Original Article

Direct oral anticoagulants versus vitamin K antagonists for patients with left ventricular thrombus

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Background: A retrospective cohort study was conducted to compare the efficacy and safety of direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) in the treatment of patients with left ventricular thrombus (LVT).

Methods: Consecutive patients admitted to our institution with LVT between February 2009 and December 2020 and treated with either DOACs or VKAs were considered for inclusion in this study. The outcomes included stroke or systemic embolism (SSE), thrombus resolution, and bleeding events.

Results: Eighty-seven patients with LVT were identified. Of these, 25 patients were treated with DOACs and 62 patients were treated with VKA. The average follow-up period was 2.37±2.1 years. DOACs were associated with similar incidences of stroke (4.0% *vs.* 4.8%; P=0.158), systemic embolism (0% *vs.* 1.6%; P=0.906), SSE (4.0% *vs.* 6.5%; P=0.657), thrombus resolution (76.0% *vs.* 74.2%; P=0.057), and blooding events (4.0% *vs.* 3.2%; P=0.858) as compared to VKAs. In the univariate logistic regression analysis, there was a significant difference between the DOAC and VKA groups in the incidence of SSE when antiplatelets were controlled [odds ratio (OR) =0.34, 95% confidence interval (CI): 0.21, 0.98; P=0.027]. However, in the multivariate analysis, antiplatelets had no significant effect on the outcome (OR =0.41, 95% CI: 0.36, 1.54; P=0.366).

Conclusions: DOACs had similar efficacy and safety to VKAs in the treatment of patients with LVT. Randomized controlled trials should be conducted to verify our findings.

Keywords: Direct oral anticoagulants (DOACs); vitamin K antagonists (VKAs); left ventricular thrombus (LVT)

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Introduction

Left ventricular thrombus (LVT) is a recognized complication of acute myocardial infarction (AMI), and is associated with a significant thromboembolic risk when left untreated (1,2). Several risk factors have been reported to be associated with the formation of LVT, including large anterior myocardial infarction, left ventricular (LV) systolic dysfunction, and severe wall motion abnormalities (3). The incidence of LVT in the pre-percutaneous coronary intervention (PCI) era was about 40%, but has been reduced to 4% in the primary PCI era (3,4).

Various societal guidelines recommend the administration of anticoagulation with warfarin (or up until thrombus resolution) to prevent thromboembolic events in patients with LVT (5-7). Under the guidelines of the European Society of Cardiology, oral vitamin K

antagonist (VKA) with warfarin is considered the standard of care (8). However, warfarin, has several disadvantages, including an initial phase of hypercoagulability and variable anticoagulation, and an association with both sub- and supratherapeutic effects (9). Over time, direct oral anticoagulants (DOACs) have been used as an alternative to VKAs for several indications. The United States Food and Drug Administration approved the use of VKAs for pulmonary embolism and non-valvular atrial fibrillation (AF) (9). DOACs have attracted considerable interest for a number of reasons, including the ease with which they can be administered, the absence of international normalized ratio (INR) monitoring, the lack of dietary restrictions, and because they may improve patients' quality of life (10,11). These advantages have driven continued interest in the application of DOACs to conditions such as LVT (12). Several clinical trials have assessed the effects and safety of DOACs and VKAs; however, the results of these trials have been inconsistent. Thus, we conducted a retrospective cohort study to compare the efficacy and safety of DOACs and VKAs in patients with LVT. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1683).

Methods

Study design

This retrospective single-center cohort study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology statement (13).

Study population

This retrospective study was conducted at Shanxi Bethune Hospital. Consecutive patients admitted to our institution for LVT between February 2009 and December 2020 and treated with either DOACs or VKAs were considered for inclusion in the study. Patients were diagnosed with definitive LVT based on their medical history, symptoms and signs, biomarkers, and transthoracic echocardiography. Patients were excluded if they had any one of the following disease conditions: valvular heart disease and mechanical valve replacement surgery, rheumatic heart disease, atrial thrombosis, artificial blood vessel thrombosis, lower extremity venous thrombosis, pulmonary embolism, recent active bleeding, anticoagulant contraindication, malignant tumors, or severe liver and kidney dysfunction. Patients were also excluded if they were treated with low molecular weight heparin or were not treated with anticoagulation due to chronic tissue thrombosis. The study was approved by the Institutional Ethical Committee of the Shanxi Bethune Hospital in China (No. 2021GLL120). Written informed consent was obtained from the patients for publication of this study and any accompanying images. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Data collection

Patients' demographic data, including age, gender, and ethnicity data, were collected from electronic medical records. Details of each patient's baseline clinical and demographic information was recorded. Moreover, cardiac data, including left ventricular ejection fraction (LVEF) and LV volume were also collected.

Echocardiography evaluation

Transthoracic echocardiography was performed in all cases using a commercially available system (ViviE9, GE healthcare, France). LVEF was measured 3 times at the end of isovolumic diastole on the long axis view of the LV; the average was taken, and the data recorded.

Anticoagulation regimen

Patients with LVT were divided into either the DOAC group or the VKA group according to practitioner preference. Dabigatran was prescribed at doses of 110 or 150 mg twice a day, and rivaroxaban at 10–20 mg once a day based on creatinine clearance, age, and weight. All patients with oral VKAs had their INR regularly monitored to ensure it was control between 2 and 3 as per the standard. The INR was measured 5–7 days after the initiation of oral VKAs, and the dose was adjusted until the INR reached the standard. For patients whose INR was measured once a week, the test was changed to once every 2 weeks when a therapeutic INR was achieved twice consecutively. The outcome measures included stroke or systemic embolism (SSE), bleeding events, and the resolution of thrombus.

Statistical analysis

The characteristics of patients treated with DOACs

Table 1 Baseline characteristics of patients receiving either DOAC or VKA

Characteristics	All patients (n=87)	DOAC (n=25)	VKA (n=62)	P value
Age (mean ± SD, years)	61.5±12.7	59.4±11.5	61.9±12.2	0.512
Sex, n (%, female)	21 (24.1)	6 (24.0)	15 (24.2)	0.985
Ethnicity (n, %)				0.140
Han	82 (94.3)	22 (88.0)	60 (96.8)	
Other	5 (5.7)	3 (12.0)	2 (3.2)	
AF (n, %)	70 (80.5)	20 (80.0)	50 (80.6)	0.945
BMI (mean ± SD)	28.6±6.2	27.2±7.3	30.5±6.7	0.331
Hypertension (n, %)	37 (42.5)	10 (40.0)	27 (43.5)	0.762
Diabetes mellitus (n, %)	18 (20.7)	6 (24.0)	12 (19.4)	0.628
Smoking (n, %)	62 (71.3)	17 (68.0)	45 (72.6)	0.669
Aspirin (n, %)	38 (43.7)	11 (44.0)	27 (43.5)	0.969
Cause of LVT (n, %)				
ICM	66 (75.9)	18 (72.0)	48 (77.4)	0.107
AMI	17 (19.5)	4 (16.0)	13 (21.0)	
HCM	4 (4.6)	3 (12.0)	1 (1.6)	

DOAC, direct acting oral anticoagulant; VKA, vitamin K antagonist; AF, atrial fibrillation; BMI, body mass index; SD, standard deviation; LVT, left ventricular thrombus; ICM, ischemic cardiomyopathy; AMI, acute myocardial infarction; HCM, hypertrophic cardiomyopathy.

or VKAs were compared. Continuous variables are presented as mean ± standard deviation (SD), and were compared using the nonparametric Mann-Whitney *U* test. Categorical variables are expressed as percentages, and were calculated using the Pearsonχ^2 test or Fisher exact test. A logistic regression model was used for the univariate and multivariate analyses to verify the effects of the factors on the SSE outcome. Candidate factors for the multivariable analyses were chosen based on previous findings and the findings of the univariate analysis. The odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs) were calculated. All analyses were performed using SPSS Statistics 19.0 for Windows (SPSS Chicago, IL, USA). A 2-tailed P value <0.05 was considered statistically significant.

Results

Baseline characteristics of patients

Between February 2009 and December 2020, 87 patients were diagnosed with LVT. The average follow-up period was 2.37±2.1 years. Among the 87 patients, 25 patients were treated with DOACs, and 62 patients were treated with VKAs. Of the patients treated with DOACs, 16 were treated with rivaroxaban (8 with 20 mg daily, 6 with 15 mg daily, and 2 with 10 mg daily), and 9 were treated with dabigatran (6 with 150 mg daily, and 3 with 110 mg daily). All patients in the VKA group were treated with warfarin.

Among the patients included in this study, 21 (24.1%) were female. The patients had an average of 61.5±12.7 years. The majority of patients were of Han ethnicity. Hypertension and diabetes mellitus were reported in 42.5% and 20.7% of patients, respectively. There was no significant difference between the DOAC and VKA groups in relation to hypertension and diabetes. Thirty-eight patients were co-administered aspirin; 11 of whom were in the DOAC group and 27 of whom were in the VKA group. The major reason for the LVT was ischemic heart disease (75.9%), followed by AMI (19.5%). With the exception of a higher LV volume and a lower platelet count in the VKA group, there was no significant difference between the 2 groups in terms of the baseline demographic, clinical data and cardiac imaging variables (see *Tables 1* and *2*).

Table 2 Cardiac imaging variables of patients receiving either DOAC or VKA

Outcome	All patients (n=87)	DOAC (n=25)	VKA (n=62)	P value
LVEF (%)	36.2±6.5	33.8±5.7	37.6±6.6	0.423
LVIDd (mm)	55±6	58±9	53±6	0.361
LV volume (mL)	243±62	227±58	265±71	0.037
MR (n, %)	15 (17.2)	4 (16)	11 (17.7)	0.846
RWMA (n, %)	77 (88.5)	21 (84)	56 (90.3)	0.403
Platelets ($\times 10^9$ per litre)	226±68	263±72	207±69	0.018
Creatinine (μmol/L)	85±31	92±35	80±29	0.532
BNP (ng/L)	5,236±5,423	5,864±5,126	5,114±5,351	0.627

DOAC, direct acting oral anticoagulant; VKA, vitamin K antagonist; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter in diastole; MR, mitral regurgitation; RWMA, regional wall motion abnormality; BNP, brain natriuretic peptide.

Table 3 Efficacy and safety outcomes of DOAC or VKA in patients with LVT

Outcome	All patients (n=87)	DOAC (n=25)	VKA (n=62)	P value
Follow-up period (years)	2.37±2.1	2.51±2.8	2.24±2.5	0.462
SSE (n, %)	5 (5.7)	1 (4.0)	4 (6.5)	0.657
Stroke	4 (4.6)	1 (4.0)	3 (4.8)	0.158
Systemic embolism	1 (11.5)	0	1 (1.6)	0.906
Blooding events (n, %)	3 (3.4)	1 (4.0)	2 (3.2)	0.858
Thrombus resolution (n, %)	65 (74.7)	19 (76.0)	46 (74.2)	0.057
Hospitalization (n, %)	31 (35.6)	9 (36.0)	22 (35.5)	0.964
Death (n, %)	5 (5.7)	2 (8.0)	3 (4.8)	0.566

DOAC, direct acting oral anticoagulant; VKA, vitamin K antagonist; LVT, left ventricular thrombus; SSE, stroke or systemic embolism.

Efficacy and safety results

During the follow-up period, 1 (4.0%) and 3 (4.8%) patients had a stroke in the DOAC and VKA groups, respectively (P=0.158), and 1 episode of systemic embolism occurred in a patient in the VKA group (see *Table 3*). There was no significant difference between the 2 groups in terms of the incidence of SSE (4.0% *vs.* 6.5%; P=0.657). Three patients experienced bleeding events; 1 in the DOAC group, and 2 in the VKA group (4.0% *vs.* 3.2%; P=0.858). Each of these patients had gastrointestinal bleeding (1 of whom required hospitalization and 2 of whom improved after symptomatic treatment). A total of 31 patients (9 in the DOAC group and 22 in the VKA group) were hospitalized during the follow-up period. There was no significant difference between the 2 groups (36.0% *vs.* 35.5%; P=0.964). Five patients died during the follow-up period [2 (8.0%) in the DOAC group and 3 (4.8%) in the VKA group]. There was no significant difference between the 2 groups (P=0.566).

Univariate and multivariate logistic regression analyses

In the univariate logistic regression model, a significant difference was found in the incidence of SSE between the DOAC and VKA groups when antiplatelets were controlled (OR =0.34, 95% CI: 0.21, 0.98; P=0.027). However, when other variables were controlled, this difference was not statistically significant (age: OR =0.63, 95% CI: 0.21, 2.35, P=0.471; sex: OR =0.58, 95% CI: 0.36, 1.94, P=0.382; follow-up period: OR =0.74, 95% CI: 0.52, 2.23, P=0.541; history of AF: OR =1.23, 95% CI: 0.25, 3.86, P=0.462; LV volume: OR =0.39, 95% CI: 0.11, 1.93, P=0.424). In the multivariate logistic regression model, none of the variables

Table 4 Results of univariate and multivariate logistic regression analysis for SSE

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	0.63	0.21, 2.35	0.471	0.55	0.14, 2.61	0.727
Sex	0.58	0.36, 1.94	0.382	0.53	0.41, 1.88	0.205
Follow-up period (years)	0.74	0.52, 2.23	0.541	0.71	0.42, 2.05	0.485
History of AF	1.23	0.25, 3.86	0.462	1.54	0.98, 3.25	0.067
LV volume (mL)	0.39	0.11, 1.93	0.424	0.42	0.32, 1.85	0.303
Antiplatelet (count)	0.34	0.21, 0.98	0.027	0.41	0.36, 1.54	0.366

SSE, stroke or systemic embolism; AF, atrial fibrillation; OR, odds ratio; CI, confidence interval.

had an effect on the incidence of SSE between the DOAC and VKA groups (see *Table 4*).

Discussion

In this retrospective cohort study, we found that the incidences of SSE, thrombus resolution, and bleeding events were comparable between patients treated with DOACs and VAKs. Notably, only 1 episode of systematic embolism occurred in the VKA-treated patients. LVT is a common complication of heart failure, and its incidence varies greatly among different populations. The incidence of LVT has been reported to be 17% in patients with AMI and 34–57% in patients with acute anterior myocardial infarction (14,15). A recently published meta-analysis was conducted of 10076 patients to investigate the estimate of the rate of LVT formation in patients treated with PCI for segment elevation myocardial infarction (STEMI) (16). Its results showed that the rate of LVT after all STEMI was 2.7% (95% CI: 1.9–3.5%) and 9.1% (95% CI: 6.6–11.6%) after anterior STEMI (16), which suggested that LVT was an important part of the management of STEMI after PCI, especially in anterior infarctions.

Currently, the factor Xa inhibitor (rivaroxaban) and the direct thrombin inhibitor (dabigatran) are the 2 most widely used novel oral anticoagulants in the prevention of thrombus development. In the present study, rivaroxaban was used in 3 doses (20, 15, or 10 mg), and dabigatran was used in 2 doses (150 or 110 mg). According to the dosage of warfarin for thrombus resolution, the INR can be controlled between 2.0 and 3.0. In patients with insoluble thrombus, the INR can be adjusted to 2.5–3.5. Thus, 20 mg of rivaroxaban daily or 150 mg of dabigatran daily is recommended as the priority anticoagulant for patients who have a low risk of bleeding or for whom antiplatelet drugs are not used. Conversely, for those who have a certain risk of bleeding, moderate renal dysfunction or a low body weight, a small dosage of rivaroxaban or dabigatran can be used as appropriate.

In this study, we found that DOACs had a similar effect in SSE prevention to VKAs. However, it should be noted that our results are in consistent with those of previous studies (17,18). Willeford *et al.* (17) performed a retrospective single-center study with 151 patients to assess whether DOACs were more effective than VKAs in the treatment of LVT. In that study, 129 patients received warfarin and 22 received DOACs. They found that, 8 patients in the warfarin group experienced a SSE compared to 0 patients in the DOAC group (17); however, the difference between the 2 groups was not significant (P=0.37). Similarly, Iqbal *et al.* (18) reported that DOACs and VKAs had a comparable effect in the management of LVT. In that retrospective cohort study of 84 patients, the rate of stroke in the DOAC and VKA groups was 2% and 0%, respectively (P=0.55), and the rate of other thromboembolic events was 10% and 0%, respectively (P=0.13). No significant differences were observed between the 2 groups in relation to SSE. However, in another cohort study that was performed at 3 tertiary care academic medical centers, DOAC was found to be associated with a higher risk of SSE than warfarin (19). Robinson *et al.* (19) examined 514 patients with LVT, of whom 300 were treated with warfarin and 185 were treated with DOACs (64 patients switched treatments groups). In the unadjusted analysis, DOAC treatment had a higher risk of SSE than warfarin [hazard ratio (HR) =2.71, 95% CI: 1.31, 5.57; P=0.01] (19). In the multivariable analysis, the DOAC group was once again found to have a higher risk of SSE than the warfarin group

(HR =2.64, 95% CI: 1.28, 5.43; P=0.01) (19). The reason for the higher rate of SSE among patients treated with DOACs was unclear. The authors speculated that different types of DOAC and even individual agents may have different therapeutic effects on LVT (19). In that study, most of the DOACs were oral Xa inhibitors (19).

To assess the effects of possible variables on the incidence of SSE between the DOAC and VKA groups, we performed univariate and multivariate logistic regression analyses, and found that antiplatelets had a significant effect on the SSE. However, when antiplatelets were added to the multivariate analysis, no significant difference was observed. Our results are consistent with those reported by others (17). Willeford *et al.* performed a post-hoc exploratory analysis with 3 logistic regression models to assess the association of DOACs with SSE (17). In Model 1, age, sex, and follow-up period were adjusted. In Model 2, CHA_2DS_2VASC score, history of AF, and follow-up period were adjusted. In Model 3, the variables in Model 2, aspirin and P2Y12 receptor inhibitor use were adjusted (17). In the analysis, none of these variables had a significant effect on the odds of composite of LVT persistence, SSE for DOAC versus warfarin (17). Another cohort study compared the outcomes associated with DOAC and warfarin in the treatment of LVT, and found that DOAC had a higher risk of SSE than warfarin, and this significant result did not change even after adjusting for other factors (19).

In relation to the safety profile, our results showed that DOACs did not reduce the risk of bleeding events as compared to VKAs. This finding was consistent with the results of previous studies (18). Iqbal *et al.* (18) reported that the rate of clinically significant bleeding did not differ significantly between the DOAC and VKA groups (10% *vs.* 0%) for the follow-up period of 3.0±1.4 years. Similar results were found in a case-control study of 14 DOAC patients and 59 VKA patients with LVT (20). In that study, 2 (14.3%) DOAC patients and 8 VKA patients (13.6%) developed bleeding events within 12 months (P=1.00) (20). However, a recently published meta-analysis of 13 studies (n=2,467) reported opposite results; that is, that DOAC users had a similar risk of any bleedings [risk ratio (RR) =0.94, 95% CI: 0.67, 1.31; P=0.70], but a lower risk of clinically relevant bleedings (RR =0.35, 95% CI: 0.13, 0.92; P=0.03) compared to VKA patients (21). However, the results of the meta-analysis should be interpreted with caution since the bleeding outcomes across the included studies were not reported according to standard definitions (such as BARC classification). Additionally, the DOAC regimens and dosages varied greatly among the included studies, which might undermine the pooled estimate of the safety outcome.

This study had a number of limitations. First, it was a single-center cohort study, and the retrospective design represents its main limitation. Second, only 87 patients were enrolled in this study, which represents a relatively small sample size. The inadequate sample size might have led to non-statistical differences in the outcomes. Third, as an observational study, it was subject to various biases, including selection bias and information bias, which are inherent weaknesses of all such studies. For example, since the treatment regimen was conducted according to individual practitioners' preferences rather than randomization, more patients were treated with warfarin. This may have contributed to the negative results in this study.

In conclusion, this retrospective cohort study suggested that DOACs had similar efficacy and safety to VKAs in the treatment of patients with LVT in terms of SSE and bleeding. Further large-scale randomized controlled trials need to be conducted to confirm our findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1683

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Institutional Ethical Committee of the

Shanxi Bethune Hospital in China (No. 2021GLL120). Written informed consent was obtained from the patient for publication of this study and any accompanying images. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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