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Original Research

Characteristics of Novel Anticoagulants versus Vitamin K Antagonists in the Ventricular Mural Thrombus

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Abstract

Background: To describe the characteristics, treatment practices, and clinical outcomes of patients with ventricular mural thrombus (VMT), with emphasis on the comparison of non-vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKAs). **Methods**: We performed a retrospective cohort study between 2010 and 2019 in Fuwai Hospital, China. Patients with VMT newly treated with either NOACs or VKAs were included. The primary outcome was the incidence rate of thrombus resolution at 3 months. **Results**: We included 196 patients in total—68.9% (n = 135) were treated with VKAs while 31.1% (n = 61) were on NOACs. Patients with a medical history of heart failure (HF) (odds ratio (OR) 2.10, 95% confidence interval (CI) 1.17 to 3.77, $p = 0.013$) and a lower left ventricular ejection fraction (OR 0.36, 95% CI 0.20 to 0.65, $p = 0.001$) had a higher thrombus resolution. At 3 months, a significant difference was observed in the thrombus resolution between the NOACs and VKAs group with or without adjustment (OR 2.61, 95% CI 1.39 to 4.89, $p = 0.003$; adjusted OR 2.93, 95% CI 1.51 to 5.66, $p = 0.001$). Further investigation revealed that in the majority of the subgroups, individuals receiving NOAC therapy had a superior thrombus resolution than those receiving VKA therapy. **Conclusions**: Patients with a medical history of HF or left ventricular ejection fraction <30% experienced greater effectiveness in thrombus resolution. Additionally, the resolution of VMT with NOAC treatment was considerably higher than that with VKA therapy at 3 months, with or without adjusting for baseline variables. **Clinical Trial Registration**: This study was registered at ClinicalTrials.gov as NCT 05006677 on August 4th, 2021.

Keywords: ventricular mural thrombus; anticoagulants; non-vitamin K antagonist oral anticoagulants; warfarin

1. Introduction

Patients with heart failure (HF) or myocardial infarction (MI) predispose to ventricular mural thrombus (VMT) formation, experiencing a combination of hypercoagulability, abnormal blood flow, and endothelial injury [1,2]. The most severe VMT complication, which carries a substantial risk of mortality and morbidity, is the incidence of thromboembolism [3]. Whereas the typical use of Vitamin K antagonists (VKAs) for anticoagulation has been largely embraced in clinics, no particular guidelines are provided for the management of VMT [4,5]. However, due to the drawbacks of warfarin's late onset, multiple food or drug interactions, and restricted therapeutic window, treatment compliance among patients is relatively low, which increases the likelihood of bleeding or embolism events [6]. Therefore, non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly used as off-label anticoagulant treatments in patients with VMT. From MI and stroke guidelines, the usage of NOACs for the treatment of left VMT was uncertain [7,8]. Apixaban or rivaroxaban demonstrated a better or comparable thrombus resolution than warfarin in patients with left VMT, and the risks of major cardiovascular adverse events were comparable, according to two prospective multicenter randomized trials [9,10]. In the No-LVT trial, for example, rivaroxaban was non-inferior to warfarin in terms of thrombus resolution (71.79% vs 47.50%) [10]. Several retrospective studies and meta-analyses also reported that NOACs were non-inferior even superior to warfarin in thrombus resolution while the risk of bleeding or stroke had not reached consensus [11–14]. Therefore, we aimed to evaluate the characteristics and clinical outcomes of patients with VMT treated with various oral anticoagulants, as well as to explore potential factors related to thrombus resolution.

2. Methods

2.1 Patient Population

This retrospective cohort study was conducted from July 2010 through October 2019 using electronic medical

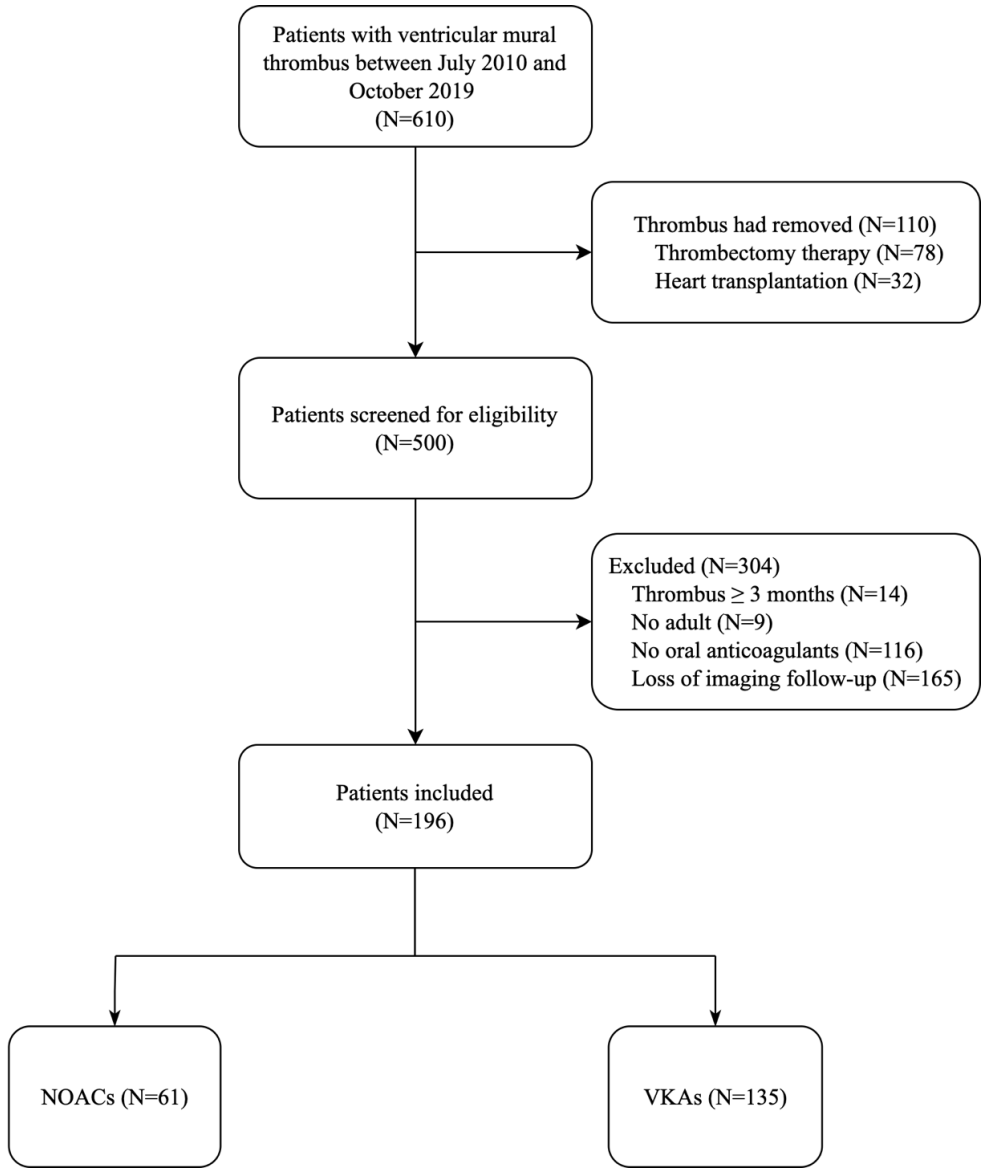

Fig. 1. Flow diagram to show the inclusion and exclusion criteria. 610 patients were found with ventricular mural thrombus and 196 were included in our analysis—61 received NOACs and 135 received VKAs. NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists.

records of Fuwai Hospital, National Center of Cardiovascular Diseases in China, which was registered in ClinicalTrials.gov: NCT 05006677. The inclusion criteria were: (1) Aged over eighteen years, regardless of sex or occupation; (2) Patients were given a new prescription for a NOAC or a VKA for less than 1 month; (3) VMT was identified newly within 3 months given that mechanized or calcified thrombus was less likely to resolve. Patients who switched medications or discontinued NOACs or VKAs over the course of treatment were excluded, as evidenced by objective data such as prescriptions from cardiologists and oral reports during the interviews. All medications according to the recommendation of guidelines for the treatment of underlying diseases were encouraged.

2.2 Definitions

The diagnosis of VMT was confirmed by transthoracic echocardiography, computer tomography (CT), or cardiac magnetic resonance (CMR) imaging. X.Q. and other experts would analyze the image and make a determination. VMT was defined as an abnormal echo mass in the ventricular cavity whose margin was distinct from the ventricular endocardium [15]. Multiple sections confirmed the existence of the thrombus.

The primary outcome was the rate of thrombus resolution determined by repeat imaging within 3 months, and the secondary outcomes included thromboembolism events, bleeding, and all-cause death within 3-month follow-up. We confirmed the resolved thrombus by screening the image data in the electronic system and conducted a survey

Table 1. Baseline characteristics of patients with VMT [N (%)].

	Total	NOACs	VKAs	*p* value
	(N = 196)	(N = 61)	(N = 135)	
Age, y [Median (IQR)]	49.0 (34.0, 58.0)	41.0 (27.0, 56.0)	50.0 (37.0, 59.0)	0.040
Male	151 (77.0)	43 (70.5)	108 (80.0)	0.200
BMI, kg/m^2 [Mean ± SD]	24.4 ± 3.9	24.6 ± 4.3	24.3 ± 3.7	0.539
Presenting diagnosis				0.150
ICM	43 (21.9)	10 (16.4)	33 (24.4)	-
DCM	39 (19.9)	9 (14.8)	30 (22.2)	-
Others[†]	114 (58.2)	42 (68.9)	72 (53.3)	-
Prior medical history				
Coronary artery diseases	87 (44.4)	21 (34.4)	66 (48.9)	0.083
Atrial fibrillation	20 (10.2)	4 (6.6)	16 (11.9)	0.316
Heart failure	118 (60.2)	37 (60.7)	81 (60.0)	1.000
Hypertension	56 (28.6)	17 (27.9)	39 (28.9)	1.000
Diabetes	31 (15.8)	7 (11.5)	24 (17.8)	0.298
Hyperlipidemia	81 (41.3)	20 (32.8)	61 (45.2)	0.140
Embolism	48 (24.5)	17 (27.9)	31 (23.0)	0.575
Chronic kidney diseases	9 (4.6)	1 (1.6)	8 (5.9)	0.278
Gastrointestinal bleeding	5 (2.6)	1 (1.6)	4 (3.0)	1.000
Current smoker	102 (52.0)	30 (49.2)	72 (53.3)	0.701
Excessive alcohol consumption[§]	45 (23.0)	17 (27.9)	28 (20.7)	0.360
Location of ventricular thrombi				0.002
Left ventricular	169 (86.2)	45 (73.8)	124 (91.9)	-
Right ventricular	19 (9.7)	10 (16.4)	9 (6.7)	-
Biventricular	8 (4.1)	6 (9.8)	2 (1.5)	-
Number of ventricular thrombi				0.445
1	176 (89.8)	53 (86.9)	123 (91.1)	-
≥2	20 (10.2)	8 (13.1)	12 (8.9)	-
Size of ventricular thrombi, mm [Median (IQR)]				
Diameter	22.0(14.5, 30.0)	22.0 (16.0, 29.5)	22.0 (14.0, 30.2)	0.776
Thickness	15.0 (11.0, 21.0)	16.0 (13.0, 22.0)	15.0 (10.0, 21.0)	0.305
Width	26.0 (11.5, 44.5)	17.5 (13.2, 21.7)	42.0 (13.0, 47.0)	0.245
LVEF, % [Median (IQR)]	31.5 (25.0, 42.2)	31.0 (25.0, 45.0)	32.0 (24.0, 41.5)	0.410
D-Dimer, ug/mL [Median (IQR)]	1.35 (0.46, 2.62)	1.39 (0.47, 2.74)	1.29 (0.47, 2.61)	0.793
Combined medications				
Parenteral anticoagulants	123 (62.8)	25 (41.0)	98 (72.6)	0.001
Antiplatelet therapy	66 (33.7)	16 (26.2)	50 (37.0)	0.187

[†]Other diagnoses included hypertrophic cardiomyopathy, peripartum cardiomyopathy, myocarditis, arrhythmogenic right ventricular cardiomyopathy, hypertensive heart disease, and noncompaction of ventricular myocardium.

[§]Excessive alcohol consumption: >40 grams per day for women and >80 grams per day for men, lasting more than 5 years.

Abbreviations: VMT, ventricular mural thrombus; SD, standard deviation; IQR, interquartile range; NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists; BMI, body mass index; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction.

by phone or media contact with patients to obtain long-term outcomes. Thromboembolism events were defined as the combination of an acute embolism in a coronary or peripheral artery, ischemic stroke, and transient ischemic attack. Bleeding events were classified as major bleeding as defined by the International Society on Thrombosis and Haemostasis [16], clinically relevant non-major bleeding [17], and minor bleeding that failed to comply with the criteria for the abovementioned two categories of bleeding.

2.3 Data Collection and Analysis

Data regarding patient demographics (age, gender), clinical characteristics (presenting diagnosis, medical history, and laboratory testing), imaging parameters (left ventricular ejection fraction (LVEF), thrombi features), treatment (type of anticoagulation and combined medications), and clinical outcomes (thrombus resolution, thromboembolism events, bleeding, and all-cause death) were collected. To assure coherence, two colleagues (Q.Y. and

Table 2. Outcomes of VMT patients within 3 months follow-up [N (%)].

	Total	NOACs	VKAs	*p* value*
	(N = 196)	(N = 61)	(N = 135)	
Primary outcome				
Thrombus resolution	97 (49.5)	40 (65.6)	57 (42.2)	0.004
Time of thrombus resolved, d [Median (IQR)]	41 (30, 60)	40 (33, 51)	43 (29, 67)	0.921
Time of thrombus unresolved, d [Median (IQR)]	48 (32, 58)	41 (30, 60)	48 (33, 57)	0.985
Secondary outcome				
Bleeding	10 (5.1)	1 (1.6)	9 (6.7)	0.258
Thromboembolism	1 (0.5)	0 (0.0)	1 (0.7)	1.000
All-cause death	3 (1.5)	0 (0.0)	3 (2.2)	0.586

*Calculated by Fisher's exact test.

Abbreviations: VMT, ventricular mural thrombus; IQR, interquartile range; NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists.

X.Q.) separately extracted the data and compared the results. A third researcher then addressed any inconsistencies. Data were obtained from electronic medical records and oral consent was acquired at the time of the telephone interview.

2.4 Statistics Analysis

Normally distributed continuous data were presented as mean and standard deviation (SD) while non-normally distributed continuous data by the median and interquartile range (IQR), and the dichotomous data were computed using frequency and percentage [18]. Analysis of variance was used to compare normally continuous variables and the Kruskal-Wallis H test was to compare non-normally distributed continuous variables. When comparing categorical data, the Fisher's exact test and Pearson chi-squared test (when more than 20% of cells have expected frequencies <5) were applied. Odds ratio (OR) and confidence interval (CI) were estimated with or without adjustment for covariates using Logistic regression models. We split interested characteristics into subgroups to investigate the potential influences on the resolution of the thrombus (e.g., age, gender, body mass index (BMI), LVEF, presenting diagnosis, location of thrombi, medical history, and combination therapy). Subgroup analyses were performed using stratified chi-square models and interactions between subgroups were analyzed using likelihood ratio tests. Two models were taken into account: (i) the unadjusted model (model 1), which contained the main predictor; (ii) model 2, which additionally included LVEF values and medical history of HF. A forest plot was created to display both multivariable Logistic regression and subgroup analysis. The cumulative event probability of resolution was estimated using the Kaplan-Meier method. In addition, a restricted cubic spline curve was used between the continuous variables and the rate of thrombus resolution. Comparisons were regarded as two-sided, and statistical significance was determined by the *p* value of 0.05. All analyses were scheduled for completion with R version 3.5.1 (The R Project for Statistical Computing, Vienna, Austria).

3. Results

3.1 Patients Characteristics

We identified 610 patients with VMT on the whole between July 2010 and October 2019 throughout this center. There were 78 patients that received thrombectomy therapy or ventricular aneurysm resection while 32 patients with heart transplantation within a 6-week follow-up. Additionally, we disqualified 14 patients with a long history of VMT (more than 3 months) and 9 patients who were not adolescents. Furthermore, 116 patients without oral anticoagulants and 165 patients lost to imaging follow-up were excluded (Fig. 1). Consequently, we enrolled 196 eligible patients: of them, 68.9% (n = 135) received VKAs while 31.1% (n = 61) received NOACs (Table 1). Both groups were predominately made up of men. In patients with NOACs, most of them were given rivaroxaban (n = 58, 95.1%) and two patients were administered dabigatran while one patient was given apixaban. Patients receiving NOACs were generally younger than those receiving VKAs. More than half of enrolled patients were diagnosed with 'others' diseases—hypertrophic cardiomyopathy, peripartum cardiomyopathy, myocarditis, arrhythmogenic right ventricular cardiomyopathy, hypertensive heart disease, noncompaction of ventricular myocardium, and other cardiovascular diseases, and approximately 20% of patients had ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM) respectively, while 55.8% of the patients with ICM experienced an acute MI with or without ventricular aneurysm. The majority of patients in our study were first diagnosed with VMT using routine echocardiography (n = 178, 90.8%), whereas the remaining patients with minor thrombus or apex thrombus were found by contrast echocardiography (n = 2, 1.0%), CT with a delayed phase scan (n = 10, 6.1%), and late gadolinium enhancement CMR imaging (n = 6, 3.1%). The median baseline LVEF was 31.5% and 83 out of 196 patients (42.3%) had LVEF $<30\%$ (8.6% with LVEF $<20\%$, 33.7% with LVEF 20% to 30%). The international normalized ratio (INR) data for 121 (61.7%) patients were available during the follow-

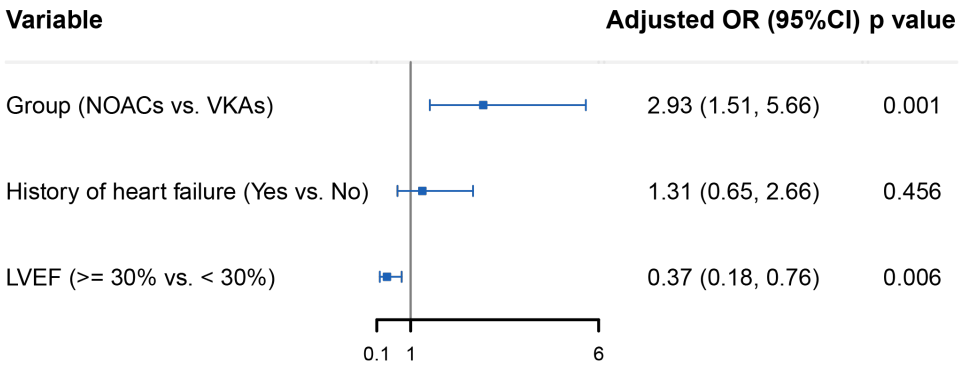

Fig. 2. Forest plot of multivariable analysis based on the statistically significant predictors in the univariable analysis. Error bars represent 95% CI. NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists; OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction.

up, while 46 out of 121 (38.0%) patients were with a time in the therapeutic range >60%. Moreover, we also compared the characteristics of included and excluded patients in the study and summarized the prognosis of patients who were not treated with oral anticoagulation or had no imaging follow-up (Details were shown in **Supplementary Tables 1,2**).

3.2 Primary Outcome

A total of 40 patients (65.5%) in NOACs use were successful in resolving their thrombi at 3 months as opposed to 57 patients (42.2%) in the VKAs group (p = 0.004). The median time of thrombus resolved or unresolved was non-significant between the two anticoagulants (p = 0.921, p = 0.985, respectively; Table 2). When assessing the relation between thrombus resolution rates and the baseline features of patients, we conducted a Logistic regression. In the univariable analysis, patients who received NOACs had a greater risk to have the thrombus resolved than those who were in the VKAs group (OR 2.61, 95% CI 1.39 to 4.89, p = 0.003). The medical history of HF in patients with VMT was associated with a close to two-fold increased resolution rate compared to VMT patients without prior HF (OR 2.10, 95% CI 1.17 to 3.77, p = 0.013). Likewise, patients with a lower LVEF had a higher likelihood of achieving thrombus resolution (OR 0.36, 95% CI 0.20 to 0.65, p = 0.001) (Table 3).

And adjusting variables that were identified in the univariate analysis to be statistically significant, NOACs remained a favorable resolution of thrombus versus VKAs (OR 2.93, 95% CI 1.51 to 5.66, p = 0.001). In multivariable Logistic regression, patients with LVEF under 30% experienced a greater thrombus resolution than those with LVEF over 30% (OR 0.37, 95% CI 0.18 to 0.76, p = 0.006) (Fig. 2).

3.3 Secondary Outcomes

Within a 3-month follow-up, a total of ten (5.1%) patients had minor bleeding events—one patient (1.6%) was in the NOACs group while nine (6.7%) patients were in the VKAs group (Table 2). No significant difference was observed in the bleeding rate among NOACs and VKAs group (p = 0.258). In the VKAs group, there was one patient (0.7%) who experienced lower extremity deep vein thrombosis. As a consequence of serious multiple organ dysfunction, progressive HF decompensation, or catastrophic infection illnesses, three patients (2.2%) died during their initial hospitalization while no patients died in the NOACs group.

3.4 Further Analysis

To determine how confounding factors influenced thrombus resolution, two models were taken into account. In the crude model, the result echoed that of univariable analysis (OR 2.61 95% CI 1.39 to 4.89, p = 0.003). The statistical significance was maintained in model 2 when the medical history of HF and LVEF levels were included (OR 2.93, 95% CI 1.51 to 5.66, p = 0.001) (Fig. 3).

According to the subgroup study, patients over 50 years old benefit more from NOAC anticoagulation than those using VKAs (OR 3.01, 95% CI 1.16 to 7.78, p = 0.023), and the interaction was not significant not only across age groups (p = 0.171) but also between age and anticoagulation treatment (p = 0.627). Compared with VKAs, males using NOACs might have superior resolution compared to VKAs (OR 2.42, 95% CI 1.16 to 5.04, p = 0.018), whereas no significance was observed in females (OR 3.40, 95% CI 0.97 to 11.91, p = 0.056). Patients who had a medical history of HF experienced a greater efficacy in NOACs use than VKAs (OR 4.10, 95% CI 1.67 to 10.05, p = 0.002), while those without a history of coronary artery diseases (CAD) had a similar outcome (OR 2.86, 95% CI 1.25 to 6.53, p = 0.013). Moreover, we conducted an additional subgroup analysis of patients with left VMT alone and there was no difference in the baseline characteristics between

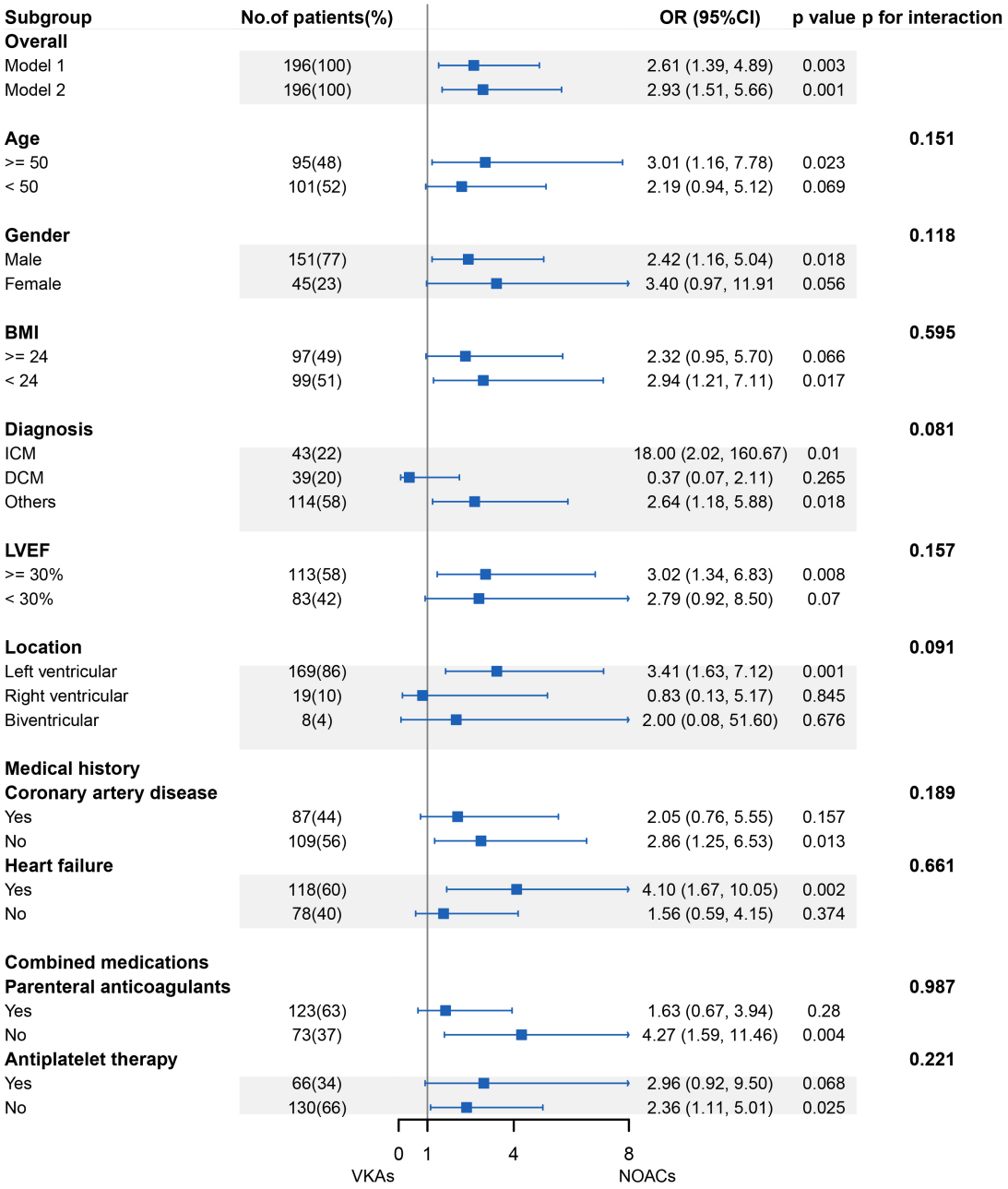

Fig. 3. Forest plot of subgroup analysis. The following adjustments were performed in regression models: model 1, crude model; model 2: model 1 + history of heart failure and LVEF. Error bars represent 95% CI. NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists; OR, odds ratio; CI, confidence interval; BMI, body mass index; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; Others, included hypertrophic cardiomyopathy, peripartum cardiomyopathy, myocarditis, arrhythmogenic right ventricular cardiomyopathy, hypertensive heart disease, and noncompaction of ventricular myocardium; LVEF, left ventricular ejection fraction.

the NOACs group and the VKAs group. And the outcome in univariate and multivariate logistic regression remained consistent with that of all VMT patients (**Supplementary Table 3**). Patients with left VMT alone in the NOACs group experienced a higher resolution of thrombus than those in the VKAs group (OR 3.41, 95% CI 1.63 to 7.12, $p = 0.001$; adjusted OR 3.79, 95% CI 1.76 to 8.19, $p < 0.001$). However, no significant differences were shown in patients with right ventricular or biventricular (OR 0.83, 95% CI 0.13 to 5.17, $p = 0.845$; OR 2.00, 95% CI 0.08 to 51.60, $p = 0.676$; separately). No significant interactions were found in the subgroups of age, gender, BMI, presenting diagnosis, medical history of CAD and HF, LVEF levels, location of thrombi, parenteral anticoagulants, and antiplatelet therapy (Fig. 3).

Table 3. Main results of univariable Logistic regression analysis.

Variable	OR (95% CI)	*p* value
Treatments		
NOACs vs VKAs	2.61 (1.39, 4.89)	0.003
Demography		
Age	0.66 (0.38, 1.16)	0.152
Male (vs Female)	1.03 (0.53, 2.01)	0.628
BMI	1.28 (0.73, 2.24)	0.392
Presenting diagnosis		0.206
DCM (vs ICM)	0.72 (0.30, 1.73)	0.462
Others[†] (vs ICM)	1.37 (0.68, 2.77)	0.379
Medical history		
Coronary artery diseases	0.66 (0.37, 1.16)	0.147
Atrial fibrillation	1.02 (0.41, 2.58)	0.962
Heart failure	2.10 (1.17, 3.77)	0.013
Hypertension	0.84 (0.45, 1.57)	0.588
Diabetes	0.95 (0.44, 2.04)	0.894
Hyperlipidemia	0.84 (0.47, 1.48)	0.545
Embolism	1.03 (0.54, 1.97)	0.935
Chronic kidney diseases	0.81 (0.21, 3.11)	0.757
Gastrointestinal bleeding	0.25 (0.03, 2.25)	0.215
Current smoker	0.82 (0.47, 1.43)	0.478
Excessive alcohol consumption[§]	0.77 (0.39, 1.50)	0.441
Location of ventricular thrombus		0.617
Right ventricular (vs left ventricular)	0.74 (0.28, 1.92)	0.531
Biventricular (vs left ventricular)	1.69 (0.39, 7.28)	0.484
Number of ventricular thrombus		
$\geq$2 (vs 1)	1.28 (0.51, 3.24)	0.604
LVEF	0.36 (0.20, 0.65)	0.001
D-Dimer	0.83 (0.42, 1.65)	0.601
Combined medications		
Parenteral anticoagulants	0.71 (0.40, 1.27)	0.253
Antiplatelet therapy	0.65 (0.36, 1.18)	0.160

[†]Other diagnoses included hypertrophic cardiomyopathy, peripartum cardiomyopathy, myocarditis, arrhythmogenic right ventricular cardiomyopathy, hypertensive heart disease, and noncompaction of ventricular myocardium.

[§]Excessive alcohol consumption: >40 grams per day for women and >80 grams per day for men, lasting more than 5 years.

Abbreviations: NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists; BMI, body mass index; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; OR, odds ratio, CI, confidence interval.

In addition, using cumulative event probability curves obtained from Kaplan-Meier estimates at one-year follow-up, we evaluated the rate of thrombus resolution between the NOACs group and the VKAs group, and the results indicated that patients receiving NOACs had higher rates of resolution than those receiving VKAs (Log-rank test, $p = 0.0041$; Fig. 4). The same analysis was conducted for patients with different levels of LVEF at baseline, which showed that patients in the group with lower LVEF had a higher rate of thrombus resolution than those with LVEF over 30% during the follow-up period (Log-rank test, $p = 0.0015$; **Supplementary Fig. 1**). And considering the LVEF as a continuous variable, we performed a restricted cubic spline curve which showed a linear relationship between the LVEF level and the thrombus resolution (p for linearity > 0.05; **Supplementary Fig. 2**). A lower LVEF level was significantly associated with an increased rate of thrombus resolution ($p = 0.0030$).

4. Discussion

In this retrospective observational study, NOACs were shown to be significantly associated with greater resolution of VMT than VKAs in the early period of observation, with or without adjustment, and patients with a medical history of HF or LVEF <30% had a greater thrombus resolution.

4.1 Comparison of NOACs versus VKAs on Efficacy and Safety in Patients with VMT

In aspects of our key findings, patients diagnosed with VMT might benefit better from NOACs as a therapy option than of VKAs, which were in line with multiple additional studies [19–35] (**Supplementary Table 4**). Albabtain *et al*. 2021 [22] found that in the warfarin group 68.6% of patients, and in the rivaroxaban group 71.4 % of patients, respectively, obtained thrombus resolution. The median time to resolution was shorter in the rivaroxaban group of patients, which was comparable to our study [22]. Several studies found that NOACs and VKAs had comparable efficacy and safety in the treatment of patients with left VMT [21–26]. Willeford *et al*. [21] analyzed that in either the unadjusted or the adjusted analysis, there was no noticeable difference between the NOACs and VKAs groups for the effectiveness or safety outcome. Herald *et al*. 2022 [36] supported that the NOACs treatment for left VMT could be as safe and effective as the warfarin treatment in the diverse population-based cohort of patients. The study especially focused on the safety outcome and it indicated that NOACs use was associated with a lower risk of bleeding without adding risks of embolism events [36]. Another meta-analysis also reported that patients with NOACs were less likely to experience major bleeding [37]. Chen *et al*. [38] included a total of thirteen retrospective studies with 2467 patients (NOACs = 489 vs warfarin = 1539), in terms of stroke events or clinically related bleeding events, NOACs had a lower risk than warfarin though no significant difference was observed in the resolution rate or bleeding events. And whether NOACs brought benefits or hazards in stroke or systemic embolism events was unknown. One study in 2021 included eighty-seven patients with left VMT, in the univariate logistic regression analysis, the NOACs group had a lower incidence of 66% in stroke or systemic embolism than the VKAs groups when antiplatelets were controlled [39]. Otherwise, a meta-analysis provided conflicting results that the incidence of systemic embolism in the

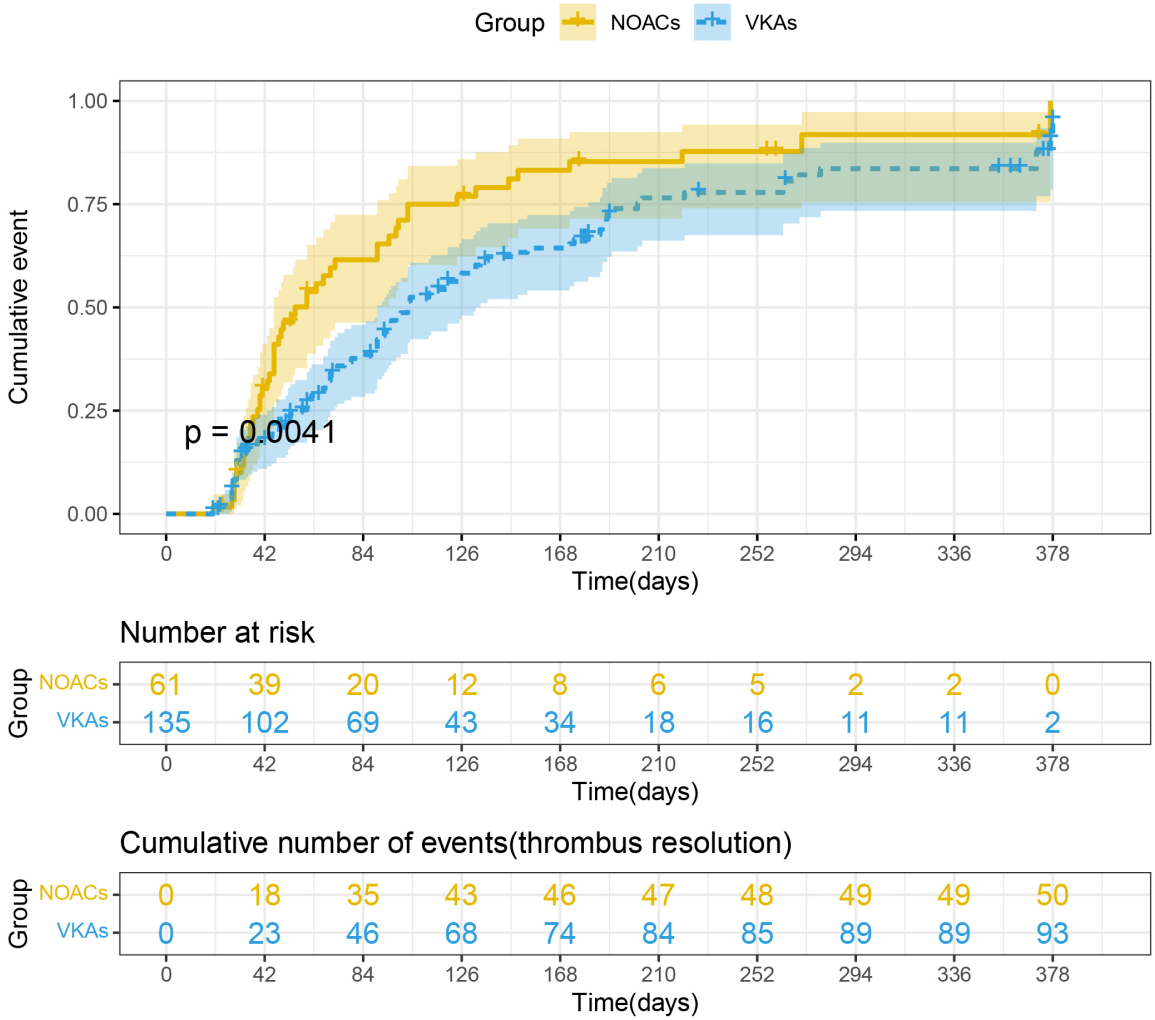

Fig. 4. Cumulative event probability curve for ventricular mural thrombus resolution of NOACs and VKAs within one-year follow-up. Kaplan-Meier method was used to calculate the cumulative event probability of two oral anticoagulants. Log-rank test was used to compare the cumulative event among groups ($p = 0.0041$). NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists.

NOACs group was 1.86 times higher than that in the VKAs group [40]. Also, Robinson *et al.* [41] discovered that the rate of systemic embolism was 2.71 times higher in the NOACs group than in the VKAs group.

4.2 Factors Related to Thrombus Resolution

Anticoagulants including NOACs and VKAs, which are extensively prescribed for the prevention and treatment of venous thromboembolism or stroke events, primarily act on clotting factors to prevent blood coagulation and block thrombosis [42,43]. From the study, most of the baseline characteristics, including demographics, presenting diagnosis, medical history, thrombi features, and agent combinations, showed no correlation with the thrombus resolution. Interestingly, the rate of VMT resolution was found to be correlated with both the history of HF and lower baseline LVEF values (either being the continuous variable or the binary variable according to a cutoff of <30%). The findings could be explained for two reasons. On the one hand, owing to the pathological conditions (e.g., blood stasis and hypercoagulability) that were associated with activation of the anticoagulation and fibrinolysis system, patients who were hospitalized with severe cardiac dysfunction and experienced reduced LVEF at baseline were more likely to develop a new onset VMT, which indicated that the thrombus among these patients was easier to resolve than those calcified ones [44]. On other hand, the standardized treatment for HF may have an effect on thrombus resolution, by improving cardiac function [45]. It is possible that some of the effects of angiotensin-converting enzyme inhibitors may be mediated by beneficial effects on platelets such as reducing fibrinogen levels and improving endothelial function [46], which in turn reduces thrombosis. According to a study with 100 patients with VMT, the mean LVEF was 28.5%

and the results showed that the mean LVEF improved considerably more in patients with resolved thrombus than in those without [24]. Hofer *et al*. 2021 [47] also reported that the median LVEF was lower in the group of resolved thrombus and that more than half of patients with thrombus resolution had LVEFs below 50%. In the current study, patients had a median LVEF of 31.5% and received systemic treatment during hospitalization. We might assume that patients with reduced LVEF at admission had better cardiac function under medication management, as proven by prescriptions, which increased the likelihood of thrombus resolution, though patient compliance after discharge was undetermined.

Considering the influence of these factors related to thrombus resolution, we performed subgroup analyses of different models and other potential factors. Patients treated with NOACs had a resolution rate that was over twice as high as those who administered VKAs in these models which created potential confounders. And in patients with a medical history of HF, NOACs showed a better rate of resolution than VKAs. Furthermore, our study indicated that patients >50 years old had a greater resolution in the NOACs group and the reason can be accounted for that the older patients are, the poorer adherence to VKAs they have, demonstrating that patients who are less likely to monitor their INR may use NOACs if they have no contraindications, particularly during the pandemic. Despite the fact that patients with ICM in the NOACs group had a higher likelihood of having the thrombus resolved than those in the VKAs group, the result would still be considered seriously because the confidence interval was too wide. Additionally, it remained unknown for the use of NOACs in patients with right VMT or biventricular thrombus, especially in those with thrombophilia. European Society of Cardiology guidelines recommended that the first-line anticoagulant treatment for people with antiphospholipid antibody syndrome should be warfarin rather than a NOAC [48,49].

4.3 Limitations

First, given the observational study's intrinsic limits and the small sample size, the externality of the result is further constrained. Additionally, it is difficult to determine the adherence of patients prescribed warfarin due to restrictions to INR measurements, and the net outcome of warfarin is still unclear in the current study. Second, we mostly relied on transthoracic echocardiography, which may have missed minor thrombi during the follow-up period since CMR or contrast echocardiography is the gold standard for detecting VMT.

More randomized controlled trials are required to assess the efficacy and hard outcomes in the comparison of NOACs versus VKAs and we hope those upcoming results from large trials will provide cheerful and reliable evidence on this topic (NCT03764241 [50], NCT 03415386, NCT03232398, NCT02982590, NCT04970576, ChiCTR2100048098). The evidence-based VMT guideline is critical for regulating clinician practice and guaranteeing consistency of treatment across specific doctors.

5. Conclusions

In this single-center retrospective cohort study, patients with a medical history of HF or LVEF <30% experienced a higher thrombus resolution. Additionally, the resolution of VMT with NOACs treatment was significantly greater than that with VKAs therapy at 3 months, with or without adjusting for baseline variables. Randomized controlled trials with long-term follow-up are required to properly evaluate the effectiveness of therapies, with the target of ultimately improving the outcome of patients with VMT.

Abbreviations

VMT, ventricular mural thrombus; NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists; BMI, body mass index; SD, standard deviation; IQR, interquartile range; OR, odds ratio; CT, computer tomography; CMR, cardiac magnetic resonance; HF, heart failure; MI, myocardial infarction; CAD, coronary artery diseases; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

QY and XQ extracted the data, and XL contributed to data analysis. QY and DG drafted the manuscript, XL performed the statistical analysis. YL reviewed and corrected the manuscript. QY, XQ and YL discussed the results and contributed to the final manuscript. All authors read and approved the manuscript.

Ethics Approval and Consent to Participate

The study protocol was approved by the local ethics committee (Ethics Committee of Fuwai Hospital, Approval No.: 20221757, Trial No.: 2022-ZX025) and oral consent was obtained at the time of the telephone interview.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.rcm2403074.

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