosendaal method [24], using the predefined therapeutic range of INR values. In addition, the percentage of values inside the therapeutic range, and the frequency of critical values (INR <1.5 or INR >5.0) were included as endpoints. Further, critical values were analyzed as number of events observed per month. The occurrence of minor clinical events was self-reported by patients. Serious clinical events and deaths were captured and kept on record by the NTS, and mortality data are included in the analysis.

TTR values and the number of critical values per month were treated as interval scaled variables in subsequent analyses. Location differences between subgroups were tested using Wilcoxon's ranksum test with adjustment for tied values. In case of more than two subgroups, this test was replaced by the Kruskal–Wallis ranksum test, also adjusted for ties.

Least squares multiple regression was used to explain the influence of the treatment (i.e. the device in use), demographic data and additional medical variables (indication, therapeutic range, medication) on TTR, with dichotomous and polytomous variables being transformed into groups of dummy indicator variables. For each group of indicator variables, the largest subgroup was used as reference group. Cox proportional hazard regression was used to assess the multivariate influence on the time to fatal events. The regression took account of repeated events per patient applying the Conditional Risk Set modelling technique proposed by Prentice et al. [25]. As standard, the computation of standard errors used the robust clustering technique proposed by Lin and Wei [26]. The simple effect of the device on the time between fatal events was determined graphically using the Kaplan–Meier curve and an associated logrank test.

Statistical analysis as conducted in STATA/SE v13.0 by StataCorp LP, College Station, USA (2013).

This article does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

Of the 5,108 patients enrolled in the NTS program from June 2011–February 2014, 2,210 used CoaguChek XS and 2,898 used INRatio2 as an INR home monitoring device. Out of these, 4,326 patients (85%) had INR measurements recorded in the database after the 90-day familiarization period and were included in the further analysis (1,961 CoaguChek XS and 2,365 INRatio2). For these patients a total of 217,369 valid INR measurements were available for analysis (104,295 CoaguChek XS and 113,074 INRatio2), of which 156,507 INR values (72%) were obtained after the 90-day familiarization period (79,418 CoaguChek XS and 77,089 INRatio2, reflecting the longer average observation period for patients using CoaguChek) and these were included in the further analysis.

Patient Characteristics

Table 1 shows a summary of patient characteristics. Males made up 67.6% of the patients, the majority of the patients were between 45 and 74 years of age, and the leading indication for anticoagulation was atrial fibrillation (54.3%) (Table 1). The predominant target range for the INR was

Table 1 Demographics and univariate analyses

Group	Number of patients	Patient distribution (%)	INR measurements per month	% values in therapeutic range	TTR	Critical values per month
All	4,326	100.0	2.809	83.9%	87.9%	0.085
Device used	*P*=		<0.0001	0.0113	0.0788	0.9746
CoaguChek XS	1,961	45.3	2.698	84.6%	88.5%	0.084
INRatio2	2,365	54.7	2.902	83.3%	87.4%	0.086
Gender	*P*=		<0.0001	<0.0001	<0.0001	0.0002
Male	2,925	67.6	2.707	84.5%	88.4%	0.070
Female	1,401	32.4	3.022	82.6%	86.7%	0.117
Age (years)	*P*=		0.0001	0.1613	0.2454	0.0188
<45	363	8.4	2.849	82.9%	86.8%	0.096
45–64	2,000	46.2	2.759	84.1%	87.9%	0.088
65–74	1,363	31.5	2.773	84.4%	88.3%	0.071
75–79	311	7.2	2.805	84.2%	87.9%	0.087
80–84	182	4.2	3.217	82.2%	87.2%	0.123
≥85	107	2.5	3.394	79.9%	85.0%	0.104
Indication	*P*=		0.0564	0.0005	0.0139	0.0007
AF, no MHV	2,303	53.2	2.777	84.5%	88.3%	0.076
AF and MHV	47	1.1	2.878	78.8%	85.3%	0.136
MHV, no AF	297	6.9	2.857	84.1%	88.3%	0.088
DVT	728	16.8	2.750	84.4%	88.2%	0.084
Other	951	22.0	2.915	82.2%	86.6%	0.104
Therapeutic range	*P*=		0.0001	0.0001	0.0001	0.0001
2.0–3.5	3,368	77.9	2.766	84.7%	88.6%	0.073
2.5–4.0	729	16.9	3.001	79.1%	84.4%	0.140
Others	229	5.3	2.842	87.4%	88.3%	0.092
Medication	*P*=		<0.0001	<0.0001	<0.0001	<0.0001
Acenocoumarol	3,359	77.6	2.831	82.9%	87.2%	0.087
Phenprocoumon	960	22.2	2.739	87.4%	90.0%	0.078
Others (warfarin)	7	0.2				

Distribution of patients numbers, average INR measurements per month, share of measurements within therapeutic range, and TTR across devices used, gender, age, indication for anticoagulation, target therapeutic range, and medication used. Statistical significance of ANOVA for each group

AF atrial fibrillation, *DVT* deep vein thrombosis, *INR* international normalized ratio, *MHV* mechanical heart valves, *TTR* time in therapeutic range, defined in this setting to include an additional 0.5 INR units (e.g. therapeutic range 2.0–3.5 for an international target range of 2.0–3.0)

2.5–3.5 (77.9%), corresponding to a therapeutic range of 2.0–3.5, and most patients were managed using acenocoumarol (77.6%). Some patients were managed with phenprocoumon (22.2%) and only seven patients (0.2%) received warfarin. Due to the low number of patients on warfarin, subgroup analysis was not performed for this medication. The patients were observed for a median of 1.44 years, or 1.20 years after the 90-day familiarization period [interquartile range (IQR) 0.49–1.76]. Data were observed from patients using CoaguChek XS for slightly longer (median of 1.37 years with an IQR of 0.95–1.83) versus INRatio2 (median of 1.06 years, IQR 0.33–1.72). The difference in observation time has been corrected for in the subsequent analyses.

Overall Quality of INR Management

Overall, 83.9% of measured INR values were within therapeutic range, resulting in a time in therapeutic range of 87.9% (Table 1). For international reference, these values correspond to a time in target range of 68.9%, although therapy was not aimed at maintenance in this narrower range. Independent of the definition of the range, only 0.085 INR measurements per month (2.4% per patient) were classified as critical values (INR <1.5 or >5.0), from an overall average of 2.8 INR measurements per month, with no statistically significant difference between critical values per month for the two INR monitors ($P = 0.97$).

Univariate Analysis of Surrogate Markers

Taken together, gender, indication, the target range, and the choice of medication consistently impacted the different surrogate metrics, although the amount of the impact was small. In contrast, patient age and choice of INR monitor only showed a small and not statistically significant effect on the most important surrogate parameters of good INR control (TTR and critical values).

Comparing the effect on the TTR of the same set of patient characteristics across the two monitors using a univariate analysis, the overall difference in the effect of the two monitors was not statistically significant ($P = 0.079$) and only became statistically significant in defined subgroups (without a correction for multiple testing) (Table 2). However, some differences were observed in the patient distribution among the two monitors, with INRatio2 being used disproportionally more often in males, patients with an age of 45–74 years, patients with atrial fibrillation as a primary indication, patients with a target INR range of 2.5–3.5, and patients receiving phenprocoumon. To take these differences in distribution into account, a multivariate analysis was subsequently performed.

Clinical Events

Self-reported minor clinical events (Table 3) were infrequently recorded by patients, with a total of 4,043 minor events being reported in the 5,185 patient-years observed. For CoaguChek XS 2,117 events were reported in 2,682 patient-years observed (average of 0.790 events per patient-year); for INRatio2 these figures were 1,926 events in 2,503 patient-years (average of 0.769 events per patient-year). The leading minor events were bruises (45%; 1,804 events) and nose bleeds (19%; 774 events), together accounting for more than half of the minor events, followed by conjunctival bleeds (11%) resulting in a reported impairment of vision (7%), blood in urine (6%), blood in stool (5%), black stool (3%), muscle bleeds and thromboembolism (2% each), and joint bleeds

Table 2 Univariate comparison of the monitor used

Group	Difference: CoaguChek vs. INRatio2		
	Patient distribution (%)	TTR (%)	*P*
All	0.0	1.1	0.079
Gender			
Male	0.8	1.1	0.199
Female	−0.8	1.2	0.199
Age (years)			
<45	−0.4	0.7	0.969
45–64	5.2	1.5	0.157
65–74	2.9	2.0	**0.033**
75–79	−1.1	0.2	0.724
80–84	−3.0	−2.0	0.451
≥85	−3.5	−3.1	0.714
Indication			
AF, no MHV	3.6	1.2	0.404
AF and MHV	0.0	4.6	**0.046**
MHV, no AF	−1.8	3.7	0.540
DVT	−3.1	1.3	**0.040**
Other	1.2	−0.3	0.252
Therapeutic range			
2.0–3.5	2.8	1.4	**0.037**
2.5–4.0	−2.6	2.3	**0.049**
Others	−0.2	−4.7	**0.027**
Medication			
Acenocoumarol	−3.5	1.4	**0.005**
Phenprocoumon	3.6	0.8	0.514
Others (warfarin)	−0.1	0.0	

Univariate comparison of the effect of the coagulometer (*P* for TTR comparison using a ranksum test, without Bonferroni adjustment)

P values in bold are below the threshold for significance (0.05)

AF atrial fibrillation, *DVT* deep vein thrombosis, *INR* international normalized ratio, *MHV* mechanical heart valves, *TTR* time in therapeutic range, defined in this setting to include an additional 0.5 INR units (e.g. therapeutic range 2.0–3.5 for an international target range of 2.0–3.0)

(1%; 39 events). The differences in frequencies of minor clinical events between the two monitors was not statistically significant for most minor clinical events in the univariate comparison. For hematuria and conjunctival bleeds, patients on CoaguChek XS experienced a statistically significant higher frequency of events than patients on INRatio2 (without correcting for multiple testing, Table 3), although the number of events was low for both groups.

Table 3 Clinical events

	Total		CoaguChek XS		INRatio2		*P*
	# events	% of total (%)	# events	% of total (%)	# events	% of total (%)	
Bruises	1,804	45	951	45	853	44	0.211
Nose bleeds	774	19	387	18	387	20	0.239
Blood in urine	233	6	150	7	83	4	**0.012**
Blood in stool	215	5	101	5	114	6	0.783
Black stool	111	3	43	2	68	4	0.207
Muscle bleeds	96	2	46	2	50	3	0.607
Joint bleeds	39	1	12	1	27	1	0.130
Conjunctival bleeds	433	11	235	11	198	10	**0.044**
Impaired vision	266	7	161	8	105	5	0.149
Thromboembolism	72	2	31	1	41	2	0.169
All minor events	4,043		2,117		1,926		
All fatal events	71		40		31		0.844

Observed minor and major clinical events, all observations. Statistical significance for the univariate differences of the mean events per time observed between the two monitors

P values in bold are below the threshold for significance (0.05)

Serious clinical events were even less frequent. In total, 71 fatal events were observed, of which 31 patients used INRatio2 and 40 used CoaguChek XS. The Kaplan–Meier survival estimate curves are shown in Fig. 1 demonstrating no difference between the groups using different monitors. The 1-year death rate was 1.9% for patients using INRatio2 and 2.1% for CoaguChek XS. The hazard ratio (HR) of 0.95 was not statistically significant in the univariate analysis, i.e., without correction for other influencing factors ($P = 0.844$, Table 3). Consequently, the Kaplan–Meier estimation showed mostly identical curves (Fig. 1). However, as the risk profile was different between these two populations, a multivariate analysis was subsequently performed for verification.

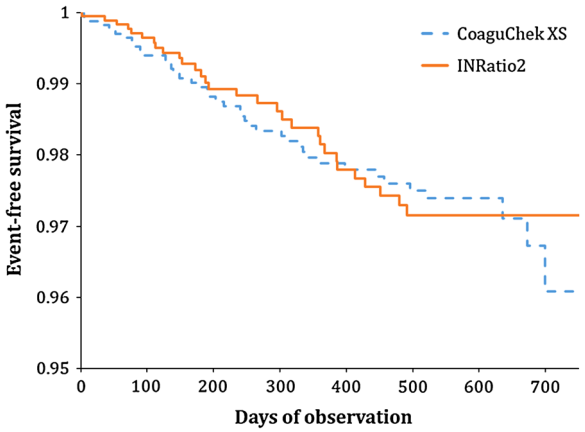

Fig. 1 Kaplan–Meier survival estimate curves of event-free survival for the two monitors

Multivariate Analysis for Surrogate Parameters

The multivariate analysis (Table 4), considering all patient characteristics, only had a small

explanatory power of $r^2 = 0.0419$ for TTR and $r^2 = 0.0258$ for the critical value rate, although it was statistically significant ($P < 0.0001$ for both models).

Correcting for all other patient characteristics, the use of CoaguChek XS had a positive effect of +1.0% on the TTR and 0.002 fewer critical values per month compared with the use of INRatio2. While the effect on TTR was smaller in magnitude than in the univariate analysis (Table 1), in the multivariate analysis it was statistically significant ($P = 0.008$). The effect of the coagulometer on the rate of critical values remained not statistically significant.

The effect of the choice of coagulometer on the TTR and critical value rate was smaller than the effect of female gender (−1.9% on TTR and +0.048 on critical values per month, both $P < 0.001$), and the choice of medication (phenprocoumon +3.1% on TTR and −0.015 critical values per month, both $P < 0.001$). A high target range (3.0–4.0) decreased the TTR significantly (−5.3%) and increased the critical events per month (+0.082, both $P < 0.001$). A primary indication for mechanical heart valves increased the TTR by 3.0% ($P < 0.001$) without a statistically significant effect on the frequency of critical values.

Multivariate Analysis for Fatal Events

The multivariate Cox regression analysis for the different parameters on patient survival showed that the choice of the device had no statistically significant influence (HR 1.05, 95% CI 0.65–1.70, $P = 0.838$) (Fig. 1). Similarly, most indications did not significantly influence the risk, while the target range and, most prominently, patient age at start, had statistically significant effects (a year higher age increased the HR by 8%, 95% CI 5–11%, $P < 0.001$) (Fig. 2).

DISCUSSION

This retrospective analysis shows that the choice of coagulation monitor had no effect on clinical outcome of 4,326 Dutch patients treated with VKAs using self-monitoring. The results of the analysis provide a good insight to the quality of INR control in patients performing self-monitoring of INR values and, consequently, the clinical efficacy and safety of VKA treatment. In addition, the analysis provides unique data allowing us to compare the quality of INR control with two different INR monitors, INRatio2 and CoaguChek XS.

Since major clinical events and deaths could not be verifiably attributed to a particular cause in the NTS data, no analysis of the rate of individual major thrombotic or hemorrhagic events could be completed. Therefore, it is not possible to compare the overall rate in the NTS data with rates reported in studies of new oral anticoagulant agents (NOACs), nor is it an objective of this analysis. In addition, this analysis is based on data collected in clinical practice, and not in the pre-specified and more tightly defined setting of randomized controlled trials. The major NOAC studies in atrial fibrillation suggest a general non-inferiority of NOACs versus warfarin with a reduction of hemorrhagic events (most notably of cerebral bleeding [27–30]). Interestingly some meta-analyses found in subgroup analyses a dependency of this effect on the quality of TTR control in the VKA group. Gómez-Outes et al. [28] found that the positive effects of NOACs versus warfarin on non-hemorrhagic strokes and systemic embolic events and on mortality were present in centers that only achieved a TTR below 65% in the warfarin arm. Similarly Ruff et al. [31] showed in a recent meta-analysis that there was a trend for a lower risk reduction of NOACs on stroke and systemic

Table 4 Multivariate analysis for TTR and critical values

Influencer	TTR					Critical INR values per month				
	Coefficient (%)	Std. error (%)	*P*	95% CI (%)		Coefficient	Std. error	*P*	95% CI	
Device: INRatio2 vs. CoaguChek	−1.0	0.4	0.008	−1.7	−0.3	−0.002	0.007	0.826	−0.016	0.013
Gender: female vs. male	−1.9	0.4	<0.001	−2.6	−1.1	0.048	0.008	<0.001	0.033	0.063
Age at program start (years)	0.0	0.0	0.454	0.0	0.0	0.000	0.000	0.894	−0.001	0.001
Length of monitoring (log days)	0.6	0.2	0.001	0.2	0.9	−0.011	0.003	0.001	−0.018	−0.004
INR therapeutic range (vs. 2.0–3.5)										
2.5–4.0	−5.3	0.6	<0.001	−6.4	−4.1	0.082	0.011	<0.001	0.060	0.104
Others	−0.8	0.8	0.312	−2.4	0.8	0.023	0.016	0.143	−0.008	0.055
Primary indication (vs. AF, no MHV)										
AF and MHV	−0.2	1.8	0.920	−3.7	3.3	0.015	0.035	0.661	−0.053	0.083
MHV, no AF	3.0	0.8	<0.001	1.4	4.6	−0.037	0.016	0.022	−0.069	−0.005
DVT	0.0	0.5	0.967	−1.1	1.0	−0.001	0.011	0.956	−0.021	0.020
Others	0.1	0.5	0.820	−0.9	1.1	−0.005	0.010	0.593	−0.025	0.014
Phenprocoumon vs. acenocoumarol	3.1	0.4	<0.001	2.2	4.0	−0.015	0.009	0.092	−0.031	0.002
Constant	84.9	1.6	<0.001	81.7	88.2	0.127	<0.001	0.000	0.064	0.190

Multiple regression of patient characteristics on TTR (overall ANOVA $P < 0.0001$; $r^2 = 0.0419$) and critical values (overall ANOVA $P < 0.0001$; $r^2 = 0.028$)

P values in bold are below the threshold for significance (0.05)

AF atrial fibrillation, *CI* confidence interval, *DVT* deep vein thrombosis, *INR* international normalized ratio, *MHV* mechanical heart valves, *TTR* time in therapeutic range, defined in this setting to include an additional 0.5 INR units (e.g. therapeutic range 2.0–3.5 for an international target range of 2.0–3.0)

embolism as well as on major bleeding in centers that achieved a TTR of 66% or better (*P* of interaction 0.60 and 0.022, respectively).

As with any antithrombotic treatment, anticoagulation with VKA bears the risk of bleeding complications which are regarded as the main adverse event of anticoagulant treatment. In our analysis, minor bleeding complications were infrequently recorded with <1 event per patient-year. More than half of these events were bruises, which are generally without any clinical relevance, and nosebleeds.

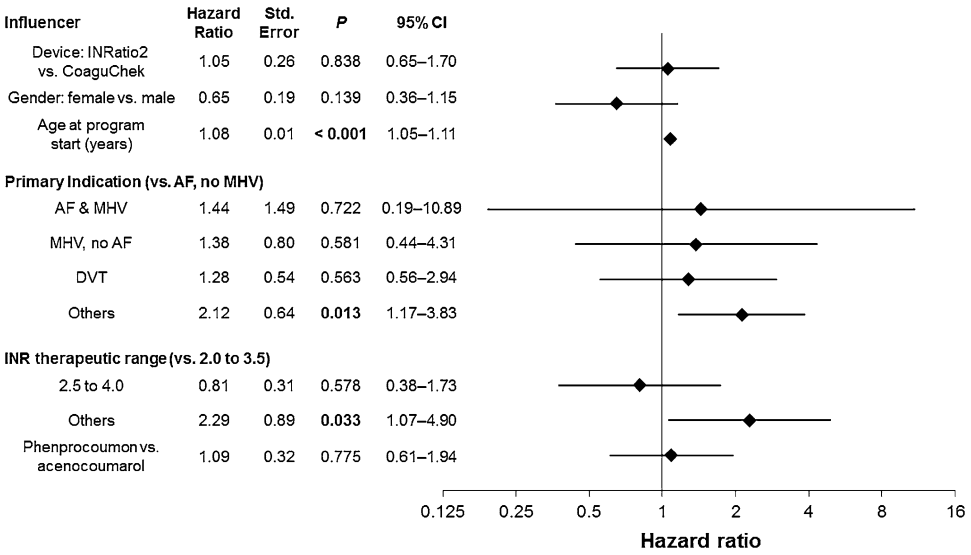

Fig. 2 Forest plot showing multivariate Cox regression analysis of the effect of different parameters on patient survival. *AF* atrial fibrillation, *DVT* deep vein thrombosis, *INR* international normalized ratio, *MHV* mechanical heart valves. Therapeutic range is defined in this setting to include an additional 0.5 INR units (e.g. therapeutic range 2.0–3.5 for an international target range of 2.0–3.0)

Other bleeding manifestations such as conjunctival bleeds, hematuria, gastrointestinal bleeding indicated by black or bloody stool, and muscle bleeds were rarely observed. This indicates that VKA accompanied by self-testing not only improves the control of INR values but also leads to acceptable bleeding rates, indicating a high level of treatment safety. It should be mentioned that the distribution and prevalence of bleeding manifestations observed for patients performing self-testing with INRatio2 or CoaguChek XS were not significantly different for most bleeding manifestations, and only for hematuria and conjunctival bleeds, patients using CoaguChek XS experienced a statistically higher frequency than patients using INRatio2. The rate of patient-reported minor thrombotic events in the NTS data was low at 2% per patient year.

Compared to the mentioned minor events, fatal events were even less frequent. In total, 71 events were reported, yielding a death rate of 1.9–2.1 per 100 patient-years. This is well below the rate of fatality observed in patients with clinic-based INR measurements, and compares favorably with the death rates for the warfarin groups reported in recent clinical trials in atrial fibrillation, 4.13%/year [32], 4.9%/year [33] and 3.94%/year [34]. The meta-analysis of Rose and colleagues [35] reported death rates of 2.3–8.1 per 100 patient-years based on 15 randomized controlled trials. Similarly, Heneghan et al. [12] found an average death rate of 3.9% while in self-monitoring this rate was reduced to 2.4%.

It should be mentioned that the frequency in use of the CoaguChek XS and the INRatio2 did not differ significantly among patients experiencing fatal events, in either univariate or multivariate analysis. In the latter statistic approach, high target INR (3.0–4.0) and, most prominently, older age at the start of anticoagulation significantly influenced the risk, and 1 year of higher age increased the HR by 8%. Thus, self-testing was found to be efficient in reduction of fatal events, regardless of the monitor used for INR determination.

Under VKA treatment, the quality of INR adjustment and the resulting TTR is strongly correlated with the outcome of patients in terms of thrombotic events and the rate of complications, particularly anticoagulant-induced bleeding. Regarding the quality of INR control, a high TTR of 87.9% was observed in the patients in this analysis. It should be noted that this analysis of Dutch patients used a therapeutic INR range of 2.0–3.5 for most of the patients, while internationally a target range of 2.0–3.0 is used for most indications for VKA anticoagulation. The corresponding time in target range for the NTS data is calculated at 68.9%, which bears close comparison to the recently published STABLE retrospective analysis of 24,907 warfarin-anticoagulated patients on INR self-testing, with an overall TTR of 69.7% [8]. It should be noted though that maintenance within this narrower range is not a priority for NTS. Comparison with TTR values reported from randomized clinical trials is difficult because of the differences in parameters measured, level of monitoring and pre-specified endpoints.

Apart from TTR, the frequency of critical INR values is an important indicator for the quality of VKA anticoagulation; this aspect has even been regarded to be more suitable for the prediction of clinical events than the TTR. As with others, critical INR values were defined as those below 1.5, bearing a considerable risk for thrombotic or thromboembolic events, and those above 5.0, predisposing for bleeding complications [8, 19]. In our data, an average of 2.4% of the INR values per patient was within the critical range. The frequency of critical values observed in this study of an average of 0.085 per month compares slightly favorably to the overall average frequency of 0.096 per month implied in the STABLE population [8]. This is interesting since the two populations not only used different VKA (in the USA predominantly warfarin, which has a longer half-life than acenocoumarol but shorter than phenprocoumon), but in addition medical practice in the NTS population favoured the somewhat more aggressive treatment of atrial fibrillation to an INR target range of 2.5–3.5. This suggests that patient self-testing is able to achieve this more aggressive target in the Netherlands with the same quality of control, shown by the equivalent TTR. In general, the results indicate a high quality of INR control in the NTS population, indicated by both high TTR and low prevalence of critical INR values. This raises the question whether the good INR control resulted in an effective prevention of thrombotic and thromboembolic events on the one hand and the prevention of serious complications of treatment on the other.

Taken together the self-testing population analyzed in the Netherlands compares very similarly in setup and therapy control to the populations studied elsewhere. This INR management system seems representative of a typical self-monitoring therapy with the associated beneficial effects on therapy control. The analysis demonstrates a good level of INR control and, consequently, high TTR in patients performing self-testing of INR. As shown, good INR control by self-testing also leads to high efficacy of treatment and high treatment safety, indicated particularly by an acceptable prevalence of minor bleeding complications and low death rate due to major clinical events under VKA treatment.

A review of the literature on the analytical performance of point of care INR monitors, including CoaguChek XS and INRatio among others, concludes that in general they have adequate precision and accuracy for clinical use [36]. The effect of the choice of home monitor to measure INR has to our knowledge so far not

been studied in a large population. A recent Health Technology Assessment (HTA) report in the UK noted that CoaguChek XS and INRatio2 had similar performance and their measurements correlated well with standard laboratory tests for INR [37]. However, this report also suggested that small differences in design or usability could have an impact on outcomes such as TTR or clinical events. Azarnoush et al. [38] did not find statistically significant differences for the clinical outcomes of 50 patients with mechanical valves using CoaguChek versus 40 patients using INRatio. Similarly Hemkens et al. [39] found that "the absolute and relative differences were not substantially different between both devices" in a study of 62 patients using INRatio and 65 patients using CoaguChek S for self-monitoring for any indication of VKA-therapy.

In contrast to these small clinical trials, in this retrospective analysis results of more than 4,000 patients managed by the NTS using CoaguChek XS and INRatio2 with the same clinical protocol are reported. The current analysis adds to this understanding regarding the differences between the two monitors on both surrogate outcome parameters and clinical endpoints. While in the univariate comparison CoaguChek XS shows a statistically non-significant advantage of 1.1%, correcting for all identified influencers on the TTR such as gender, age, indications, medication, and target range still resulted in only a 1.0% difference in TTR, which was statistically significant. However, there was no difference in the distribution of minor clinical events that were self-reported by patients and the effect of the minor clinical events of the two monitors was not statistically significant and varied between the monitors. More importantly, there was no statistically significant influence of the monitor type on mortality. Hence, the current evidence suggests that there is no clinically relevant difference on clinical events between these two monitors.

One of the key questions to be addressed is whether a 1.0% difference in TTR is relevant on outcomes other than clinical events. In accordance with others, this small difference was not considered to be practically relevant. Supporting this hypothesis, Rose et al. [35] showed in their model for a population of 67,077 patients based on a comprehensive meta-analysis that even TTR changes of 2.5% did not statistically significantly influence major clinical events like ischemic strokes or major hemorrhages, while impacting the death rate only marginally. Only at a 5% TTR change was there a significant influence on major clinical events. Similarly, Lam and colleagues [40] concluded that a TTR difference of 3.5% is not clinically relevant. The 1.0% difference observed between users of the two different monitors in the population of the NTS is well below these comparable TTR changes. Furthermore, the difference in TTR of the observed magnitude did not result in a notable difference between the incidences of minor clinical events. The CoaguChek XS showed a slight difference in two types of clinical event in multivariate statistical testing; however, this is deemed not to be clinically relevant and more likely due to the multiple tests performed in the large population analyzed. Most importantly, fatal events were not shown to be affected by the choice of the monitor in this analysis of over 4,000 patients.

Strengths and Limitations

The key strength of this retrospective analysis is the large population of more than 4,000 patients included, to our knowledge the largest consecutive cohort of self-monitoring

patients studied in Europe. This population was analyzed based on the clinical practice observed in standard treatment, as opposed to the tightly defined processes of a randomized controlled trial. The population mix of gender, age and indications is representative of many INR patient self-monitoring programs.

In addition to the methodological shortcomings inherent to every retrospective study, the elimination of the first 3 months familiarization period removes initial non-therapeutic INRs and may not be consistent with how TTR is calculated in other studies. Another limitation is the slightly different definition of the therapeutic and target ranges used in the Netherlands. Lack of verified causes of major clinical events, including death, in the NTS data prevents comparison of safety parameters with other studies. Finally, patients referred for patient self-monitoring may represent a select population, although this would not impact the applicability of the data to other patient self-monitoring settings.

Taken together, we believe that these limitations do not materially impact our major conclusion on the clinically similar performance of INRatio2 and CoaguChek XS.

CONCLUSION

In our analysis of self-testing data from a large cohort of patients in the Netherlands, the effect of the choice of coagulation monitor (CoaguChek XS or INRatio2) on the TTR, minor and major safety outcomes of long-term anticoagulation management is clinically irrelevant. In contrast, other factors like patient gender, indication, choice of target range, and the VKA used exert a larger and statistically significant effect on the quality of INR management. Good INR control and high TTR, both of which can be achieved by self-testing, improve therapeutic efficacy and treatment safety for patients. Thus, self-testing should be promoted and recommended as an indispensable element in the monitoring of VKA coagulation. These results open the opportunity to look for other parameters to determine the choice of INR monitor, such as cost of the monitor and strips, ease of use and value added by the manufacturers in terms of service to patients and healthcare providers.

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Christoph Sucker drafted sections and provided critical review and approval of the manuscript.

All authors had full access to all of the data in this study and take complete responsibility

for the integrity of the data and accuracy of the data analysis. All authors meet the ICMJE criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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Compliance with ethics guidelines. The analysis in this article is based on a retrospective examination of anonymous, aggregated patient data, and does not involve any new studies of human subjects performed by any of the authors.

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