Original Article

Non-vitamin K oral antagonist (NOAC) compared to vitamin K antagonist (VKA) in left ventricular thrombus

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Abstract

Background: Thromboembolic events are serious left ventricular thrombus (LVT) complications. Despite the limitations of vitamin K antagonist (VKA) drugs, it continues to be the recommended oral anticoagulation for LVT. Recently, nonvitamin K oral antagonist (NOAC) has gained popularity as an off-labeled treatment for systemic embolism prevention in LVT. **Objective:** In this study, we aim to compare the outcomes (stroke and bleeding) of warfarin versus NOAC therapy in patients with LVT. **Methods:** This retrospective cohort study compares NOAC and VKA therapy in LVT patients. We enrolled 201 patients with an echocardiography-confirmed LVT from January 2018 to December 2022. Patients who received NOAC therapy (NOAC, $n = 77$) were compared to VKA patients (VKA, $n = 124$). The primary endpoint was a composite of stroke, minor and major bleeding. **Results:** The median follow-up time was 17 months (25^{th}–75^{th} percentiles: 8–38). On unmatched analysis, both groups had no difference in major bleeding (log-rank, $P = 0.61$) and stroke (log-rank, $P = 0.77$). However, all bleeding events were higher with NOAC (log-rank, $P = 0.01$). On matched analysis, there was no difference between both groups in the overall bleeding events ($P = 0.08$), major bleeding ($P = 0.57$), and stroke ($P = 0.66$). Minor bleeding was significantly lower in the VKA group ($P = 0.04$). **Conclusion:** In patients with LVT, NOAC was as effective as VKA in stroke prevention without increasing the risk of major bleeding.

Keywords: Left ventricular thrombus, oral antagonist, vitamin K antagonist, warfarin

Introduction

Left ventricular thrombus (LVT) is a common incident in different types of cardiomyopathies, mainly postmyocardial infarction (MI).[1-3] Thromboembolic events are a potentially severe complication of LVT, leading to a considerable morbidity and mortality risk.[4,5] Current guidelines recommend vitamin K antagonist (VKA) oral anticoagulation for at least three months.[6,7] However, VKA has well-known limitations such as slow onset and bridging requirement, the need for INR monitoring, and multiple drug–drug and food interactions.[8] Moreover, subtherapeutic INR during VKA treatment is recognized as a risk of thromboembolic events.[9]

Nonvitamin K oral antagonist (NOAC) has been recommended in preference to VKA in nonvalvular atrial fibrillation (AF), deep vein thrombosis (DVT), and pulmonary embolism (PE).[10,11] Recently, NOAC has gained popularity as an off-labeled treatment for systemic embolism prevention in LVT.[12-14] However, despite recent observational trial controversy about the efficacy of NOAC in LVT compared to VKA, a large randomized prospective study is still indicated.

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Methods

This single-center retrospective cohort study compares the outcome efficacy of NOAC and VKA drug therapies in echocardiography-confirmed LVT patients. During the period from January 2018 until December 2022, a total of 50,223 echocardiography reports were reviewed. Of this total number, 333 patients with confirmed diagnoses of LVT were screened, from which 132 were excluded owing to missed therapy and follow-up information data.

Two hundred and one patients were included in the study and were divided into two groups: Group 1 (n = 77 patients) on NOAC therapy compared to Group 2 (n = 124 patients) on VKA therapy [Figure 1]. Composite endpoint of stroke, major and minor bleeding were compared between the two groups. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) as any fatal bleeding, symptomatic bleeding in a critical area (intracerebral hemorrhage, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with the compartmental syndrome) or bleeding causing fall of hemoglobin ≥2 g/dl or leading to blood transfusion of ≥2 units of packed red blood cells. Minor bleeding was defined as any sign or symptom of hemorrhage that does not fit the criteria for the ISTH definition of major bleeding.[15,16]

The Institutional Review Board approved this study (2019), and informed consent was waived owing to the study's retrospective nature.

Statistical analysis

Propensity score matching

A propensity score-matched pair analysis was used to compare outcomes between the two groups with similar predicted probabilities of receiving anticoagulants. The propensity score was calculated using the baseline patient characteristics presented in Table 1. Propensity score matching was performed using the nearest neighbor 1:1 match with a caliper of 0.5. An absolute bias correction of 20% was considered satisfactory. We identified 66 matched pairs. The distribution of the propensity score and standardized bias across covariates before and after matching are shown in Figure 2.

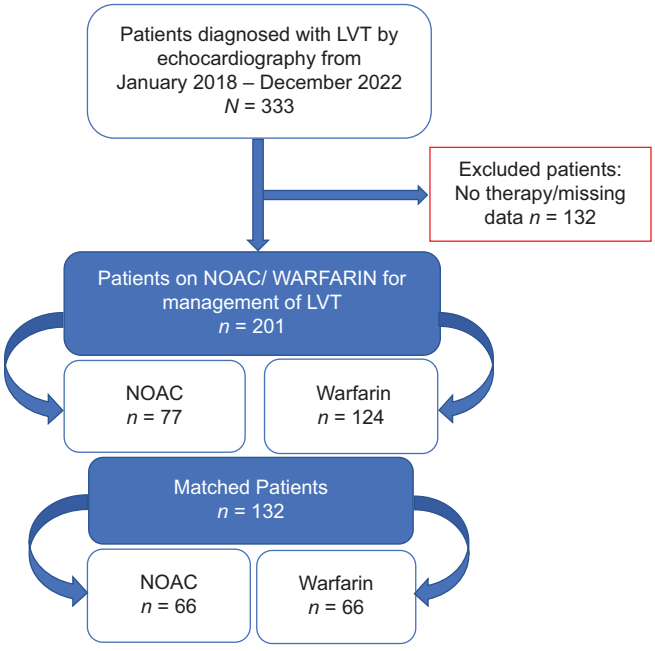

Figure 1: Study flowchart

Competing risk regression and time-to-event analysis

We performed a competing risk analysis where death was considered a competing risk with the clinical composite endpoint of any bleeding event and stroke. Competing risk regression models were performed with the Fine and Gray method, and the cumulative incidence of any bleeding event or stroke was reported. In the matched groups, competing risk analysis was performed using the Fine–Gray method for clustered pairs. The log-rank test was used to compare survival in the unmatched groups and Cox regression for the clustered pairs in the matched groups.

Intention-to-treat analysis

We performed an intention-to-treat analysis where patients were analyzed in their original treatment group if they were treated with warfarin and NOAC. Intention-to-treat analysis mimics randomized clinical trials, and the complications occurring in those patients were usually because of the initial therapy.

Data presentation and analysis

Continuous variables were presented as mean and SD if normally distributed, median, and 25th and 75th percentiles if non-normally distributed. Discrete variables were presented as counts and percentages. Normality was assessed with Shapiro–Wilk and checked with distributional plots. An independent t-test or Mann–Whitney test was used for unmatched pairs to compare continuous variables. Categorical variables were compared using Pearson's Chi-square or Fisher's exact test if the expected frequency was less than 5. Matched groups were compared with the McNemar test for categorical data and the paired t-test or Wilcoxon test for continuous data. All statistical analyses were performed using STATA 16 (Stata Corp, College Station, TX, USA). A P value of less than 0.05 was considered statistically significant.

Results

Baseline data

Baseline data are presented in Table 1. Hypertension and diabetes were more prevalent in patients who had warfarin. A total of 10 patients (5.0%) were shifted to the other group, three (1.49%) patients from NOAC to warfarin, and seven (3.48%) patients from warfarin to NOAC. Reasons for change from NOAC to warfarin therapy were progression/increase in LVT size, one patient, because of stroke. Four patients were shifted from warfarin to NOAC because of poor compliance, and three patients had no documented reason.

Table 1: Patients' characteristics of the study population

Variable	Unmatched				Matched			
	NOAC *n*=77	VKA *n*=124	*P*	SMD	NOAC *n*=66	VKA *n*=66	*P*	SMD
Demographics								
Age	55.1±16	57.2±15.7	0.615	−0.07	55.4±15	55.1±17.1	0.907	0.02
Male	78 (92.2)	118 (95.6)	0.542	0.12	61 (92.4)	62 (93.9)	>0.99	0.06
Weight	79 (68–87)	79 (70–87)	0.807	0.10	79 (68–87)	80 (70–90)	0.788	−0.04
Concomitant antiplatelets								
Aspirin	48 (62.3)	89 (71.8)	0.163	−0.20	41 (62.1)	40 (60.6)	>0.99	0.03
Plavix	38 (49.4)	70 (56.5)	0.326	−0.14	34 (51.5)	36 (54.6)	0.864	−0.06
Ticagrelor	0	4 (3.23)	0.111	−0.28	0	0	>0.99	
Risk factors								
Hypertension	36 (46.8)	76 (61.3)	0.044	−0.29	32 (48.5)	34 (51.5)	0.855	−0.06
Diabetes	39 (50.7)	81 (65.3)	0.039	−0.30	35 (53)	37 (56.1)	0.851	−0.06
IHD	58 (75.3)	102 (82.3)	0.236	−0.17	50 (75.8)	51 (77.3)	>0.99	−0.04
Old CVA	9 (11.7)	27 (21.8)	0.070	−0.27	8 (12.1)	8 (12.1)	>0.99	0.00
PVD	6 (7.8)	1 (0.8)	0.013	0.35	1 (1.5)	1 (1.5)	>0.99	0.00
AF	6 (7.8)	12 (9.7)	0.801	−0.07	5 (7.6)	4 (6.1)	>0.99	0.06
Labs								
Hemoglobin (g/dl)	14 (12–15)	13.6 (12–15)	0.099	0.26	14 (12–15)	14 (13–15	0.923	−0.05
Creatinine (µmol/l)	89 (78–104)	99 (80–142)	0.005	−0.48	90 (78–104)	86 (72–109)	0.789	0.13
Echo								
LVEF (%)	28.5±8.5	26.3±8.3	0.075	0.26	27.5±8.6	27.6±8.7	0.954	−0.01
MR	24 (31.2)	28 (22.6)	0.176	0.19	21 (31.8)	21 (31.8)	>0.99	0.00
AR	0	2 (1.61)	0.263	−0.18	0	0	>0.99	
TR	13 (16.9)	19 (15.3)	0.769	0.04	13 (19.7)	11 (16.7)	0.824	0.08

IHD=ischemic heart disease; ICM=ischemic cardiomyopathy; CVA=cerebrovascular accident; PVD=peripheral vascular disease; AF=atrial fibrillation; EF=left ventricular ejection fraction; MR=mitral regurgitation (moderate or higher); AR=aortic regurgitation; TR=tricuspid regurgitation (moderate or higher). Continuous data were presented as mean and SD if normally distributed, and median (25^{th}–75^{th}) percentiles in non-normally distributed. Categorical data were presented as number (percentage)

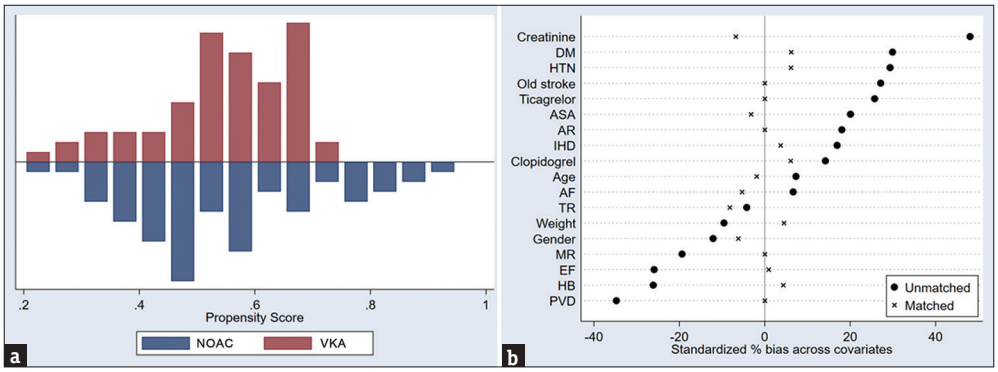

Figure 2: (a) Distribution of propensity score and (b) standardized percentage of bias across covariates before and after propensity score matching

In the crossover patients, minor bleeding occurred in one patient in the NOAC group and one patient in the VKA group. One patient also had a stroke in the VKA group. There was one mortality in each group.

Outcomes

Unmatched patients

The median follow-up time was 17 months (25^{th}–75^{th} percentiles: 8–38). Fourteen patients had minor bleeding in the NOAC group (18.2%) versus eight in the VKA group (6.5%). Major bleeding occurred in one patient in the NOAC group (1.3%) and four (3.23%) in the VKA group. Two patients (2.6%) had a stroke in the NOAC group, and four patients in the VKA group (three ischemic and one hemorrhagic). The risk of bleeding and stroke was lower in the VKA group (subdistributional hazard ratio [SHR]: 0.63 (95% CI: 0.33–1.18), $P = 0.15$). The endpoint's cumulative incidence was 19.3%, 26.8%, and 31.6% at one, two, and three years in the NOAC group, respectively. In the VKA group, the cumulative incidence of the composite endpoint was 9.6%, 14%, and 19.2% at one, two, and three years, respectively [Figure 3a]. Survival at one, two, and three years was 93.8%, 86%, and 80.6% in the NOAC group, and 93%, 90%, and 88% in the VKA group (log-rank, $P = 0.73$) [Figure 4a]. There was no difference in major bleeding (log-rank, $P = 0.61$) and stroke (log-rank, $P = 0.77$) between both groups. However, all bleeding events were higher with NOAC (log-rank, $P = 0.01$).

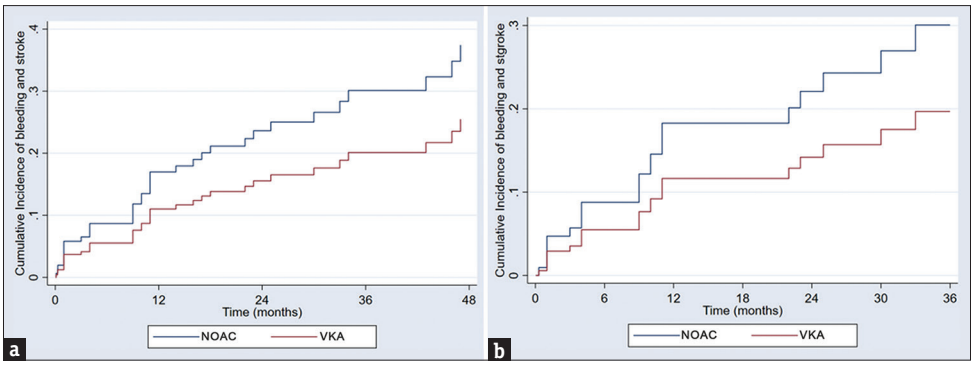

Figure 3: Cumulative incidence of bleeding and stroke before (a) and after (b) matching

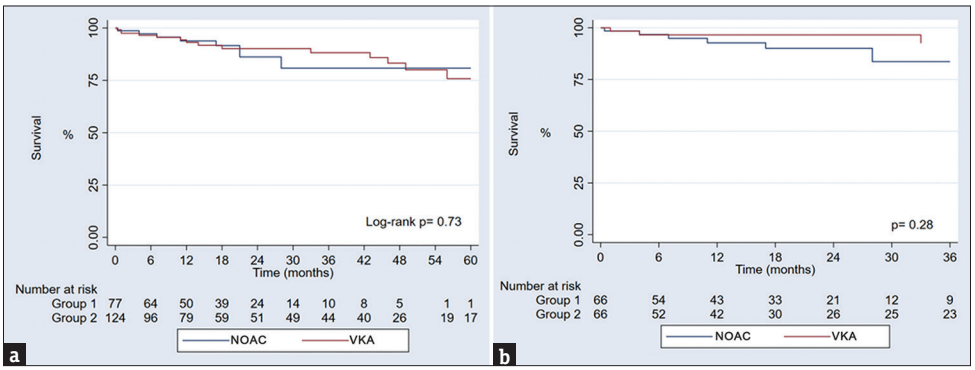

Figure 4: Kaplan-Meier survival curves before (a) and after (b) matching

Matched patients

In the match groups, 11 patients had minor bleeding (16.7%) in NOAC versus 7 (10.61%) in the VKA group. Major bleeding occurred in one patient (1.52%) in the NOAC group and three patients (4.55%) in the VKA group. Stroke occurred in two patients (3.03%) in each group. The risk of bleeding and stroke was lower in the VKA group (SHR: 0.61 [95% CI: 0.28–1.36], $P = 0.23$). Cumulative incidence of the endpoint was 19.5%, 25.9%, and 32% at one, two, and three years in the NOAC group, respectively. In the VKA group, the cumulative incidence of the composite endpoint was 10.8% and 17.7% at two and three years, respectively [Figure 3b].

Survival at one year was 92.7%, at two years, it was 90%; and at three years was 83.6% in the NOAC group. In the VKA group, survival was 96.5% at one and two years and 92.5% at three years [Figure 4b]. There were no differences between both groups in the overall bleeding events ($P = 0.08$), major bleeding ($P = 0.57$), and stroke ($P = 0.66$). Minor bleeding was significantly lower in the VKA group ($P = 0.04$).

Discussion

LVT is a commonly encountered phenomenon in patients with reduced left ventricular function, predominantly post-MI.[1,2] Notably, a significant decrease in the incidence of LVT postprimary percutaneous coronary intervention (PPCI), compared to the oldest studies preceding the myocardial reperfusion, was about 4% versus 46%, respectively.[17,18] LVT formation has a vast pathophysiological mechanism, which may include all three components of Virchow's triad; stasis in akinetic and dyskinetic LV wall, endothelial injury with inflammatory changes secondary to prolonged ischemia and hypercoagulable state in acute coronary syndrome.[19]

Although cardiac magnetic resonance (CMR) is the most sensitive test for LVT diagnosis, transthoracic echocardiogram (TTE), with its advantages of wide availability, low cost, and adequate sensitivity and specificity, remains the most common screening modality for LVT diagnosis.[20,21] Despite the management of anticoagulation, thromboembolism is one of the severe complications of LVT.[4] In a recent matched cohort study of patients with LVT diagnosed by CMR, the annual incident rate of thromboembolic in a long-term follow-up was about 3.7%.[4]

To prevent thromboembolic events, in patients with LVT current guidelines recommend anticoagulation with VKA for at least three months.[6,7] Traditionally, VKA is the most widely used oral anticoagulation. The main VKA clinical limitation is the difficulty of maintaining an effective therapeutic rang, attributed to the narrow therapeutic window, slow onset, INR monitoring and drug-to-drug and food interaction.[8] Consequent to that, subtherapeutic INR can increase the risk of thromboembolic events.[9] In a recent subanalysis of LVT study treated by VKA, subtherapeutic range INR led to a 19% risk of systemic emboli as compared to 2.9% only in patients who can maintain therapeutic VKA range more than 50% of the time.[9]

AHA/American Stroke Association guidelines recommend NOAC as an alternative to VKA in LVT.[7] NOAC has a wider therapeutic range, a more consistent therapeutic level, and less interaction.[22] The efficacy of NOAC in thromboembolic prevention, when compared to VKA, has been approved in nonvalvular AF, DVT, and PE.[10,11] However, there is a worldwide tendency to replace VKA with NOAC.[10,11] Furthermore, NOAC has been used at many health institutions as an off-label treatment of thromboembolic prevention in LVT.[12-14] NOAC safety and efficacy as a treatment of LVT have been investigated by retrospective trials. In a systemic review analysis, NOAC was effective in LV thrombus resolution and thromboembolic prevention.[13,14] In another recent trial, which included 101 patients diagnosed postacute MI with LVT, the NOAC group has earlier LVT resolution and lower major bleeding compared to the VKA group. On the other hand, a recent multicenter retrospective study showed a higher risk of stroke or embolic events in LVT treated by NOAC compared to VKA use.[23] The present retrospective trial shows a local experience of a single cardiac center. The findings support the efficacy of NOAC in LVT in comparison to VKA. In a median follow-up time of 17 months, the two groups had no difference in major bleeding (log-rank, $P = 0.61$), stroke (log-rank, $P = 0.77$) or survival rate. The endpoint of our study depends on clinical events of thromboembolic or stroke, which looks more realistic than only documentation of LVT resolution by images. Documentation of LVT resolution by echocardiography or CMR will not exclude LVT reformation in future, considering the presence of the same pathophysiology that causes initial LVT formation. On the other hand, echocardiography has a lower sensitivity in diagnosing a small LVT, which could appear clinically as a cryptogenic stroke or emboli with an undetermined source.[24]

Conclusion

In patients with LVT, the use of NOAC is associated with the same risk of stroke without increasing the risk of major bleeding compared to warfarin. A large prospective randomized clinical trial is still needed.

Data availability

The data underlying this article were provided by the research department of Prince Sultan Cardiac Center-Riyadh under license/by permission. Data will be shared on request with the corresponding author with the permission of the research department of Prince Sultan Cardiac Center.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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