Evaluation of Anticoagulation Outcome among Patients Taking Warfarin: A Single-Center Experience, Northwest Ethiopia

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Research

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Abstract

Background

Warfarin is a widely used oral anticoagulant in clinical practice. It is used to prevent arterial emboli in patients with atrial fibrillation, or prevent and treat venous thromboembolism. The efficacy and safety of warfarin depends on maintaining the INR within the therapeutic range. The proportion of time spent in the therapeutic INR range (TTR) is used to evaluate quality of anticoagulation control.

Methods

A hospital-based cross sectional study was conducted between November 1, 2019 and October 31, 2020 at Cardiac and Hematology Clinic, University of Gondar hospital. A consecutive sampling method was used to recruit 338 study subjects. Proportion of time spent in the therapeutic range (TTR) was calculated using the Rosendaal's linear interpolation method. TTR ≥65% was described as 'optimal' International Normalized Ratio (INR) control. The Data were entered into EPI Info version 4.4.1 and transported to SPSS version 20 for analysis. Logistic regression analysis was used to identify associated factors with optimal anticoagulation outcome (TTR ≥65%). P-values <0.05 were used to declare significant association.

Result

A total of 338 study subjects were included in the study. The mean age of patients was 49 years. The majority of study participants attended formal education (79%) and were urban dwellers (57%). Atrial fibrillation was the commonest indication for warfarin therapy. One-third (33%) of study subjects achieved the desired INRs (INR=2.0-3.0), while about one-tenth (13%) of patients attained optimal INR control (TTR≥65%). There were no significant association of socio-demographic characteristics including age, gender, educational level and monthly income with optimal INR control (TTR ≥65%). Likewise, clinical characteristics including dose of warfarin, warfarin adherence, frequency of INR determination, other concomitant drug intake, co-existing comorbidities, consumption of green leafy vegetables and alcohol intake didn't show significant association with optimal INR control (TTR≥65%).

Conclusion

Institution-based validated protocol might be required to overcome the poor TTR level. 'Anticoagulation (INR) clinic' would be required to 'scale-up' INR control.

Background

Warfarin is the widely prescribed oral anticoagulant in clinical practice. It is used to prevent arterial emboli in patients with atrial fibrillation, or prevent and treat venous thromboembolism (1-4). Warfarin has variable dose response and narrow therapeutic window, and thus requires frequent and regular international normalized ratio (INR) monitoring (3,4). The proportion of time spent in the therapeutic INR

range (TTR) is interpreted as the duration of time in which patient's INR values lie within the desired INR range (INR=2.0-3.0). It is used to evaluate quality of anticoagulation control. TTR ≥65% of the follow-up time is required to declare 'optimal' INR control. TTR< 65% increases the risk of thromboembolic or bleeding episodes (5,7,11,13,14). Global studies documented that old age, obese individuals, dietary habits and other drugs intake, excessive alcohol consumption, renal or hepatic dysfunction were among the listed causes of poor INR control (TTR<65%) (8,9,11,13,19-24). The aim of the study is to determine the TTR and associated factors among patients taking warfarin in hospital setting, Northwest Ethiopia.

Methods

Study design and setting

A hospital-based cross sectional study was conducted between November 1, 2019 and October 31, 2020 at Cardiac and Hematology Clinic, University of Gondar hospital. The hospital is located in Northwest Ethiopia, which is 750 km away from the capital, Addis Ababa. The hospital had a catchment population of 5 million people.

Study subjects and variables

Study subjects

Patients older than 18 years old, and were on warfarin with follow up at Cardiac and Hematology Clinic, University of Gondar hospital were considered as study population.

Patients older than 18 years old, who were on warfarin for at least 6 months, had at least six INR determinations with each consecutive INR determination ≤ 56 days apart were included in the study. Frequent records of INR at first month of drug initiation or during dose adjustments were excluded until stable INR values were obtained.

Study variables

Dependent variables: Proportion of time spent in the therapeutic INR range (TTR)

Independent variables: 1) Socio-demographic characteristics include age, gender, occupation, marital status, educational level, income level, residence and religion .2) Clinical characteristics include indication for warfarin, warfarin dosage, warfarin-plus drugs intake, adherence to warfarin, frequency of INR monitoring, co-existing comorbidities, nutritional status, alcohol intake and dietary habits.

Sample size and sampling procedure

The sample size was calculated using single population proportion formula with the assumption of 95% confidence level, 5% margin of error, and taking 30% for TTR in sub-Saharan African region. Consecutive sampling method was used to recruit 338 study subjects.

Data collection instrument and procedures

Data were collected through an investigator administered pre-designed questionnaire. The questionnaire was prepared in English and translated into local language (Amharic) for data collection, and then re-translated back to English with maintaining its consistency. Patients were interviewed to obtain socio-demographic data. Relevant medical history and laboratory parameters were obtained from patients' records.

The proportion of INRs within the therapeutic range of 2.0-3.0 was calculated as number of INRs within the therapeutic range divided by the total number of INR measurements. TTR was calculated using Rosendaal's method, which used linear interpolation to assign an INR value to each day between successive observed INR values. The individual TTR determined the proportion of time spent in the therapeutic range of 2.0-3.0 for each patient. Those individuals with TTR ≥65% were declared to achieve 'optimal' INR control.

Data analysis

Data were entered into EPI Info version 4.4.1 and transported to SPSS version 20 for analysis.

Patient characteristics were reported as counts (percentages) for categorical variables, and mean with standard deviation for continuous variables. Bi-variable and multi-variable logistic regression models were constructed to identify independently associated factors with optimal INR control (TTR ≥65%). Those variables with a P-value < 0.25 in the bi-variate analysis were exported to multi-variate analysis to control the possible effect of confounders. Crude odds ratio (COR) and adjusted odds ratio (AOR) were reported. P-values < 0.05 were used to declare significant association.

Ethical considerations

The research protocol complied with Declaration of Helsinki and was approved by local ethics committee. Study subjects were recruited only after informed written consent was obtained. All data obtained were treated confidentially. During the data collection process, those patients who were found to have atrial fibrillation and venous thromboembolism were taken care of as per the recommendations of AHA/ACC guideline and American Society of Hematology guideline respectively.

Definition of terms

TTR (proportion of time spent in the therapeutic range): The duration of time in which the patient's international normalized range (INR) values were within a desired range (INR = 2.0–3.0).

Chronic kidney disease: Abnormalities of kidney structure or function present for more than 3 months, with implications for health. Diagnosis of chronic kidney disease was settled by clinical, biochemical (raised serum creatinine) and/or imaging (ultrasound-proven reduced kidney size) findings.

Chronic liver disease: Distorted liver architecture and decreased hepatic function as a result of chronic inflammation leading to chronic hepatitis or hepatic cirrhosis. Diagnosis was settled by ultrasound-evidenced liver surface irregularity and/or elevated serum transaminase >3x upper limit of normal.

Heart failure: Clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The Framingham criteria were used to diagnose heart failure.

Hyperthyroidism: Clinical state that involves excess synthesis and secretion of thyroid hormones by the thyroid gland. Diagnosis of hyperthyroidism was made in the presence of suggestive clinical symptoms and signs including enlarged thyroid gland, and confirmed by radioimmunoassay (RIA) test revealing low serum TSH and/or raised free T3/T4.

Results

Socio-demographic characteristics of study participants

A total of 338 patients taking warfarin, who had follow-up at Cardiac and Hematology Clinic, university of Gondar hospital were included in the study. The mean age of study subjects was 49 years. The majority of study participants were females (64%), married (73%) and urban dwellers (57%). Most respondents were Christian by religion (86%), and attended formal education (79%) (Table-1).

Clinical characteristics of study participants

Three-quarters (75%) of patients received warfarin for atrial fibrillation (Figure-1). More than half (59%) of patients were taking warfarin < 5 mg daily. Most patients (90%) received other concomitant drugs like anti-hypertensive drugs, anti-platelets, lipid lowering drugs (statins), anti-thyroid drug (PTU) and anti-retroviral drugs (ART). Most patients (84%) got INR determination every month. Heart failure and hyperthyroidism was detected in 43% and 15% of patients respectively. One-third (36%) of patients often consumed green leafy vegetables. Most (82%) patients never had alcohol intake (Table-2).

Proportion of INRs and Time in Therapeutic Ranges

The mean proportion of INRs and TTR obtained from the study were shown in Figure-2 and 3. One-third (33%) of study subjects achieved the proportion of INRs within the therapeutic range, while about one-tenth (13%) of patients attained optimal INR control (TTR≥65%). A quarter (25%) of patients on warfarin experienced bleeding episodes like epistaxis and vaginal bleeding, which required weekly INR determination and dose adjustment. Among those with bleeding episodes, 90% of patients had TTR < 65 %, and the remaining 10% had TTR ≥ 65 %.

Factors associated with TTR <65% or ≥65%

On bi-variable analysis, venous thromboembolism as indication for warfarin therapy was found to have significant association with TTR ≥65% (COR=0.135, 95% CI: 0.02-0.99, P-value=0.049), but not found to

be significant on multivariable analysis. Multi-variable analysis didn't reveal significant association of socio-demographic characteristics including age, gender, educational level and monthly income with optimal INR control (TTR ≥65%). By the same token, clinical characteristics including dose of warfarin, warfarin adherence, frequency of INR determination, other concomitant drug intake, co-existing comorbidities, consumption of green leafy vegetables and alcohol intake didn't show significant association with optimal INR control (TTR≥65%) (Table-3).

Discussion

A total of 338 patients who were taking warfarin were included in the study. Atrial fibrillation (75%) was the commonest indication for warfarin therapy. Atrial fibrillation, prosthetic heart valves, and venous thromboembolism were the shared indications for anticoagulation in sub-Saharan African settings (14-17). Studies from United States and Europe had shown the proportions of desired INRs (INR=2.0-3.0) and TTR ≥65% were 50-70% and 40-60% respectively (7-11). Likewise, it was 40-50% and 30-40% respectively in Middle-Income countries (12,13). Sub-Saharan African studies indicated that 30-40% and 15-25% were reported magnitude of desired INRs and TTR ≥65% respectively (14-18). In this study, one-third of study subjects (33%) achieved mean desired INRs, while about one-tenth (13%) of patients attained TTR ≥65%. The finding in this study showed 'poor' anticoagulation outcome, congruent with reports from other sub-Saharan African countries. Half of the patients attained sub-therapeutic INR range (INR<2.0) and were taking warfarin < 5 mg daily, which might explain physicians' less comfort on up-titration of warfarin dose. Lack of an institution validated protocol for warfarin dosage titration might contribute to poor INR outcome. A quarter (25%) of patients experienced bleeding episodes. Most (90%) bleeding episodes occurred among those who had poor INR control. African studies reported that 14-17% of patients bled while on warfarin therapy (15,20). Western literatures documented 'optimal' INR control prevents bleeding episodes and thrombotic events (2,4,5,7,10). Bi-variable analysis showed 'indication of warfarin' for venous thromboembolism was significantly associated with good INR control, which might be explained by appropriate adherence to warfarin among those who required warfarin for limited period. There were no significant association of socio-demographic characteristics including age, gender, educational level and monthly income with optimal INR outcome (TTR≥65%). Likewise, clinical characteristics including dose of warfarin, warfarin adherence, frequency of INR determination, other concomitant drug intake, coexisting comorbidities, consumption of green leafy vegetables and alcohol intake didn't show significant association with optimal INR control. Global studies documented that old age, obese individuals, other concomitant drug intake, excessive alcohol intake, renal or hepatic dysfunction were among listed causes of poor INR control (TTR<65%) (8-13,19-24). Novel oral anticoagulants (NOACs) are recently introduced anticoagulants, which have a number of advantages over warfarin, despite limited access, cost issue and availability of antidote. NOACs are prescribed in fixed doses, have fewer interactions with food and drugs, and do not require routine anticoagulant monitoring. Their use might be considered for eligible patients with atrial fibrillation and venous thromboembolism (9,11-13,16,18).

Limitation of the study

Selection bias couldn't be avoided as consecutive sampling method was used to recruit study subjects.

Conclusion

One-third (33%) of patients taking warfarin achieved therapeutic INR range (INR=2.0-3.0). Majority (87%) of patients had poor INR control (TTR<65%). One-fourth (25%) of patients experienced adverse bleeding episodes.

Recommendation

The authors recommend large scale prospective study to determine risk factors for poor INR control (TTR<65%) in Ethiopia. Institution-based validated protocol might be required to overcome the poor TTR level. "Anticoagulation (INR) clinic' would be required to 'scale-up' INR control.

Declarations

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Authors' contributions

ZL contributed to the conception, design, data collection, analysis, writing, and review of the manuscript. AT contributed to the conception, design, analysis, writing and review of the manuscript. NB and TT contributed to conception, design, analysis and review of the manuscript. All authors read and approved the final manuscript and approved its submission for publication.

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Availability of data and materials

All data generated and analyzed are included in this research article.

Ethics approval and consent to participate

Ethical approval was obtained from the Institutional Review Board of College of Medicine and Health Sciences, University of Gondar. Formal letter of permission was obtained from University of Gondar hospital administrative body. Study subjects were recruited only after informed written consent was obtained.

Consent for publication

NA

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1: Socio-demographic characteristics of patients taking warfarin in University of Gondar hospital, Northwest Ethiopia, November 1, 2019 to October 31, 2020 (n=338)

Variables	Frequency (No.)	Percentage (%)
Age (years)		
< 40 Years	115	34.0
40-60 years	110	32.5
>60 Years	113	33.5
Gender		
Male	121	35.8
Female	217	64.2
Residence		
Urban	193	57.1
Rural	145	42.9
Religion		
Christian	290	85.8
Muslim	48	14.2
Marital status		
Single	61	18.0
Married	247	73.1
Others	30	8.9
Educational level		
Can't read and write	71	21.0
Can read and write	103	30.5
Elementary school	51	15.1
Secondary school	64	18.9
College and above	49	14.5
Occupation		
Government employee	39	11.5
Merchant	61	18.0
House wife	127	37.6
Farmer	73	21.6
Student	38	11.3
Monthly income (in Birr)		
<1500	183	54.1
1500-3000	85	25.1
>3000	70	20.8

Table 2: Clinical characteristics of patients taking warfarin in University of Gondar hospital, Northwest Ethiopia, November 1, 2019 to October 31, 2020 (n=338)

Clinical characteristics	Frequency (No.)	Percentage (%)
BMI (kg/M^2)		
<18.5	29	8.6
18.5-24.9	229	67.8
≥25.0	80	23.6
Indication for warfarin		
Atrial fibrillation	252	74.6
Venous thromboembolism	72	21.3
Others	14	4.1
Dose of warfarin		
< 5 mg, daily	199	58.9
5 mg, daily	118	34.9
>5 mg, daily	21	6.2
Ever missed warfarin dose		
Yes	42	12.4
No	296	87.6
Warfarin-plus drugs use		
Yes	305	90.2
No	33	9.8
Frequency of INR monitoring		
Every 2 weeks	32	9.5
Every 1 month	283	83.7
Every 2 months	23	6.8
Alcohol intake		
Yes	61	18.0
No	277	82.0
Often use leafy vegetables		
Yes	122	36.1
No	216	63.9
LFT (serum ALT)		
Normal ALT	138	40.8
Raised ALT	17	5.0
Unknown	183	54.2
RFT (serum Cr)		
Normal Cr	212	62.7
Raised Cr	29	8.6
Unknown	97	28.7
Heart failure		
Yes	144	42.6
No	194	57.4
Hyperthyroidism		
Yes	46	13.6
No	292	86.4

NB:, ALT, alanine aminotransferase; BMI, body mass index, Cr, creatinine; GFR, glomerular filtration rate; LFT, liver function test; RFT, renal function test

Table 3: Bivariate and multivariate regression analysis of time in therapeutic INR range (TTR) among patients taking warfarin in University of Gondar, Northwest Ethiopia, November 1, 2019 to October 31, 2020 (n=338)

Variables	TTR		COR (CI)	AOR (CI)	P-value
	TTR<65%	TTR≥65%			
Age					
<40 years	100	15	1.04 (0.48, 2.27)	0.45 (0.13, 1.59)	0.214
40-60 years	97	13	0.94 (0.42, 2.12)	0.73 (0.28, 1.90)	0.515
>60 years	99	14	1		
Gender					
Male	103	18	1		
Female	193	24	1.41 (0.73, 2.71)	1.23 (0.55, 2.76)	0.617
Marital status					
Single	50	11	1		
Married	218	28	1.98 (0.51, 7.71)	1.77 (0.24, 13.29)	0.579
Others	27	3	1.15 (0.33, 4.04)	1.70 (0.44, 6.58)	0.442
Monthly income					
<1500 birr	157	26	1		
1500-3000 birr	77	8	1.28 (0.55, 2.99)		
>3000 birr	62	8	0.81 (0.29, 2.27)		
Educational level					
Can't read and write	61	10	1		
Can read and write	91	12	1.80 (0.53, 6.12)		
Elementary school	45	6	1.45 (0.44, 4.76)		
Secondary school	54	10	1.47 (0.39, 5.56)		
College and above	44	4	2.04 (0.60, 6.94)		
Residence					
Urban	170	23	0.89 (0.47, 1.72)		
Rural	126	19	1		
BMI (kg/M^2)					
<18.5	25	4	1		
18.5-24.9	199	30	1.44 (0.39, 5.19)		
≥25	72	8	1.36 (0.59, 3.09)		
Indication for warfarin					
Atrial fibrillation	222	30	1		
VTE	64	8	0.14 (0.02, 0.99)	0.49 (0.11, 2.14)	0.341
Others	10	4	0.31 (0.08, 1.23)	0.48 (0.09, 2.51)	0.386
Dose of warfarin					
< 5mg daily	181	18	1		
5 mg daily	98	20	0.39 (0.12, 1.32)	0.40 (0.09, 1.64)	0.206
>5 mg daily	17	4	0.91 (0.28, 2.98)	0.94 (0.24, 3.74)	0.930
Ever missed VKA dose					
Yes	40	2	1		
No	266	30	2.26 (0.52, 9.81)	1.9 (0.99, 9.21)	0.426
VKA-plus drugs use					
Yes	268	37	1		
No	28	5	1,29 (0.47, 3.56)		
Frequency of INR monitoring					
Every 2 weeks	28	4	0.68 (0.15, 3.05)		
Every 1 month	249	34	0.68 (0.15, 3.05)		
Every 2 months	19	4	1		
Alcohol intake					
Yes	54	6	1		
No	241	36	1.34 (0.54, 3.34)		
Often use leafy vegetables (≥ 3x weekly)					
Yes	105	17	1		
No	191	25	0.80 (0.41, 1.56)		
Liver function tests					
Normal	122	16	1		
Abnormal	14	3	0.91 (0.46, 1.80)		
Unknown	160	23	1.49 (0.39, 5.59)		
Renal function test (GFR)					
Normal	184	28	1		
Reduced	25	4	1.32 (0.62, 2.85)		
Unknown	87	10	1.39 (0.40, 4.82)		
Heart failure					
Yes	130	14	1		
No	166	28	0.64 (0.32, 1.26)	1.59 (0.69, 3.68)	0.276
Hyperthyroidism					
Yes	45	6	1		
No	251	36	0.93 (0.37, 2.33)		

NB: BMI, body mass index; VKA, vitamin K antagonist; VTE, venous thromboembolism

Figures

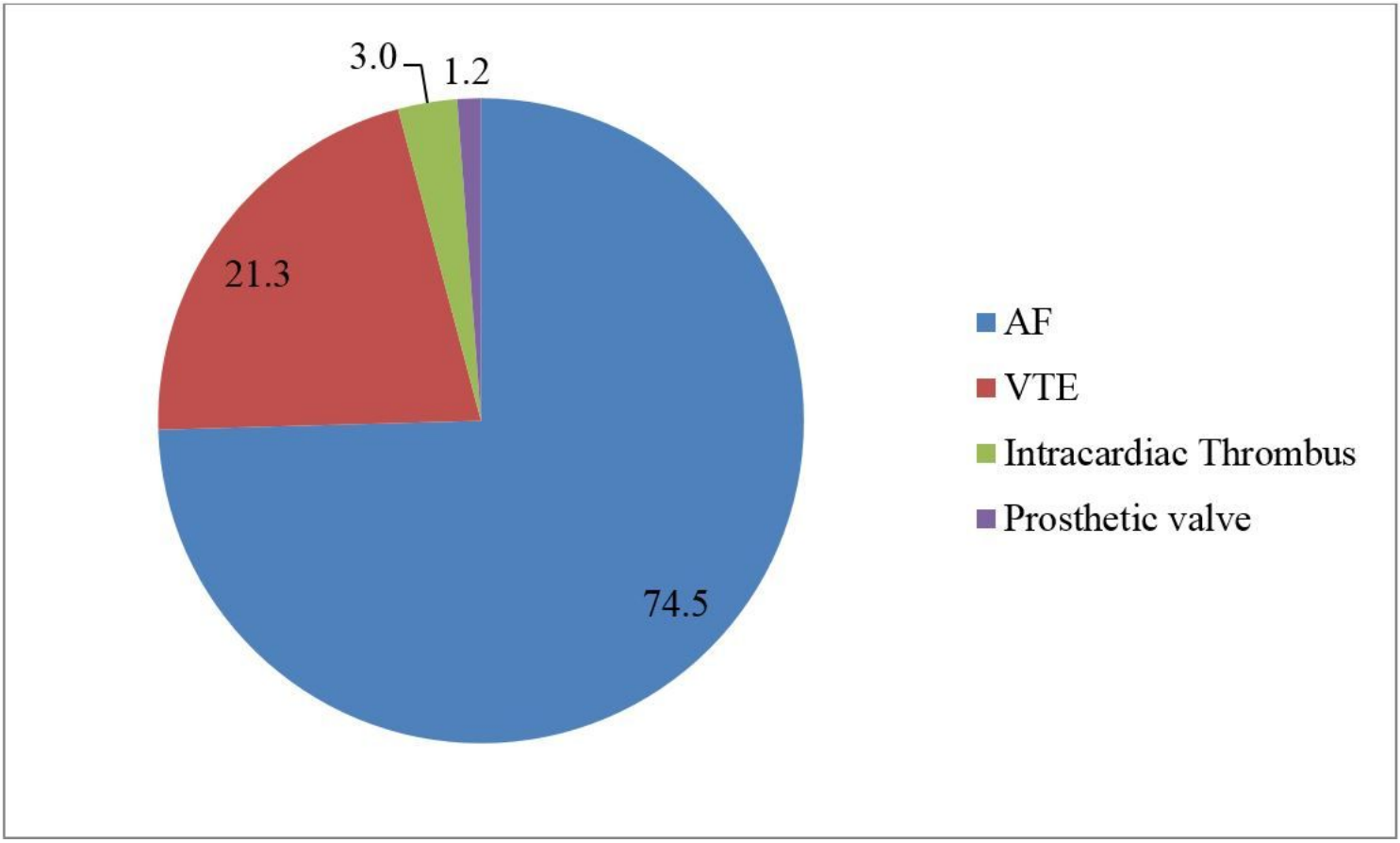

Figure 1

Pie chart for indication of warfarin therapy. NB: AF, atrial fibrillation; VTE, venous thromboembolism;

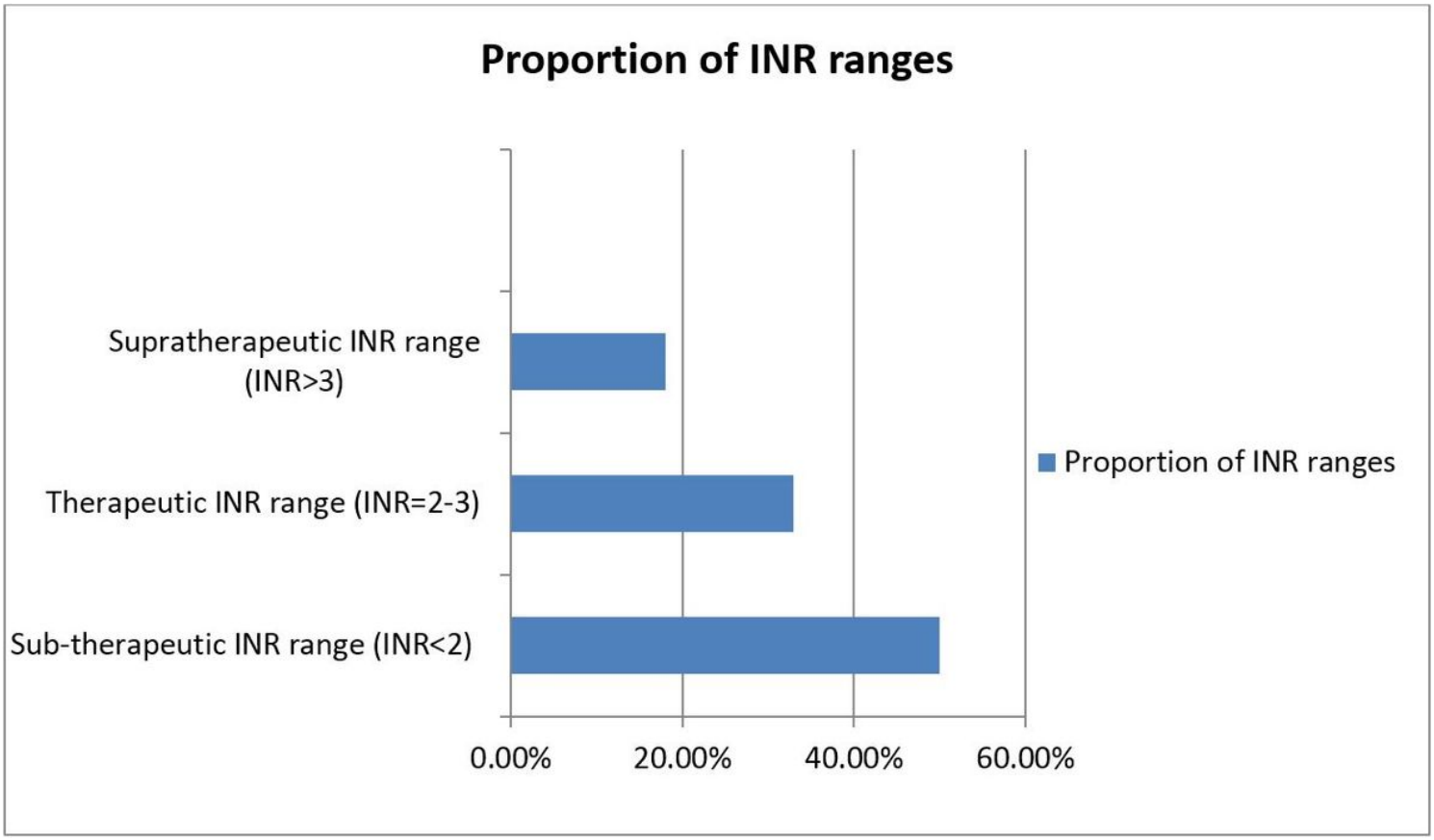

Figure 2

Bar diagram for proportion of INR range

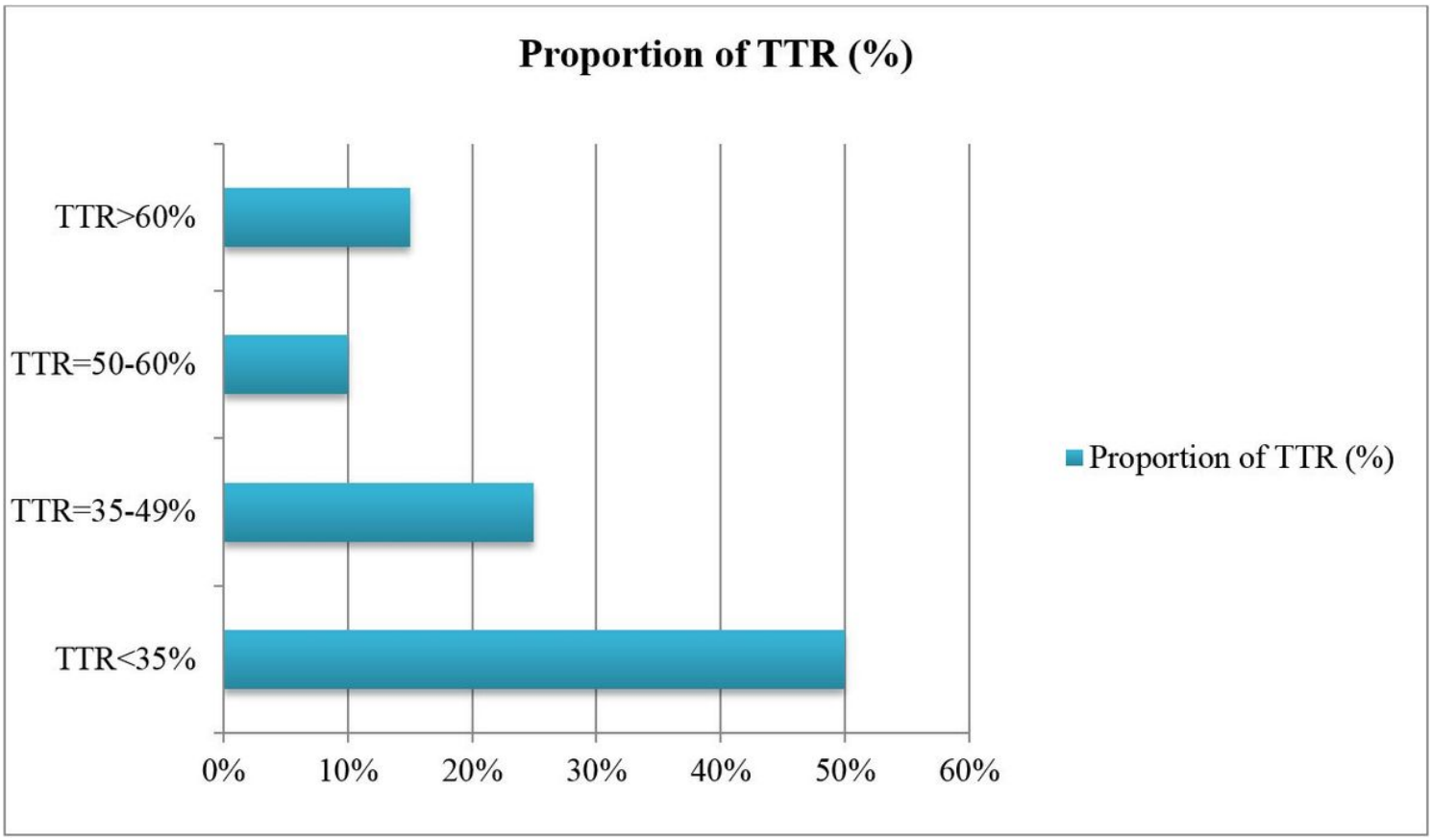

Figure 3

Bar diagram for proportion of time in therapeutic INR range