Original Article

Apixaban versus Warfarin in Patients with Left Ventricular Thrombus: A Pilot Prospective Randomized Outcome Blinded Study Investigating Size Reduction or Resolution of Left Ventricular Thrombus

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Abstract

Background: Treatment of the left ventricular thrombus (LVT) with Vitamin K antagonists (VKAs) such as warfarin may lead to longer hospitalization. Thus, the potential of non-VKA oral anticoagulants as alternative to warfarin need to be explored. This study aims to investigate the size reduction or resolution of LVT with apixaban compared to conventional warfarin. **Materials and Methods:** This is a pilot, prospective, single-center, randomized, single-blinded outcome study with patients diagnosed with LVT. Patients diagnosed with LVT by echocardiography were randomized into two treatment groups: apixaban or warfarin, with target international normalized ratio 2–3. Echocardiography was repeated at weeks 6 and 12 to assess the LVT size. The percentage of reduction or total resolution during the first 12 weeks was the primary endpoint. Repeated measure ANCOVA was used to evaluate the differences in left ventricular (LV) thrombus size between treatment groups. **Results:** Twenty-seven patients were recruited: 14 were treated with apixaban and 13 patients with warfarin. Thirteen patients completed treatment in the apixaban arm with one patient lost to follow-up, and one death observed. In the warfarin arm, nine patients completed the study follow-up, and four died during the follow-up. The mean (standard deviation [SD]) reduction in LV thrombus size in apixaban arm was 65.1% (SD 31.3) versus warfarin arm, 61.5% (SD 44.0) at the 12th week follow-up (P = 0.816). Safety outcomes were similar with both treatment arms. **Conclusions:** This pilot study suggests that apixaban may have similar effectiveness and safety to warfarin for LVT resolution.

Keywords: *Acute myocardial infarction, apixaban, congestive heart failure, echocardiography, left ventricular thrombus, warfarin*

Introduction

The left ventricular thrombus (LVT) is a well-recognized complication of acute myocardial infarction (AMI) and congestive heart failure, often in association with severely impaired LV systolic function. LVT incidence has been reported to be as high as 30%–40% in patients with an anterior AMI, while in patients with a nonanterior AMI, the risk is lower than 5%.[1] With early revascularization and aggressive anticoagulation, LVT incidence among patients with anterior AMI reduced to 5%–15%.[2-4] However, some studies reported that despite aggressive revascularization, LVT prevalence may remain high in anterior AMI patients (23.5%).[1,5,6] Meanwhile, in patients with dilated cardiomyopathy and congestive heart failure, the reported LVT prevalence varies, from 10% to 30%.[7,8]

In the Malaysian population, ischemic-induced left ventricular (LV) failure is common, due to the low rate (16.4%) of primary angioplasty.[9] As a result, the LVT prevalence is higher in this population compared with the Western population. Conventionally, the first-line therapy for LVT is the combination of the Vitamin K antagonist (VKA) warfarin and intravenous (IV) heparin. However, this standard therapy often leads to extended hospitalization to achieve the targeted international normalized ratio (INR). Non-VKA oral anticoagulants (NOACs) are potential good alternative, and

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no anticoagulation monitoring is needed. However, routine NOAC usage in LVT is not recommended due to the lack of evidence. Apixaban is one of the NOACs used in multiple LVT case reports and has shown efficacy, with low bleeding complications.[10-13]

Our aim was to conduct a pilot prospective randomized single-blinded outcome study investigating the size reduction or resolution of LVT with apixaban compared to conventional warfarin.

Materials and Methods

The procedures of this study have been approved by the Research Ethics Committee (human) of Universiti Sains Malaysia and conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent. Patients were recruited following set inclusion criteria namely, age 18–80 years old; heart failure diagnosis with newly discovered LV thrombus confirmed on two-dimensional echocardiography by two operators (to obtain average and increase accuracy); and HAS-BLED score of <3. Exclusion criteria included episodes of major bleeding in the past 6 months. Major bleeding was defined as history of significant drop in hemoglobin level of at least 2 g/dL with or without blood transfusion of at least two packed cell units. Other exclusion criteria were as follows: a history of intracranial bleeding or large ischemic stroke; advanced renal and liver disease on cardiac devices; clinically unstable or in shock. In terms of echocardiography findings, old and organized thrombus was excluded based on the two echocardiographers' experience.

Treatment allocation was carried out by permuted block randomization using computer software into two groups. The first arm was given the study drug, apixaban 5 mg twice daily (BD) for 12 weeks, with the dose of 2.5 mg BD chosen for patients with two of the following characteristics: age ≥75 years, weight ≤60 kg, or serum creatinine ≥133 μmol/L. The other treatment arm received the standard therapy of warfarin with initial heparin infusion, aiming for a target INR of 2–3. In the presence of recent acute coronary syndrome and for patients who did not undergo angioplasty, only a single antiplatelet was used concurrently. Postangioplasty patients were placed on triple therapy (apixaban/warfarin + dual antiplatelet therapy).

Echocardiographers were blinded to the patient's treatment, and a previous echocardiography report was made available for reference. The completed echocardiography data entry forms were kept separately out of reach from investigators for blinding purposes. Unblinding of the reports was conducted only when any suspected adverse events occurred. The study visits were scheduled at weeks 0, 1, 2, 3, 6, 9, and not more than 15 weeks. Weeks 0, 6, and 12 were for echocardiography, whereas the other visits were for INR monitoring and to screen for any adverse events. These methods include blood investigations for hemoglobin level and renal or liver function for both arms.

In total, three echocardiographic examinations were conducted to each patient. The size was measured by universal tracing function by Toshiba Aplio 300 (Toshiba Medical System Corporation, Japan) and was reported as area in cm^2 [example shown in Figure 1]. During the study duration, the treatment (apixaban/warfarin) was continued after total resolution of LVT until the next visit with echocardiography when no contraindication was observed. The purpose was to ensure that the resolution was maintained on two echocardiographic examinations (6 weeks apart). The primary endpoint was the LV thrombus size resolution in percentage after 3 months.

Where there was residual small thrombus present, all anticoagulants were switched to warfarin as per local protocol after week 15. After 15 weeks had elapsed, follow-up was conducted by every 2 months until the end of the study duration of 24 months. Any major cardiovascular events, including bleeding, stroke and death from any cause, was recorded and analyzed.

For a pilot study, the minimum number per group was 12 using "the rule of 12."[14] Schoenfeld suggested that in most cases, 25 subjects would be sufficient for a meaningful difference between the groups.[15]

Statistical analysis

Statistical analysis was based on intention to treat analysis. The full analysis set included patients who received at least one dose of medication or had one or more postrandomization, follow-up evaluation (s). For the primary and secondary outcomes, descriptive statistics and 95% confidence intervals were used to summarize the differences between groups. All data were entered into IBM® SPSS® Statistics version 24(IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, New York, United States: IBM Corp). The descriptive statistics of variables was presented as mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables.

The comparison of LV thrombus size (cm^2) between the warfarin and apixaban treatment groups was analyzed using repeated measures of ANCOVA. Model assumptions for the repeated measures ANCOVA analysis were then checked for normality, homogeneity of variance, and compound symmetry. Homogeneity of variance was tested using Levene's test, and the equal variance assumption was fulfilled. Box test was applied to test covariance ($P > 0.05$). Compound symmetry was then checked for all of the measurements using Mauchly's test of sphericity. $P < 0.05$ indicates that assumption of compound symmetry was not met. Thus, analysis continued with multivariate test or univariate test with Epsilon correction. When the time and LVT area interaction was significant ($P < 0.05$), further analysis then produced adjusted means with 95% confidence interval. The analysis was continued with adjusted confidence intervals using Bonferroni adjustment method. Differences exhibiting $P < 0.05$ was considered statistically significant.

Results

A total of 112 patients were screened. Of these, 20 had organized LVT, 24 had old thrombus, two had advance

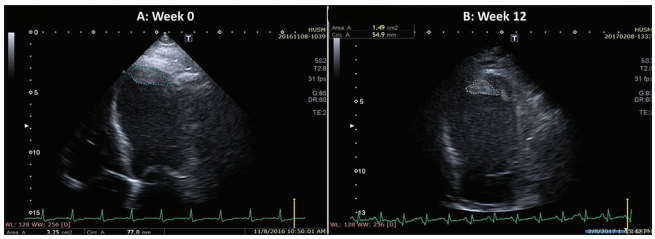

Figure 1: Left ventricular thrombus size measurement. A: At week 0. B: At week 12

chronic kidney disease, 10 were in critical clinical condition and 20 refused to participate due to logistical issues. Thus, 27 patients (mean age 55.19, SD 11.01 years) were finally included in this study, with 14 patients in the apixaban arm and 13 patients in the warfarin arm. Mean ejection fraction on echocardiography was 33.5% (SD 5.73) [Table 1].

Thirteen patients completed the treatment in the apixaban arm with one patient lost to follow-up. Two patients died in the apixaban arm at the end of the study period: one was caused by massive ischemic stroke with hemorrhagic transformation, the second by worsening heart failure. Meanwhile, nine patients completed the study, and four died during the first 12 weeks in the warfarin arm.

LVT mean size reduction throughout the study period for both arms is shown in Figure 2. Repeated measure ANCOVA analysis showed a statistically significant mean difference in the LVT size reduction when comparing week 0 versus week 6 and week 0 versus week 12 of both arms. Mean difference was greater in the apixaban arm than in the warfarin arm [Table 2]. Repeated measures ANCOVA within group analysis was applied followed by pairwise comparison with 95% confidence interval adjustment by Bonferroni correction. The LVT size from weeks 0 to 12 showed no significant difference of percentage of reduction for both arms [Table 3].

There were no statistically significant differences in LVT mean size (cm^2) between two treatment arms in baseline, week 6 and week 12 [Table 4]. The mean (SD) reduction in LV thrombus size in apixaban arm was 65.1% (SD 31.3) versus warfarin arm, 61.5% (SD 44.0) at the 12th week follow-up (P = 0.816) [Table 5].

In this study, we found safety outcomes were similar with both treatment arms.

Meanwhile, interobserver reliability analysis by intraclass correlation coefficient between the cardiologist and the staff nurse showed the lowest correlation in week 0 (0.72) with higher correlation in both week 6 (0.91) and 12 (0.98).

Discussion

In this pilot study, apixaban demonstrated similar effectiveness and safety to warfarin for LVT resolution. Further large prospective randomized trials are needed to explore this group of patients.

Multiple case reports have suggested that apixaban and NOACs are efficacious for the treatment of LVT.[16] Robinson *et al*. reported a single-center study of patients with LVT, in which NOAC was used off label. In their study, NOAC-treated patients had similar systemic embolism-free survival compared with the warfarin-treated patients.[17] The X-TRA study was the only prospective study of NOACs used for intracardiac thrombus, especially within the left atrial appendage.[18] The present study provides unique prospectively collected data for the use of NOACs with LVT.

This study showed consistent LVT size reduction in both treatment groups. Thrombus size upon admission could be one of the predictors of thrombus resolution.[19] The apixaban group had achieved significant size reduction between weeks

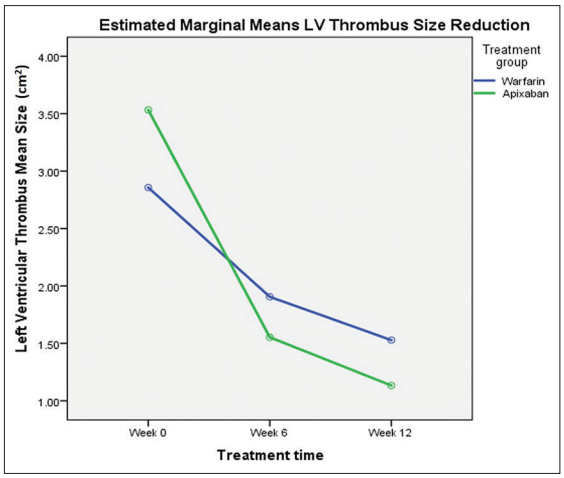

Figure 2: Left ventricular thrombus size reduction based on time

Table 1: Demographic characteristics and selected clinical parameters of patients with left ventricular thrombus

Variables	Apixaban group (n=14)	Warfarin group (n=13)
Gender		
Male	13	12
Female	1	1
Age (years)[a]	55.36 (11.04)	55.00 (11.42)
Diabetes mellitus	7 (50.0)	9 (69.2)
Hypertension	8 (57.1)	9 (69.2)
Ischemic heart disease	9 (64.3)	8 (61.5)
Atrial fibrillation	1 (7.1)	0 (0)
Chronic kidney disease	5 (35.7)	7 (53.8)
Hyperlipidemia	8 (57.1)	9 (69.2)
HAS-BLED score[a]	1.0 (0.68)	1.46 (0.66)

[a]Mean (SD). HAS-BLED: H=Hypertension systolic blood pressure >160 mmHg, A=Abnormal liver and renal function, Abnormal liver function=History of cirrhosis, or bilirubin >2x the upper limit of normal in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase levels >3x the upper limit of normal, Abnormal renal function=On dialysis, a history of kidney transplantation, or serum creatinine value >200 µmol/L, S=Stroke in history, B=Bleeding in history, L=Labile INRs=Time within therapeutic range <60%, E=Elderly age >65, D=Drugs. Use of platelet inhibitors or nonsteroidal anti-inflammatory drugs/alcohol use (more than 8 units per week). SD=Standard deviation

Table 2: Comparison of mean left ventricular thrombus size within each treatment groups based on time (time effect)

Comparison	Apixaban		Warfarin	
	Mean difference (cm^2) (95% CI)	*P*	Mean difference (cm^2) (95% CI)	*P*
Week 0 - week 6	1.98 (0.41-3.55)	0.013	0.95 cm^2 (0.17-1.73)	0.017
Week 0 - week 12	2.40 (0.76-4.04)	0.005	1.33 cm^2 (0.22-2.43)	0.018
Week 6 - week 12	0.42 (−0.19-1.03)	0.233	0.38 cm^2 (−0.27-1.02)	0.380

CI=Confidence interval

Table 3: Overall mean difference of mean left ventricular thrombus between treatment groups (treatment effect)

Comparison	Mean difference (cm^2) (95% CI)	*P*
Apixaban - Warfarin	−0.01 (−1.02-0.99)	>0.950

Repeated measures ANCOVA between group analysis was applied. *F*-stat (df)=0.001 (1). CI=Confidence interval

Table 4: Comparison of mean left ventricular thrombus between two treatment groups based on time (time-treatment interaction)

	Comparison	Mean difference (95% CI)	*P*
Week 0	Apixaban - Warfarin	0.68 cm^2 (−0.59-1.95)	0.278
Week 6	Apixaban - Warfarin	−0.34 cm^2 (−1.49-0.82)	0.550
Week 12	Apixaban - Warfarin	−0.38 cm^2 (−1.62-0.85)	0.529

Repeated measures ANCOVA between group analysis with regard to time was applied followed by pairwise comparison with 95% CI adjustment by Bonferroni correction. Assumptions of normality, homogeneity of variances and compound symmetry were checked and were fulfilled. CI=Confidence interval

Table 5: Mean left ventricular thrombus reduction in percentage comparison between apixaban and warfarin

Treatment group	*n*	Mean percentage reduction (SD)	Mean difference (95% CI)	*P*
Apixaban	13	65.08 (31.34)	−3.62 (−35.57-28.32)	0.816
Warfarin	11	61.45 (43.95)		

Percentage was calculated at week 12 reduction compared with week 0. When no data are available in week 12, data in week 6 were used. SD=Standard deviation, CI=Confidence interval

0 and 6 and weeks 0 and 12, similar to the outcome in the warfarin group. Similarly, the mean percentage of reduction for LVT was no different between the two groups although the reduction rate was greater in apixaban group for the first 6 weeks. Of note, LVT was diagnosed and monitored by transthoracic echocardiography which is an acceptable measurement tool employed in other case reports for the use of NOAC in LVT. In addition, utilizing echocardiography to measure the LVT volume quantitatively by planimetry measurement has the advantage of intra- and inter-reader reproducibility.[20] The lower intraclass correlation in week 0 could be due to higher measurement variability in early or actively forming thrombus which may appear echo-lucent and highly mobile. In contrast, older and organized thrombus generally has smooth cavitary surface, which may explain the higher correlation toward the end of treatment.

Additional imaging by contrast-enhanced cardiac magnetic resonance could improve the intracardiac thrombus detection and further characterizes the thrombus morphology.[21]

In terms of adverse events, four death in the warfarin arm occurred during 12 weeks while two deaths in the apixaban arm occurred later. All hospitalization was caused by worsening heart failure. The stroke event only occurred in the apixaban arm. The number of deaths was small in both treatment arms for a meaningful interpretation.

Limitations

This pilot study has many limitations. First, the sample size of the study was small due to the pilot nature of the study, being a single-center strict study and strict exclusion criteria. The high rate of early angioplasty in this center also contributed to the low number of patients with LVT. In addition, many patients with LVT were excluded because of their ill clinical condition on presentation, deranged renal/liver functions on diagnosis, organized or old LVT and other logistic issues. When patients with LVT were newly diagnosed together with deranged liver and/or renal functions, they had to be treated as soon as possible with IV heparin to avoid thromboembolism. Warfarin was usually added as part of the protocol while they were in the ward, and such patients could not be enrolled. Second, wide variation of data for the thrombus size was expected due to high mobility and deformity of early thrombus.[22,23] This has also been seen in other echocardiographic measurements.[24-26] A bigger sample size would attenuate this effect and narrow the confidence interval. No further LVT evaluation was observed by cardiovascular magnetic resonance due to limited availability and high cost. Complementing transthoracic echocardiography with additional contrast-enhanced cardiac magnetic resonance imaging may improve these shortcomings.[21]

Conclusions

This pilot study suggests that apixaban may be used with similar effectiveness and safety to warfarin for LVT resolution. Further large prospective randomized trials are needed to explore treatment options in this group of patients.

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Conflicts of interest

There are no conflicts of interest.

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