PATIENTS USING WARFARIN FOR STROKE PREVENTION

Warfarin: time in therapeutic range, a single centre study on patients using warfarin for stroke prevention in non-valvular atrial fibrillation and prosthetic heart valves

D. Sadhabiriss* and S.L. Brown*,#

*Division of Internal Medicine, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa
#Clinical unit, Mahatma Gandhi Memorial Hospital, Durban, KwaZulu-Natal, South Africa

Address for correspondence:
Dr D. Sadhabiriss
Mahatma Gandhi Memorial Hospital
100 Phoenix Highway
Phoenix
Durban
4091
South Africa

Email:
dhiren.sadhabiriss@gmail.com

ABSTRACT

Background: Two common indications for oral anticoagulants are patients with non-valvular atrial fibrillation (AF) or prosthetic heart valves (PHV).The degree of anticoagulation is monitored by evaluating the international normalised ratio (INR); however, the quality of anticoagulation, determined by the time in therapeutic range (TTR), is less often evaluated.TTR has significant clinical implications in patient outcomes.
Objectives: We sought to identify the indications for anticoagulation and determine its quality via the TTR at a single centre, community-based and district level hospital in the setting of usual care. We documented the prevalence of thrombo-embolic and haemorrhagic adverse events and we also collected data on factors that may contribute to a poor TTR or increased risk of adverse events.
Methods: We conducted a retrospective, descriptive and observational study with chart audits evaluating the anticoagulation indication and control for the preceding 1 year for each patient. Descriptive statistics included mean and standard deviation for quantitative data and frequencies for categorical data. Chi-square tests were used to analyse comparisons of categorical data and the student's t-test for continuous variables. Two-tailed p-values less than 0.05 were considered significant.
Results: TTR was poor for patients with AF and PHV (44.5% and 13.7% respectively). We identified older age, less frequent testing and high target ranges as significant factors associated with poorer outcomes. We demonstrated a high prevalence of adverse events (25.4%).
Conclusion: Patients in this setting demonstrated poor quality of anticoagulation and had a high prevalence of adverse events. SAHeart 2021;18:28-38

INTRODUCTION

Warfarin is a vitamin K antagonist and is widely prescribed as an oral anticoagulant for treating and preventing thrombosis and embolism in atrial fibrillation (AF) and in prosthetic heart valves (PHV).[1] Due to its complex pharmacokinetics, pharmacodynamics and inter-individual variability, there is usually no standard dose and therefore international normalised ratio (INR) testing is required to monitor its efficacy and reduce the risk of bleeding complications. The quality of this anticoagulation is less often measured and the time in the therapeutic range (TTR) is an important, validated, and acceptable measure of this. The three most common methods of evaluating TTR are the fraction of INRs in range or the direct method (number of INRs in range divided by the number of INRs tested as a percentage); the Rosendaal linear interpolation method which assumes a linear relationship between 2 INR values and computes the INR for any specific day; and the cross-section-of-the-files method which takes each patient whose INR is in range at one point in time divided by the total number of INRs performed on all patients at that point in time.[2]

The TTR is a measurement not only of the efficacy of anticoagulation with warfarin but also as a measure to ensure its safety. When comparing the direct anticoagulant dabigatran with warfarin no difference in stroke prevention at higher TTR was shown.[3] TTR greater than 70% conferred better survival for patients with moderate or high-risk patients.[4] In patients with AF, the quality of anticoagulation is stratified according to the percentage TTR where less than 50% is considered bad quality, more than 60% being satisfactory and more than 70% conferring optimal anticoagulation. The report from a post-hoc analysis of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) indicated that if

the TTR was below 58% - 65%, the benefit of warfarin therapy over aspirin was lost.[5]

Valve thrombosis is most often encountered in patients with mechanical valves and inadequate antithrombotic therapy.[6] A correlation between treatment quality with warfarin as measured by TTR and serious complications has been shown. It is recommended that best benefit in patients with PHV is achieved when the TTR is at least 83% but a TTR of at least 70% is likely to be sufficient to prevent valve thrombosis.[7]

Further to the efficacy of anticoagulation, improved TTR confers reduced risk of bleeding and mortality and is therefore considered as a measure to ensure safety in anticoagulation. In the Stroke Prevention using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation (SPORTIF III) trial, patients with a TTR of less than 60% had significantly higher incidence of major haemorrhage and mortality than patients with TTR above 75%.[8] The study by Wan, et al., evaluated anticoagulation control and prediction of adverse events in patients with AF by a systemic review of 47 studies. They found that TTR negatively correlated with major haemorrhage and thrombo-embolic rates. This effect was significant in retrospective but not in randomised controlled trials. For retrospective studies, a 6.9% improvement in the TTR significantly reduced major haemorrhage by 1 event per 100 patient-years of treatment. Furthermore, they concluded that a 12% increase in TTR can reduce the thrombo-embolic rate by 1 event per 100 patient-years.[9] Data from the Rivaroxaban once daily oral direct factor XA inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET-AF) trial evaluated the relationship between TTR and the comparative treatment effects of rivaroxaban and warfarin and found that patients in the highest quartile of TTR had a lower event rate per 100 person-years than patients in the lowest quartile of TTR (1.3 vs. 2.0) when analysing stroke or systemic thrombo-embolism.[10]

It is therefore accepted and emphasised that the TTR matters and has far reaching implications in both assessing the quality of anticoagulation, determining efficient anticoagulation, and reducing the incidence of mortality and major adverse events.

MATERIALS AND METHODS

Study sample

We conducted a retrospective, descriptive and observational study with chart audits of patients attending the adult medical outpatient department at Mahatma Gandhi Memorial Hospital in KwaZulu-Natal, South Africa. This comprised a setting of usual care and not a specialised anticoagulation clinic. We included all patients using warfarin for AF or PHV for at least one year. We excluded patients who had interrupted warfarin therapy for longer than 2 months and inpatient INR testing. The target INR value for patients with PHV was determined using established recommendations[1] which consider valve thrombogenicity and patient risk factors in determining the target INR. To create a target INR range, we accepted these targets as the minimum acceptable INR value and allocated a 0.5 higher limit to create a range. The target INR range for patients with AF was consistent at 2.0 - 3.0. These recommendations are consistent with the laboratory reference at the study site to ensure consistency between the treating clinician and the study methods. The TTR was determined by the direct method and the Rosendaal method. Time out of range (time below range, above range and with an INR greater than 4.00) was determined using only the direct method. Documented adverse events at any time for a particular patient were included unless sustained before commencing warfarin therapy. Adverse events were categorised as stroke and haemorrhage or over-warfarinisation (determined as needing antidote treatment or inpatient care).

Statistical analysis

Data were analysed by the IBM Statistical Package for the Social Sciences for WindowsR, version 23 (IBM Corp., Armonk, N.Y., USA) software programme. Descriptive statistics included mean and standard deviation for quantitative data and frequencies for categorical data. The student's t-test and the chi-square test were used for comparison of data. The Pearson correlation test was used to compare the Direct and the Rosendaal methods. Any 2-tailed p-value less than 0.05 were considered significant.

Ethical considerations

This study commenced following full ethical approval obtained from the Biomedical Research Ethics Committee, University of KwaZulu-Natal (ref.no.BE320/15) and permissions from the KwaZulu-Natal Department of Health (ref. no.KZ_2016RP26_295). The study was conducted in accordance with the National Institutes of Health Office of Extramural Research course (Certification No. 1768624).

RESULTS

Description of the sample population

We evaluated 263 patients who were on warfarin. The most common indication was for stroke prevention in non-valvular AF (39.5%) followed by PHV (35.8%). Venous thrombosis or embolism (12.2%), arterial or left ventricle thrombus (4.9%), valvular AF (3.8%) and heart failure with reduced ejection fraction (0.4%) comprised the remaining indications. Charts could not be located for 9 (3.4%) patients. Hereinafter, we excluded 86 cases (65 patients on warfarin for reasons other than non-valvular AF and PHV and a further 21 patients who had less than 1 year of warfarin use). This resulted in a sample population of 96 patients with AF and 81 patients with PHV (Figure 1).

Most patients were female (n=122, 68.9%). The mean age of patients with AF was 64.68 ± 11.3 years and 41.83 ± 15.7 years for patients with PHV. Patients with AF were categorised in line with the CHA_2DS_2-Vasc scoring system; 34 (35.4%) patients were 65 years old to less than 75 years old and 17 (17.7%) patients were 75 years or older.[11] The AF cohort was evaluated for 39 937 days with a mean of 416 ± 111.8 days per patient and patients with PHV for 39 038 days with a mean of 481.9 ± 192.4 days per patient. The mean number of days between INR tests for the entire cohort was 33.3 ±12.0 days; 31.05 ± 6.8 days for the AF cohort and 35 ± 15.8 days for those with PHV. A total of 2 382 INR values were analysed; 1 285 for patients with AF cohort and 1 097 in those with PHV. (Table 1).

Time in therapeutic range

Patients with AF had a significantly higher percentage of TTR than patients with PHV when tested by the direct and the

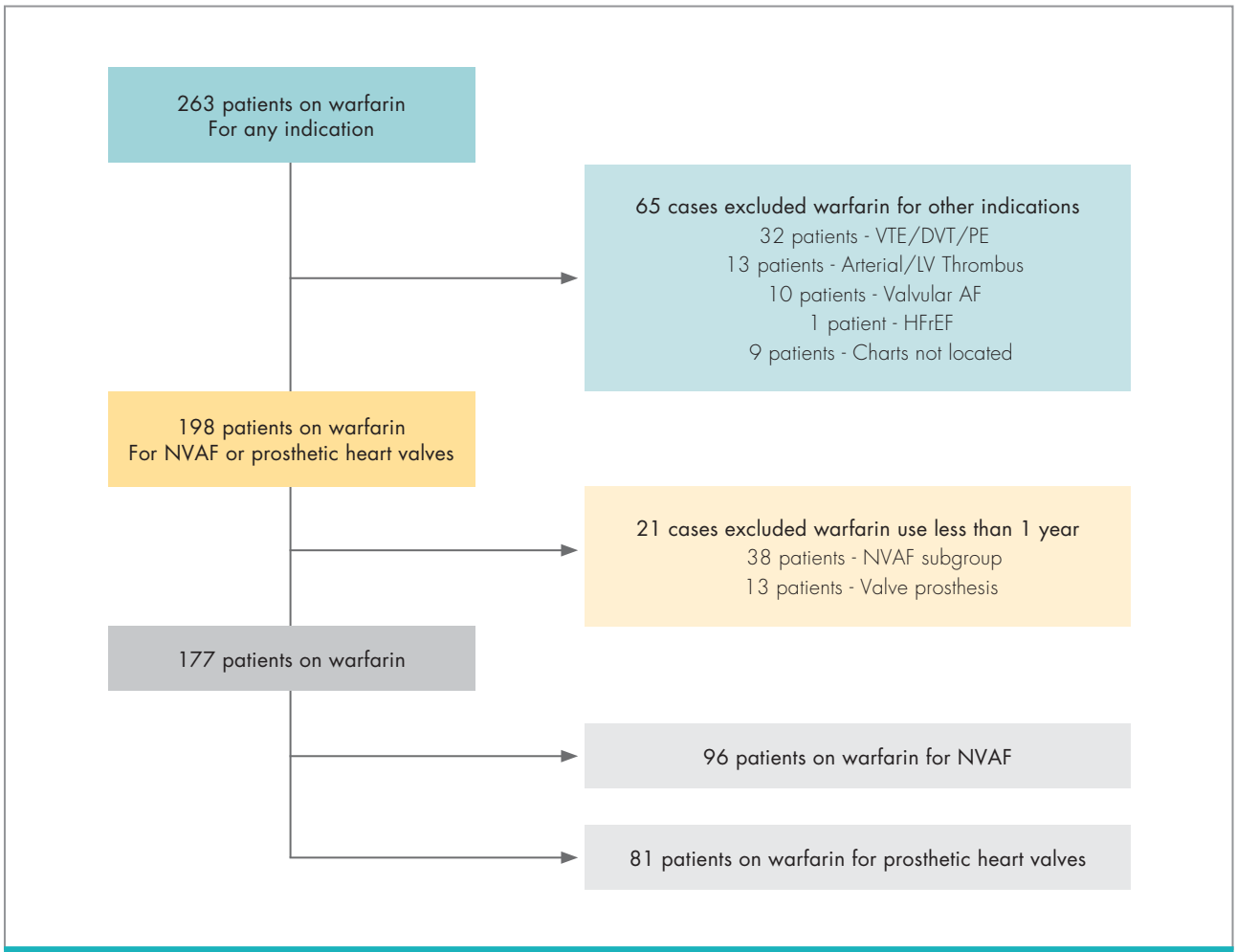

FIGURE 1: Selection of patients for the study analyses.
VTE = Venous thromboembolism, DVT = Deep vein thrombosis, PE = Pulmonary embolus, LV = Left ventricle, AF = Atrial fibrillation, HFrEF = Heart failure with reduced ejection fraction, NVAF = Non-valvular atrial fibrillation.

TABLE I: Characteristics of the sample population.

Sample population (n=177)	
Female, n (%)	122 (68.9)
Mean age (IQR)	54.23 (40 - 69)
Total days studied (mean per patient)	78 975 (446.2)
Total INRs sampled (mean per patient)	2 382 (13.5)
Mean days between INR tests (SD)	33.3 (12.0)
Less than 28 days apart, n (%)	41 (23.2)
28 - 32 days apart, n (%)	75 (42.3)
More than 32 days apart, n (%)	61 (34.5)
AF cohort (n=96)	
Female, n (%)	63 (65.6)
Mean age (IQR)	64.7 (57 - 72)
Less than 65 years old, n (%)	45 (46.9)
65 to less than 75 years old, n (%)	34 (35.4)
75 years or older, n (%)	17 (17.7)
Total days studied (mean per patient)	39 937 (416)
Total INRs sampled (mean per patient)	1 285 (13.4)
Mean days between INR tests (SD)	31.1 (6.8)
Less than 28 days apart, n (%)	31 (32.3)
28 - 32 days apart, n (%)	36 (37.5)
More than 32 days apart, n (%)	29 (30.2)
Valve prosthesis cohort (n=81)	
Female, n (%)	59 (72.8)
Mean age (IQR)	41.8 (30 - 55)
Less than 20 years old, n (%)	2 (2.5)
20 - 29 years old, n (%)	18 (22.2)
30 - 39 years old, n (%)	21 (25.9)
40 - 49 years old, n (%)	14 (17.3)
50 - 59 years old, n (%)	12 (14.8)
60 years or older, n (%)	14 (17.3)
Total Days studied (mean per patient)	39 038 (482)
Total INRs sampled (mean per patient)	1 097 (13.5)
Mean days between tests (SD)	36 (15.8)
Less than 28 days apart, n (%)	10 (12.3)
28 - 32 days apart, n (%)	39 (48.2)
More than 32 days apart, n (%)	32 (39.5)

AIQR = Inter-quartile range, INR = international normalisation ratio, AF = Atrial fibrillation.

Rosendaal methods (41.9% ± 19.6 vs. 13.8% ± 12.7; p<0.001 and 44.5% ± 18.5 vs. 13.7% ± 11.9; p<0.001 respectively).

Patients with AF spent significantly less time below range than the patients with PHV (29.19% ± 19.9 compared to 67.69% ± 20.0; p<0.001) and significantly more time above range than the patients in the valve prosthesis cohort (28.38% ± 17.2 compared to 18.61% ± 13.9; p<0.001). The mean percentage time with an INR value of greater than 4.0 was significantly lower in the AF cohort (9.11% ± 11.04) than the valve prosthesis cohort (13.34% ± 10.9); p=0.012 (Table II). A positive correlation between the results of the direct and the Rosendaal methods using a Pearson correlation test (r=.823, p<0.001) was demonstrated.

TABLE II: Distribution of mean percentage time in range and out of range for the subgroups of AF and valve prosthesis.

	AF cohort (n=96)	Valve prosthesis cohort (n=81)
Mean age in years	64.7	41.8
Female, n (%)	63 (65.6)	59 (72.8)
Time below range (%)	29.2*	67.7
Time above range (%)	28.4*	18.6
Time INR >4.00 (%)	9.1**	13.3
TTR-Direct method (%)	41.9*	13.8
TTR-Rosendaal method (%)	44.5*	13.7

**p<.001 when compared to valve prosthesis subgroup using independent samples t-test.*
***p<.05 when compared to valve prosthesis subgroup using independent samples t-test.*
AF = Atrial fibrillation, INR = International normalised ratio, TTR = Time in therapeutic range.

A total of ten (10.4%) patients in the AF cohort had INR values in the therapeutic range for more than 70% of the time and therefore considered to have good anticoagulation; 73 (76.1%) patients were in therapeutic range for less than 60% of the time and had suboptimal anticoagulation and at increased risk for thrombotic events and 62 (84.9% of this subset or 64.6% of all patients with AF) patients demonstrated a bad quality of anticoagulation (Figure 2).

The mean TTR in 81 patients with PHV was less than 14%. None of the patients with PHV in our study demonstrated a satisfactory quality of anticoagulation and all patients did not achieve the minimum desired level of 70% TTR.

Factors associated with time in range and time out of range

Gender

There was no difference in TTR between males and females when using either the direct or Rosendaal method (p=0.165 and p=0.640, respectively). Males with AF spent significantly more time with sub therapeutic INR values compared to females (35.5% vs. 25.5%, p=0.044). Overall, the mean TTR in patients with PHV was low and there was no gender difference demonstrated (p=0.684 and p=0.729 for the direct and Rosendaal methods, respectively).

Age

In patients with AF, the mean TTR was similar for patients less than 65 years old, 65 years to less than 75 years old and patients

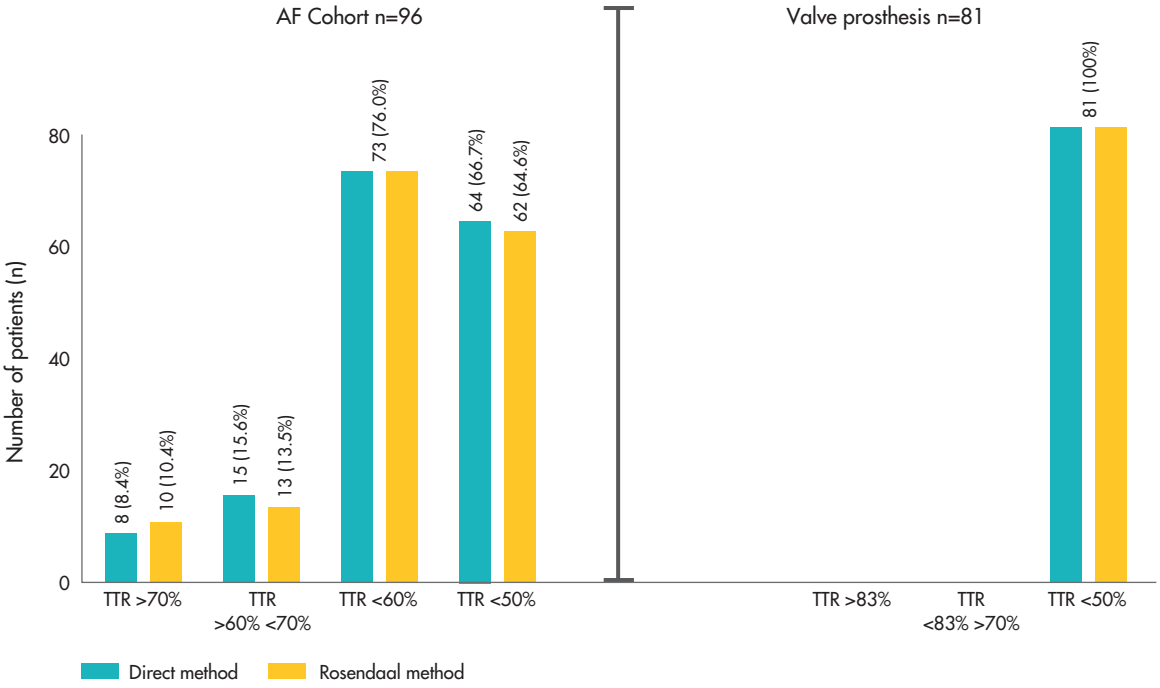

FIGURE 2: Distribution of patients in the AF cohort (n=96) and valve prosthesis cohort (n=81) according to percentage TTR according to the Direct method and the Rosendaal method. Percentages reflect that of the specific cohort.
AF = Atrial fibrillation, TTR = Time in therapeutic range.

at least 75 years old (41.7%, 40.7% and 44.7%, respectively, p-=0.794). There was no age association and TTR in patients with PHV.

INR testing frequency

In patients with AF, there was no significant association of TTR and time out of range when the INR testing intervals were considered (p=0.984, p=0.613, p=0.792, p=0.911 for TTR, time below range, above range and time above INR of 4.00 respectively). The INR testing interval was significantly associated with TTR and time out of range in patients with PHV. Analysis by the Rosendaal method, demonstrated patients who had INR tests between 28 and 32 days apart had higher TTR than those who had tests more than 32 days apart (17.4% vs. 10.4% respectively, p=0.023). Further, patients who had tests less than 28 days apart had significantly less time below range than those tested more than 32 days apart (68.7% and 74.4% respectively, p=0.030). The time above range was also significantly influenced by INR testing interval in patients with PHV; patients tested more than 32 days apart spent significantly less time above range than those tested 28 - 32 days apart (13.6% and 22.4%, p=0.030) as well as when compared to patients tested less than 28 days apart for time with an INR value exceeding 4.00 (9.3% and 18.8%, p=0.016).

INR Target range

All patients with AF constituted the subgroup of patients with a target INR of 2.0 - 3.0. Most patients with PHV had a target INR range of 3.5 - 4.0. Fourteen (17.3%) and 21 (25.9%) patients had target ranges of 2.5 - 3.0 and 3.0 - 3.5, respectively. Patients with the lowest target INR range had significantly superior TTR than those with target ranges of 2.5 - 3.0, 3.0 - 3.5 and 3.5 - 4.0 (44.5% vs. 30.0%, 12.1% and 9.4% respectively, p<0.001). Consistent with this finding, this subgroup of patients had significantly less time below range (29.2% vs. 42.6%, 70.1% and 74.2% respectively, p<0.001). However, patients with a target INR of 2.0 - 3.0 demonstrated significantly more time above range than those with highest 2 tiers of target ranges (28.4% vs. 17.9% and 15.5% respectively, p<0.05). There was no difference when evaluating time with an INR above 4.00. Similarly, patients with PHV with the lowest target range i.e., 2.5 - 3.0 demonstrated superior TTR than those with higher targets as well as less time below range and more time above range (44.5% vs. 12.1% and 9.4%, p<0.05; 29.2% vs. 70.1% and 74.2%, p<0.05; 29.9% vs. 15.5%, p<0.05 respectively) (Table III).

TABLE III: Factors associated with time in range and time out of range.

	TTR		Time out of therapeutic range		
	Direct	Rosendaal	Below	Above	INR >4.00
AF cohort (n=96)					
Gender					
Male	38.0	43.2	35.5	25.5	7.5
Female	43.9	45.1	25.5	29.8	9.9
	p=0.165	p=0.640	p=0.044	p=0.242	p=0.299
Age					
Less than 65 years old	41.7	45	26.8	30.7	7.9
65 to less than 75 years old	40.7	43.8	31.8	27.5	10.3
75 years or older	44.7	44.5	30.2	23.9	9.8
	p=0.794	p=0.959	p=0.542	p=0.352	p=0.616
Days between INR tests					
Less than 28 days apart	43.1	44.5	26.8	29.8	9.8
28 - 32 days apart	41.5	44.9	29.1	28.5	8.7
More than 32 days apart	40.1	44.1	31.9	26.8	8.9
	p=0.899	p=0.984	p=0.613	p=0.792	p=0.911
Valve prosthesis cohort (n=81)					
Gender					
Male	12.8	14.4	65.2	22.3	14.3
Female	14.1	13.4	68.6	17.2	12.9
	p=0.684	p=0.729	p=0.506	p=0.141	p=0.629
Age					
Less than 20 years old	5.0	12.5	68.5	26.6	19.1
20 - 29 years old	20.6	18.3	59.5	20.5	10.7
30 - 39 years old	15.6	11.9	70.5	16.2	11.6
40 - 49 years old	15.3	13.0	72.1	12.6	9.5
50 - 59 years old	8.3	11.3	73.6	18.0	15.8
60 years or older	10.3	15.2	64.4	25.3	20.1
	p=0.086	p=0.636	p=0.360	p=0.184	p=0.063
Days between INR tests					
Less than 28 days apart	8.9	9.6	68.7	22.4	18.8
28 - 32 days apart	16.3	17.4	61.9	21.8	15.2
More than 32 days apart	12.3	10.4	74.4	13.6	9.3
	p=0.180	p=0.023**	p=0.030*	p=0.030**	p=0.016*
INR Target range					
Target INR : 2.0 - 3.0 - n=96	41.9†§	44.5†§	29.2†§	28.4†	9.1
Target INR : 2.5 - 3.0 - n=14	28.2†	30.0†	42.6†	29.9‡	9.6
Target INR: 3.0 - 3.5 - n=21	12.0	12.1	70.1	17.9	11.1
Target INR: 3.5 - 4.0 - n=46	10.3	9.4	74.2	15.5	15.5
	p-<0.001	p<0.001	p<0.001	p<0.001	p=0.112

**Post hoc analysis Tukey HSD showed differences only between patients who were monitored less than 28 days apart and those monitored more than 32 days apart.*
***Post hoc analysis Tukey HSD revealed a significant difference only between the group being monitored from 28 - 32 days apart and those patients being monitored more than 32 days apart. §p<.05when compared to target groups 2.5 - 3.0 by Tukey HSD post hoc analysis. †p<.05 when compared to target groups 3.0 - 3.5 and 3.5 - 4.0 by Tukey HSD post hoc analysis. ‡p<.05 when compared to target group 3.5 - 4.0 by Tukey HSD post hoc analysis.*
INR = international normalised ratio, AF = Atrial fibrillation.

Adverse events

Thirty-one (17.5%) patients had at least 1 adverse event, 10 (5.6%) of whom, sustained multiple events resulting in a total of 45 documented adverse events (25.4% point prevalence). Stroke accounted for 21 of the events (46.7%) and haemorrhage or admission for over-anticoagulation the remaining 24 (53.3%) events. There were no documented cases of an obstructed prosthetic valve. Patients with AF accounted for 28 (62.2%) of the 45 adverse events, 18 (64.3%) of which were strokes. There were three strokes and 14 (82.4% of adverse

events in PHV patients) haemorrhagic or toxic events in patients with PHV.

There was no gender association in patients who sustained an adverse event or between the types of event. In patients with PHV, the mean age of patients who did not sustain an adverse event was significantly lower than patients who had at least 1 event (39.8 vs. 53.6 years, p=0.004). In patients with AF, the mean age showed no significant association with sustaining an adverse event, however, in those who did have an adverse event the mean age was significantly higher in patients who had bleeding or over-anticoagulation compared to those with stroke (74.4 years compared to 63.7 years respectively, p<0.05). The mean number of days between tests did not yield statistically significant differences when evaluating adverse events for either cohort.

Overall, the mean TTR was higher in patients with multiple events as compared to patients with only a single event (49.2% vs. 33.0%, p=0.012) however still with an undesirable TTR. There was no association in sustaining an adverse event with TTR. In the AF cohort, patients with a stroke spent significantly less time below range than those with haemorrhage or toxicity, otherwise there was no demonstrated difference for associations with time out of range and adverse events. In patients with PHV, the target INR had no statistically significant associations on adverse events (Table IV).

TABLE IV: Characteristics of the sample population, AF and valve prosthesis subgroups and adverse events.

				Adverse event sustained	
	No adverse event	**Cases with multiple events**	**Cases with at least one event**	**Stroke**	**Toxicity**
Sample (n=177)	146 (82.5%)	10 (5.6%)	31 (17.5%)	21 (46.7%)	24 (53.3%)
Male	50 (34.2%)	4 (2.2%)	5 (16.1%)	2 (19%)	8 (33.3%)
Female	96 (65.8%)	6 (3.4%)	26 (83.9%)	14 (81%)	16 (66.7%)
Mean age (years)	54.2	63.6	61.6	54.2	63.6
Mean days between tests	33.6	30.4	31.9	34.2	29.3
Mean time below range	48.3%	28.5%	39.9%	27.7%	49.4%
Mean time above range	23.2%	22.3%	27.1%	29.4%	22.6%
Mean time with INR >4.00	10.2%	12.3%	14.9%	11.7%	16.7%
Mean TTR	28.2%	49.2%†	33.0%	42.9%	28.8%
AF cohort (n=96)	77 (80.2%)	7 (7.3%)	19 (19.8%)	18 (85.7%)	10 (41.7%)
Male	30 (39%)	3 (3.1%)	3 (3.1%)	2 (22.2%)	3 (30%)
Female	47 (61%)	4 (4.2%)	16 (16.7%)	13 (77.8%)	7 (70%)
Mean age	64.2	67.8	66.6	63.7*	74.4*
Mean days between tests	31.5	31	29.1	30	27.3
Mean time below range	31.2%	17.6%	21.9%	15.6%*	32.4%
Mean time above range	27.5%	19.7%	31.9%	32.7%	24.6%
Mean time with INR >4.00	8.1%	6.6%	13.4%	10.9%	15.1%
Mean TTR	40.8%	56.0%	46.1%	51.6%	42.9%
Valve prosthesis cohort (n=81)	69 (85.2%)	3 (3.7%)	12 (14.8%)	3 (14.3%)	14(58.3%)
Male	20 (29.0%)	1 (33.3%)	2 (16.7%)	0 (0%)	5 (35.7%)
Female	49 (71.0%)	2 (66.7%)	10 (83.3%)	3 (100%)	9 (64.3%)
Mean age	39.8**	53.7	53.6	52.3	54.1
Mean days between tests	35.9	29	36.3	52	31.1
Mean time below range	67.5%	53.8%	68.5%	80.1%	64.6%
Mean time above range	18.5%	28.2%	19.3%	14.9%	20.8%
Mean time with INR >4.00	12.6%	25.7%	17.3%	14.9%	18.1%
Mean TTR	14.1%	17.9%	12.2%	4.9%	14.6%
Target INR: 2.5 - 3.0	14 (20.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Target INR: 3.0 - 3.5	16 (23.2%)	1 (33.3%)	5 (41.7%)	0 (0%)	6 (42.9%)
Target INR: 3.5 - 4.0	39 (56.5%)	2 (66.7%)	7 (58.3%)	3 (100%)	8 (57.1%)

**- p<.05 when compared to patients with haemorrhage or toxicity. **-p =.004 when compared to patients who sustained at least one adverse event. †p=0.012 when compared to patients with only one event.*

AF = Atrial fibrillation, TTR = Time in therapeutic range, INR = International normalised ratio.

DISCUSSION

The Global Burden of Disease study reported a male predominance of AF.[12] In contrast, females in our study constituted almost twice as many as males (65.6% vs. 34.4) and this finding was comparable to 2 South African studies evaluating patients on warfarin.[13,14] In the larger ROCKET-AF trial only 124 (2%) of the 6 983 patients were from South Africa;[10] 98 patients of the 6 706 patients represented South Africa in the ACTIVE-W study[5] and therefore the South African context may be less understood. In the South African context, women visit health centres more often and this coupled with the higher employment percentage of men over women may explain why women are higher represented in these studies. Nonetheless, the clinical implications of a female predominance in patients with AF confers the increased stroke risk consistent with CHA_2DS_2-Vasc risk scoring. The mean age of patients with PHV is lower than those studied internationally and this is likely explained by the high prevalence of rheumatic heart disease as compared to high income regions which report a higher prevalence of degenerative valve lesions.[15]

The direct and the Rosendaal methods correlated well; this is consistent with reports of Caldeira, et al. in a study of 377 patients and the meta-analysis by Wan, et al. where a good correlation between the two methods was demonstrated. [9,16]

Patients with AF had a significantly higher TTR than those with PHV AuriculA, a Swedish study, evaluated INRs from 18 391 patients in 67 different centres which reported patients with AF had a mean TTR of 76.5% and those with mechanical valves a TTR of 79.9%.[17] These findings contrast to those in our study although some study design differences exist; the participants from AuriculA were not exclusively managed out of specialised anticoagulation clinics and that study utilised only a low target INR range of 2 - 3. Furthermore, AF represented most of the patients (64%) and heart valve dysfunction accounted for 13% whereas our study had almost equal representation and a higher female representation.

Only 10.4% of patients with AF had a TTR better than 70%. The ACTIVE-W,[5] ROCKET-AF,[10] ARISTOTLE[18] and RE-LY[19] were randomised controlled trials (RCT) which reported a mean TTR superior to that in our patients, however, the South African patients in these studies demonstrated less impressive TTR and is closer in line to our findings. In a South African study conducted at an anticoagulation clinic the mean TTR was 48.5%.[14] Other studies which demonstrated superior mean TTR (69.7%) included the STABLE trial, which evaluated self-monitoring.[20] However, our study evaluated patients in a usual care setting, not as part of a specialised anticoagulation clinic

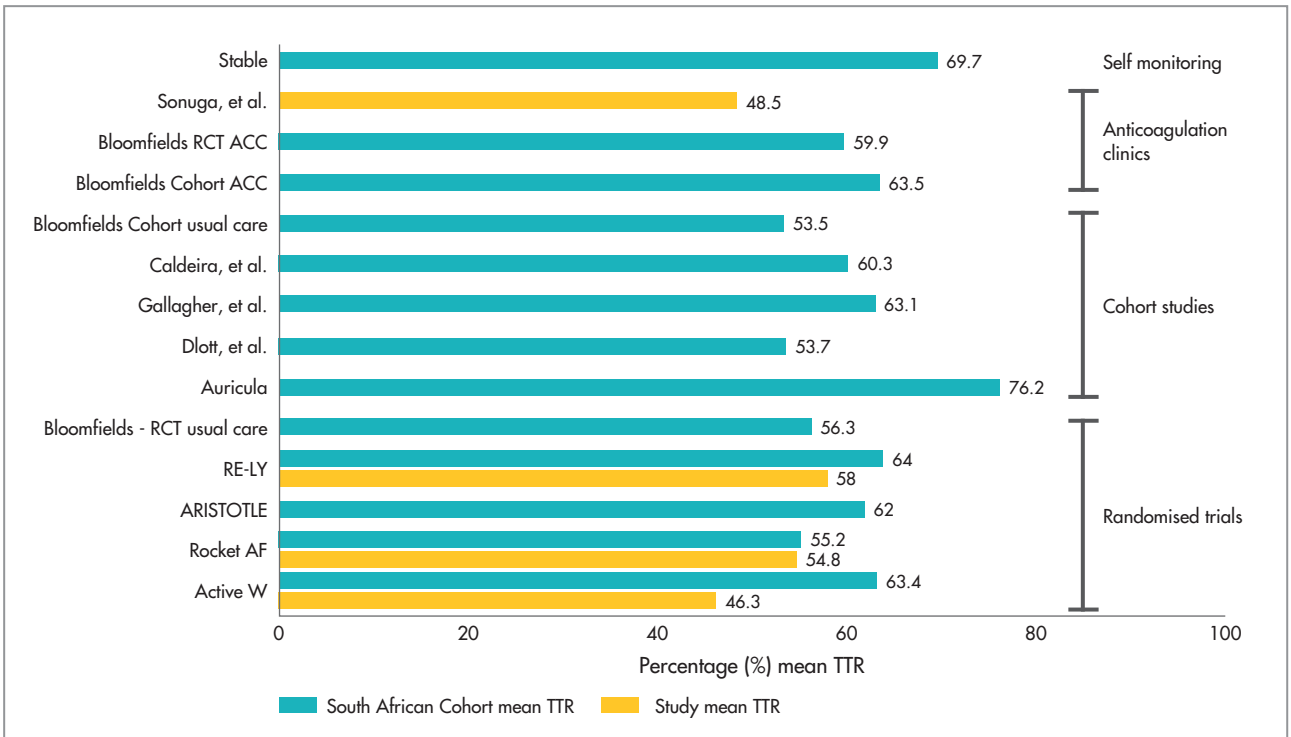

FIGURE 3: Comparisons of TTR from different studies.

and represents a real-life analysis and not part of an RCT, all of which may be significant factors contributing to poorer TTR. Bloomfields RCT demonstrated superior TTR in patients attending specialised anticoagulation clinics as compared to usual care.[21] Overall, the TTR is poorer in African countries compared to the European and Western Regions. This difference is likely contributed by the burden of communicable diseases and over-extended health care budgets and challenging socioeconomic conditions (Figure 3).

Patients with PHV demonstrated especially poor results with a mean TTR of less than 14% and all patients were categorised with suboptimal anticoagulation. Patients in this category were on average younger, had higher target INR values and had a more female representation, all of which are validated factors associated with poor quality of anticoagulation.

Studies that evaluated factors impacting on TTR included Apostolakis, et al., which evaluated 4 060 patients with AF from the AFFIRM trial and reported female gender and a younger age to be associated with poor anticoagulation.[22] Dlott, et al., identified 138 319 individuals with AF and found females had lower TTR than males and reported a significantly better mean TTR in patients aged 75 years or older than those who were 45 years or younger. They also found INR testing frequency was positively associated with TTR among patients with fewer than 14 INR tests per year, but inversely associated with TTR among those with more frequent testing.[23] Rose, et al., in their US study, enrolled 3 396 patients from 101 community-based practices in 38 states and found a trend of poorer anticoagulation quality in females but similar mean ages for patients with variable TTR and reported longer INR monitoring intervals to be associated with improved INR control. Further, they noted patients in the low target group had a lower mean percentage TTR than those with normal INR target range.[24] The STABLE study evaluated 29 457 patients who performed home monitoring and reported higher TTR in patients aged 65 to less than 75 years old compared to patients between 46 - 64 years as well as in patients with more frequent INR testing.[20] Overall, patients in our study population had neither statistically significant gender nor age association to TTR and time out of range. These findings are neither in line with the findings of Apostolakis, et al., Dlott, et al., Rose, et al. nor to the reports of the STABLE study. This may be due to the female representation in our study contrasting with the global reported prevalence; however, this finding is likely a result of the overall poor TTR across all age groups in our population.

Patients with PHV demonstrated a superior TTR if monitored more frequently, which is in line with the findings from The Home INR Study (THINRS)[25] and the STABLE study. However, this was not consistent in patients with AF. Patients at our location are prescribed warfarin for a maximum of 28 days before prescription-renewal and it is likely that there were periods with no anticoagulation, and this is probably the reason for low INR values in patients tested less frequently. It is probable that patients identified as being poorly anticoagulated or at high risk for adverse events may have been monitored more frequently.

Patients with the lowest target range had a superior TTR than patients with higher targets. This is contrary to the findings from the study by Rose, et al., where patients in the low target group had a lower mean percentage TTR than those with normal INR target range. However, the study by Rose, et al., was conducted on patients with AF and not with prosthetic valves and the target INR ranges were lower than for the patients with valve prostheses in this study. Our findings suggest that patients with low target ranges are easier to achieve effective anticoagulation but are also at risk for over-anticoagulation and therefore bleeding.

Patients with AF sustained most of the adverse events, with the majority being stroke. Patients with PHV in our study had 14 bleeding events and 3 stroke events. In the AuriculA trial, the frequency of bleeding events was 2.03% and 1.36% for thrombosis for the whole study population. The AF subgroup in that study demonstrated 2.13% cases of bleeding and 1.16% of the total AF subgroup accounted for thrombotic events. The subgroup with heart valve dysfunction demonstrated 2.01% of bleeding and 2.35% of thrombosis. Connolly, et al., evaluated a regional influence using data from the ACTIVE-W trial.[5] Sonuga, et al., studied 136 patients attending an anticoagulation clinic in Cape Town, South Africa, of which 14% had bleeding events and 2.2% had thrombotic events.[14] While the high prevalence of adverse events in our study is closer to other South African samples, there are some differences between the studies. The participants in AuriculA demonstrated a much higher TTR (mean of 74.9%) than our patients. The AF cohort in AuriculA was not exclusively comprised of non-valvular AF and the patients in their valve disease subgroup included participants not limited to mechanical prosthetic valves. The ACTIVE-W included myocardial infarction and death in their count of events.

Interestingly, despite most of the patients with PHV having high percentage time below range, there were no documented events of valve thrombosis. The most likely reason is that valve thrombosis is rare and patients most susceptible to this event are those within the first 6 months of implantation. In our study, we evaluated patients on warfarin for at least 1 year and therefore the findings may not be inclusive of such patients. Furthermore, given the devastating effect of valve thrombosis and high risk of mortality, we may not have included these patients as we enrolled participants based on their attendance.

STUDY LIMITATIONS

The main limitation of this study was that it was retrospective and single centre based and may not be entirely representative for a region. It is, however, to the best of our knowledge the first study evaluating the quality of anticoagulation in a community-based and usual care setting for both AF and PHV in KwaZulu-Natal. Only outpatient folders were analysed and therefore INR values registered in inpatient files or at other facilities were not included as these would not constitute usual care. The patient population was derived from record keeping of INR sampling and therefore only live cases were analysed. As a result, we were unable to evaluate for associated mortality which remains the most important clinically relevant outcome. Nonetheless, we believe this method of sample recruitment remains the best to achieve the most real-life representation of anticoagulated patients in community practice.

Adverse events were reliant on the documentation of such by the attending clinician and this may have resulted in under-representation of events. The most important limitations in evaluating events however, was the lack of documented neuro-imaging findings and we were therefore unable to establish any stroke as ischaemic or haemorrhagic and the study design precluded us from accurately evaluating for haemorrhage as defined by the International Society of Thrombosis and Haemostasis guidelines[26] and this may have over-reported the number of major bleeding events. The data did not include some factors that are known to affect TTR like patient education on warfarin use, patient compliance, concomitant drug use, socioeconomic conditions, ethnicity, tobacco use, alcohol use, warfarin resistance and lastly, although age was used as factor conferring high risk in AF, a complete CHA_2DS_2-Vasc assessment was not performed.

CONCLUSIONS

Non-valvular AF and PHV accounted for most cases requiring warfarin therapy. There is a poor quality of anticoagulation in AF and patients with PHV demonstrated especially poorer results. The study demonstrates a major gap in quality of anticoagulation compared to developed regions and confirms that most patients are not achieving the recommended minimum TTR of 60%. The fraction of INRs is a reasonable method for evaluating TTR and correlates well with the Rosendaal method. The lack of gender or age association with TTR suggest that in our region, both males and females, regardless of age have equally high risk for poor anticoagulation and therefore adverse events. A variable follow-up period based on recent INR results should replace fixed testing periods. Patients with the highest target ranges have the highest risk of inadequate anticoagulation and may need closer monitoring. Further research is required to determine the factors contributing to poor anticoagulation in this population. Some considerations to improve the quality of anticoagulation include using a dedicated and specialised anticoagulation clinic, the use of point-of-care devices, adjustment of visit frequencies and perhaps the use of direct acting anticoagulants.

ACKNOWLEDGEMENTS

We thank the National Health Laboratory Services for providing laboratory logbooks and INR results.

Conflict of interest: none declared.

REFERENCES

1. Keeling D, Baglin T, Tait C, et al., British Committee for Standard in Haematology. Guidelines on oral anticoagulation with warfarin – fourth edition. British Journal of Haematology 2011;154(3):311-324.
2. Schmitt L, Speckman J, Ansell J. Quality assessment of anticoagulation dose management: Comparative evaluation of measures of time-in-therapeutic range. Journal of Thrombosis and Thrombolysis 2003;15(3):213-216.
3. Lane DA, Lip GYH. Quality of anticoagulation control in atrial fibrillation. Lancet 2010;376(9745):935-937.
4. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: Observing outcomes associated with varying levels of INR control. Thrombosis Research 2009; 124(1):37-41.
5. Connolly SJ, Pogue J, Eikelboom J, et al., ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalised ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118(20):2029-2037.
6. Pibarot P, Dumesnil JG. Prosthetic heart valves: Selection of the optimal prosthesis and long-term management. Circulation 2009;119(7):1034-1048.
7. Grzymala-Lubanski B, Labaf A, Englund E, Svensson PJ, Sjalander A. A mechanical heart valve prosthesis and warfarin - treatment quality and prognosis. Thrombosis Research 2014;133(5):795-798.
8. White HD, Gruber M, Feyzi J, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: Results from SPORTIF III and V. Archives of Internal Medicine 2007;167(3):239-245.
9. Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: A systematic review. Circulation Cardiovascular Quality and Outcomes 2008;1(2):84-91.
10. Singer DE, Hellkamp AS, Piccini JP, et al., ROCKET AF Investigators. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: Data from the ROCKET AF clinical trial. Journal of the American Heart Association 2013;2(1):e000067.
11. Lopes RD, Crowley MJ, Shah BR, et al. Stroke prevention in atrial fibrillation. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Aug. Report No.:13-EHC113-EF.
12. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 Study. Circulation 2014;129(8):837-847.
13. Njovane XW, Fasinu PS, Rosenkranz B. Comparative evaluation of warfarin utilisation in two primary healthcare clinics in the Cape Town area. Cardiovascular Journal of Africa 2013;24(2):19-23.
14. Sonuga BO, Hellenberg DA, Cupido CS, Jaeger C. Profile and anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. African Journal of Primary Health Care & Family Medicine 2016;8(1):e1-e8.
15. Mayosi BM. 2016 National rheumatic fever week: The status of rheumatic heart disease in South Africa. South African Medical Journal 2016;106(8): 740-741.
16. Caldeira D, Cruz I, Morgado G, et al. Is the time in therapeutic range using the ratio of tests equivalent to the Rosendaal method? Blood coagulation & fibrinolysis: Blood Coagulation and Fibrinolysis 2015;26(8):972-976.
17. Wieloch M, Själander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden: Reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. European Heart Journal 2011;32(18):2282-2289.
18. Wallentin L, Lopes RD, Hanna M, et al. Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Investigators. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalised ratio control for stroke prevention in atrial fibrillation. Circulation 2013;127(22):2166-2176.
19. Camm AJ. The RE-LY study: Randomised Evaluation of Long-term anti-coagulant therapy: Dabigatran vs. warfarin. European Heart Journal 2009; 30(21):2554-2555.
20. DeSantis G, Hogan-Schlientz J, Liska G, et al. STABLE results: Warfarin home monitoring achieves excellent INR control. The American Journal of Managed Care 2014; 20(3):202-209.
21. Bloomfield HE, Taylor BC, Krause A, et al. In safe and effective anticoagulation in the outpatient setting: A systematic review of the evidence. VA Evidence-based Synthesis Programme Reports. Washington (DC): Department of Veterans Affairs (US); 2011 Feb.
22. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: The SAMe-TT(2)R(2) score. Chest 2013;144(5):1555-1563.
23. Dlott JS, George RA, Huang X, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. Circulation 2014;129(13):1407-1414.
24. Rose AJ, Ozonoff A, Henault LE, Hylek EM. Warfarin for atrial fibrillation in community-based practise. Journal of Thrombosis and Haemostasis 2008; 6(10):1647-1654.
25. Matchar DB, Jacobson AK, Edson RG, et al. The impact of patient self-testing of prothrombin time for managing anticoagulation: Rationale and design of VA cooperative study #481 – the Home INR Study (THINRS). Journal of Thrombosis and Thrombolysis 2005;19(3):163-172.
26. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Tthrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis 2005;3(4):692-694.