Thoracoscopic Left Atrial Appendage Occlusion for Stroke Prevention Compared with Long-Term Warfarin Therapy in Patients With Nonvalvular Atrial Fibrillation

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Thoracoscopic left atrial appendage (LAA) occlusion is an alternative treatment for stroke prevention in patients with atrial fibrillation. Prospective study comparing thoracoscopic LAA occlusion and warfarin therapy is still lacking. The goal of this prospective cohort study was to assess the safety and efficacy of thoracoscopic LAA occlusion for stroke prevention in patients with nonvalvular atrial fibrillation compared with long-term warfarin therapy. Four hundred and ninety-two nonvalvular atrial fibrillation patients were enrolled. Two hundred and fifty-seven patients were treated with thoracoscopic LAA occlusion and 235 with long-term warfarin therapy. At 24 months, the rate of the first efficacy endpoint (composite of stroke, systemic embolism, and death) was 0.018 in the surgical group versus 0.043 in the warfarin group ($p = 0.033$). The rate of the second efficacy endpoint (stroke and systemic embolism excluding the first 7 days after procedure) was 0.010 versus 0.034 ($p = 0.019$). The rate of the first safety endpoint of bleeding was 0.016 versus 0.044 ($p = 0.022$). In conclusion, this study showed that thoracoscopic LAA occlusion was superior to warfarin for stroke prevention. The surgical group also had significantly lower bleeding risk. The incidence of surgical complications was low, and all occurred in hospital without causing serious outcomes. **© 2018 Published by Elsevier Inc.** **(Am J Cardiol 2019;123:50−56)**

Atrial fibrillation (AF) is associated with a fivefold increased risk of ischemic stroke after adjustment for other risk factors.[1] Stroke is a major cause of death and disability. Therefore, stroke prevention is the focus of AF management.

Despite the proven efficacy of warfarin,[2] it has several limitations such as drug interactions, narrow security window, and high risk of bleeding, which leads to underutilization and frequent discontinuation.[3] Only 50% patients could persist in long-term warfarin therapy.[4] Both percutaneous left atrial appendage (LAA) occlusion and thoracoscopic LAA occlusion are the alternative local treatments for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). Profound evidence of large-scale prospective study comparing thoracoscopic LAA occlusion and warfarin therapy is still lacking.

Methods

This study is a prospective cohort study that assesses the safety and efficacy of thoracoscopic LAA occlusion for stroke prevention in patients with NVAF.

From January 1, 2013 to December 31, 2015, 492 consecutive patients with recurrent AF after radiofrequency ablation, who were collected from Atrial Fibrillation Center (jointly formed by Department of Cardiology and Cardiac Surgery) of Beijing Anzhen Hospital, were enrolled in this study. Of these, 257 consecutive patients with NVAF were treated with thoracoscopic LAA occlusion and 235 NVAF patients were treated with long-term warfarin therapy. This study is a single-centered prospective cohort study. In accordance with contemporary guidelines for stroke prevention in AF, patients could be enrolled with a CHADS2 ((hypertension/diabetes/stroke/age ≥ 75/congestive heart failure) score ≥ 1. The inclusion criteria were as follows: age ≥ 18 years; history of paroxysmal, persistent, and permanent NVAF; CHADS2 ≥ 1. Exclusion criteria included diseases that required long-term anticoagulant therapy except AF; Surgical LAA occlusion combined with coronary artery bypass grafting or valve replacement; the diseases that could cause embolism except AF, include atrial septal defect, mechanical heart valve prosthesis, patent foramen ovale with atrial septal aneurysm, left ventricular ejection fraction $< 30\%$, intracardiac thrombus, complex (mobile or ulcerated) atherosclerotic aorta, symptomatic carotid artery disease, contraindication to warfarin, or aspirin. Patients treated

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See page 56 for disclosure information.

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with clopidogrel were excluded to avoid the confounding variable of chronic thienopyridines for its effects on stroke, bleeding, and thromboembolism. Neurological examinations were performed. For patients with previous cerebral infarction, head computed tomography (CT) or magnetic resonance imaging (MRI) was collected as the baseline data for later comparison with the postprocedure data. The Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University, approved this study and all patients provided written informed consent for participation in this study.

In the surgical group, thoracoscopic-assisted bilateral intercostal small incisions were performed without cardiopulmonary bypass. Use a modern stapler (Johnson & Johnson EZ-45G) employing 2 lines of staples to resect and suture the LAA, which was proved to be the most durable sutures for LAA resection. They were significantly better than single layered sutures in terms of resilience to pneumatic pressure.[5] The line of surgical closure is placed strictly at the border zone of the LAA entrance in order to prevent potentially thrombogenic stumps. Thoracoscopic LAA occlusion has been applied to clinical practice for a long time and is a mature technique. Warfarin was not bridged to heparin at the time of surgery. After procedure, patients were treated with warfarin for 3 months and international normalized ratio (INR) was monitored. Warfarin was stopped after 3 months. Transesophageal echocardiography (TEE) was performed at 3 months', and 12 months' follow-up to confirm if the LAA were completely resected. The success rate of LAA resection was 76.7% (197/257, LAA stump <1 cm). If the 3-month TEE documented either complete closure of the LAA, or if LAA stump <1 cm in width and there was no definite visible large thrombus, warfarin was discontinued. In the chronic warfarin group, patients were treated with warfarin for life to achieve INR 2.0 to 3.0. Patients were followed-up for 2 years. Telephone and outpatient follow-up was undertaken after one week/3 months/6 months/12 months/18 months/24 months, recording when stroke/embolism/death/bleeding occurred.

There were 4 coprimary endpoints. The first efficacy endpoint was a composite of stroke, systemic embolism (SE), and cardiovascular/unexplained death. The second efficacy endpoint was late-ischemic efficacy, a composite of stroke or SE excluding the first 7 days after procedure, and subgroup analysis was conducted. The first safety endpoint was all the bleeding events including surgery-related hemorrhage such as pericardial effusion/chest wall hematoma/LAA suture bleeding, and surgery-unrelated hemorrhage such as gastrointestinal bleeding/hematuria/nose bleeding/cranial bleed /anemia requiring transfusion/any bleeding event requiring transfusion/other types of bleeding. Surgery-related stroke were calculated in the first efficacy endpoint and excluded from this safety endpoint. The second safety endpoint was surgical complications in the first week after surgery for the surgical group, including pericardial effusion/chest wall hematoma/surgery-related stroke/in-hospital death/intraoperative thoracotomy.

The time in therapeutic range (TTR) is the percentage of time that INR is within the range between 2.0 to 3.0, which is a biomarker to assess the quality of anticoagulation control.[6] The calculation method is the proportion of the time of reaching target INR to the follow-up time, excluding the initial time of INR fluctuations. Patients should be given the necessary diet and medication guidance, and be cautious with food and drugs that affect the efficacy of warfarin. Severe bleeding (digestive tract/urinary tract/cerebral hemorrhage, etc.) occurred in patients requires immediate warfarin withdrawal and vitamin K correction. Calculate the ratio of patients that discontinue medication. Neurological assessments were conducted at baseline, 12 months, and 24 months. Neurologic events happened at any time required additional examination.

Continuous variables were expressed as mean $\pm$ standard deviation in case of normal distribution and differences between the surgical group and the warfarin group were determined by two-independent samples *t* test. Categorical variables were presented as counts and percentages and compared by chi-square test. In analyses of each outcome, follow-up continued until the date of an endpoint event, death, or until 2 years at the end of the follow-up period, whichever occurred first. All patients without an event or lost to follow-up were censored at the time of the last known event status. Mantel-Cox method was used to calculate hazard ratios and 95% confidence intervals for comparisons of clinical outcomes between the surgical group and the warfarin group. Kaplan-Meier curves for the primary end point were also constructed. Patients in the warfarin group were used as the reference group in the analyses. Log-rank tests were used to compare Kaplan-Meier curves for overall follow-up and beyond 7 days and 3 months to assess the influence of thoracoscopic LAA occlusion and chronic warfarin therapy on the rates of primary efficacy end points and bleeding events. Consistency of the primary efficacy results across different patient subgroups beyond 7 days and 3 months was assessed by use of Cox proportional hazard models that incorporated an interaction term between treatment groups and patient subgroups. p values for the interaction between endpoints and treatment with respect to the different subgroups were calculated.

Statistical analyses were performed using SPSS software for Windows (version 22.0, SPSS Inc., Chicago, Illinois). A probability value of $p < 0.05$ in two-side was considered statistically significant in all analyses.

Results

The study enrolled up to 492 NVAF patients including 257 (52.2%) patients treated with thoracoscopic LAA occlusion (17 were lost to follow-up) and 235 (47.8%) patients treated with long-term warfarin therapy (14 were lost to follow-up). Baseline characteristics are summarized in Table 1.There was no significant difference in baseline data between the two groups (Table 2).

The 24-month event rates of the first primary efficacy endpoint were significantly different between the 2 groups. The event rate was 1.8 events per 100 patient-years in the surgical group, and 4.3 events per 100 patient-years in the warfarin group. However, the incidence of stroke/TIA was only 0.778 events per 100 patient-years in the surgical group, which dropped by 66.75% comparing with 2.340 events per 100 patient-years in the warfarin group. K-M

Table 1
Baseline characteristics of the study population

Variable	Long-term warfarin (n = 235)	Thoracoscopic LAA Occlusion (n = 257)	p Value
Age (years)	67.69 ± 9.87	67.68 ± 9.84	0.992
BMI (kg/m^2)	26.50 ± 3.42	26.48 ± 4.46	0.958
Men/Women	167 (71.1%)/68 (28.9%)	175 (68.1%)/82 (31.9%)	0.475
Type of nonvalvular atrial fibrillation			0.738
Paroxysmal	68 (28.9%)	69 (26.8%)	
Persistent	78 (33.2%)	82 (31.9%)	
Permanent	89 (37.9%)	106 (41.2%)	
Risk factors for stroke			
Age > 65 years	73 (31.1%)	75 (29.2%)	0.650
Chronic heart failure	37 (15.7%)	35 (13.6%)	0.505
Hypertension	191 (81.3%)	203 (79.0%)	0.526
Diabetes mellitus	67 (28.5%)	70 (27.2%)	0.753
Previous stroke/transient ischemic attack	57 (24.3%)	65 (25.3%)	0.790
$CHADS_2$ score (continuous)	2.05 ± 1.05	1.99 ± 1.01	0.525
$CHADS_2$ score (categorical)			0.872
1	84 (35.7%)	97 (37.7%)	
2	86 (36.6%)	92 (35.8%)	
3	41 (17.4%)	48 (18.7%)	
4	17 (7.2%)	13 (5.1%)	
5	7 (3.0%)	7 (2.7%)	
HAS-BLED score (continuous)	1.84 ± 0.83	1.88 ± 0.86	0.631
HAS-BLED score (categorical)			0.989
0	5 (2.1%)	6 (2.3%)	
1	81 (34.5%)	84 (32.7%)	
2	100 (42.6%)	111 (43.2%)	
3	45 (19.1%)	49 (19.1%)	
4	3 (1.3%)	5 (1.9%)	
5	1 (0.4%)	2 (0.8%)	

Table 2
Primary efficacy results of 2-year follow-up

	Long-term warfarin (n = 235)		Thoracoscopic LAA Occlusion (n = 257)		HR (Surgical group/Warfarin group)	95% CI	p
	Events/Patient-Years	Observed rate: Events per 100 Patient-Years (95% CI)	Events/Patient-Years	Observed rate: Events per 100 Patient-Years (95% CI)			
Primary efficacy	19/439.8	4.3 (2.4−6.2)	9/493.6	1.8 (0.6−3.0)	0.42	0.19−0.93	0.033
Stroke/TIA	11/448.5	2.5 (1.0−3.9)	4/496.6	0.8 (0.0−1.6)	0.33	0.11−1.03	0.057
Systemic embolism	4/454.3	0.9 (0.0−1.7)	2/499.5	0.4 (0.0−1.0)	0.46	0.08−2.49	0.363
All−cause mortality	4/455.9	0.9 (0.0−1.7)	3/500.3	0.6 (0.0−1.3)	0.68	0.15−3.05	0.616

curve survival analysis showed significant difference between the two groups (as shown in Figure 1).

The difference of late-ischemic primary efficacy endpoint has statistical significance (as showed in Table 3). K-M curve survival analysis showed significant difference between the two groups (p = 0.019; as shown in Figure 1). A subgroup analysis was stratified by clinical characteristics on composite stroke from 7 days after procedure to 2 years between surgical and warfarin groups (as shown in Figure 2).

The bleeding distribution and incidence of hemorrhage were shown in Tables 1 and 4. The total hemorrhage events in surgical group were significantly less than those in the warfarin chronic group. There was a significant difference in the incidence of digestive tract hemorrhage between the two groups. The incidence of intracranial hemorrhage in the warfarin group was 2/235 (0.9%), whereas no intracranial hemorrhage happened in the surgical group. There were 6 surgery-unrelated bleeding events in the surgical group, which accounted for 75% of the total bleeding events. Surgery-related bleeding events were mainly pericardial effusion (1/257) and chest wall wound bleeding (1/257), which accounted for 25% of the total bleeding events. In the surgical group, 5 of 8 bleeding events (62.5%) happened in the 3 months of warfarin therapy after procedure; There were 19 bleeding events in the warfarin

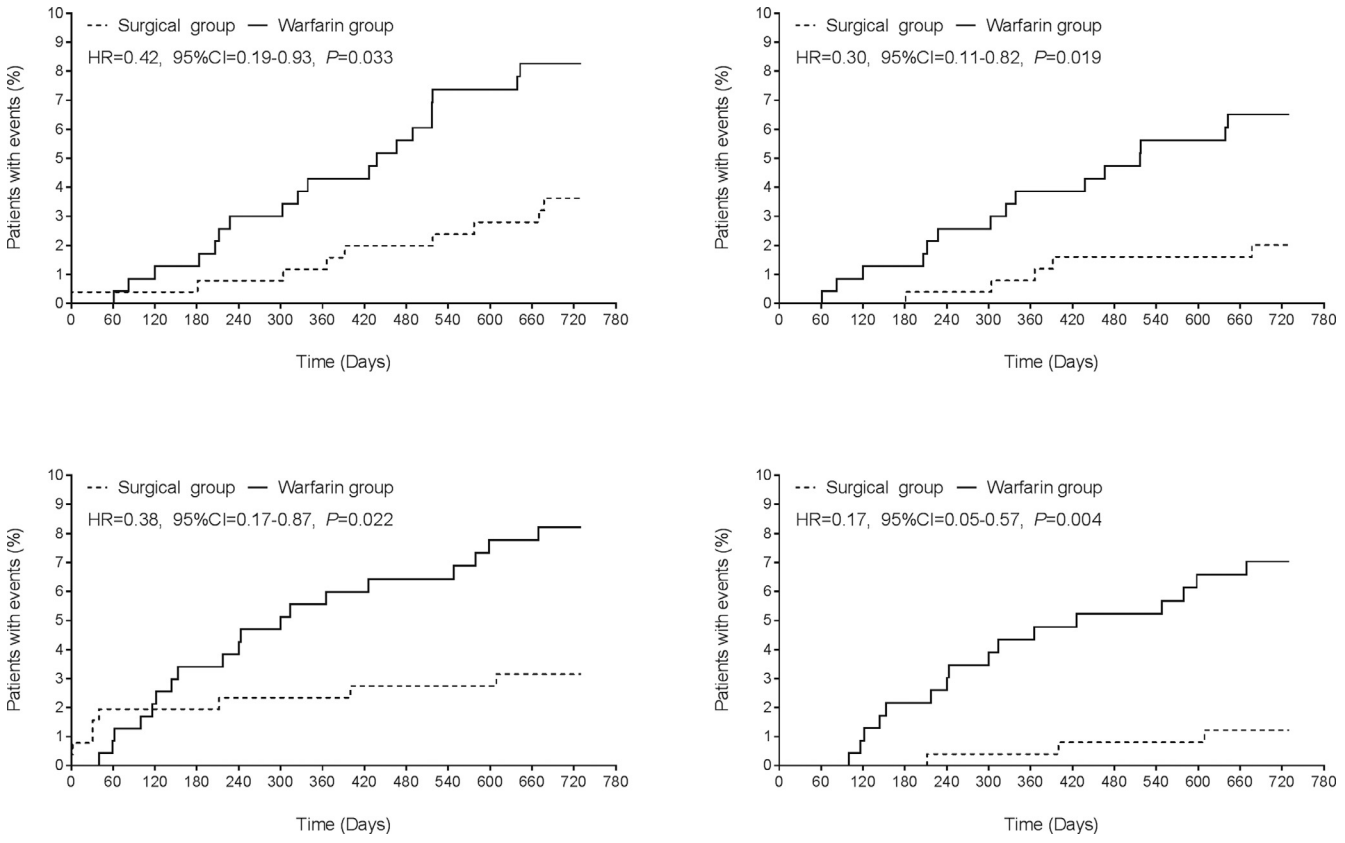

Figure 1. Kaplan-Meier curves for primary efficacy and primary safety.

Table 3
Composite stroke or systemic embolism (SE) from 7 days after procedure to 2 years

	Long-term warfarin (n = 235)		Thoracoscopic LAA Occlusion (n = 256)		HR (Surgical group/Warfarin group)	95% CI	p
	Events/Patient-Years	Observed rate: Events per 100 Patient-Years (95% CI)	Events/Patient-Years	Observed rate: Events per 100 Patient-Years (95% CI)			
Composite endpoint events	15/443.4	3.4 (1.7−5.1)	5/494.7	1.0 (0.1−1.9)	0.30	0.11−0.82	0.019
Stroke/TIA	11/448.5	2.5 (1.0−3.9)	3/496.6	0.6 (0.0−1.3)	0.25	0.07−0.88	0.032
Systemic embolism	4/454.3	0.9 (0.0−1.7)	2/497.5	0.4 (0.0−1.0)	0.46	0.08−2.50	0.366

group, and events of digestive tract hemorrhage accounted for 12/19 (63.2%). Bleeding events beyond 7 days postoperation and beyond 3 months were less in the surgical group than those in the warfarin group (as shown in Table 5). K-M curve survival analysis showed significant difference between the 2 groups (2 years follow-up, p = 0.022), beyond 7 days postoperation (p = 0.007), beyond 3 months (p = 0.004) (as shown in Figure 1).

The relationships between clinical characteristics and bleeding beyond 3 months postprocedure are shown in Figure 3. Thoracoscopic LAA occlusion significantly reduced hemorrhage irrespective of age, sex, thromboembolic risk score or baseline bleeding risk. The relative magnitude of surgical benefit was significantly greater in those with modified HAS-BLED scores ≥ 3 (p = 0.033).

The incidence of surgical complications during the first week in the surgical group was 3/257 (1.2%), including surgery-related cerebral embolism occurred in 1 case, pericardial effusion in 1 case, chest wall wound bleeding in 1 case.

Discussion

The major findings of the trial were: (1) Thoracoscopic LAA occlusion was superior to warfarin for the primary efficacy composite endpoint of preventing stroke, SE, and cardiovascular/unexplained death; (2) the thoracoscopic LAA occlusion was superior to warfarin for the occurrence of late ischemic events, such as stroke or SE $>$ 7 days' postoperation to exclude the effect of early periprocedural events; (3) The surgical group also had significantly lower

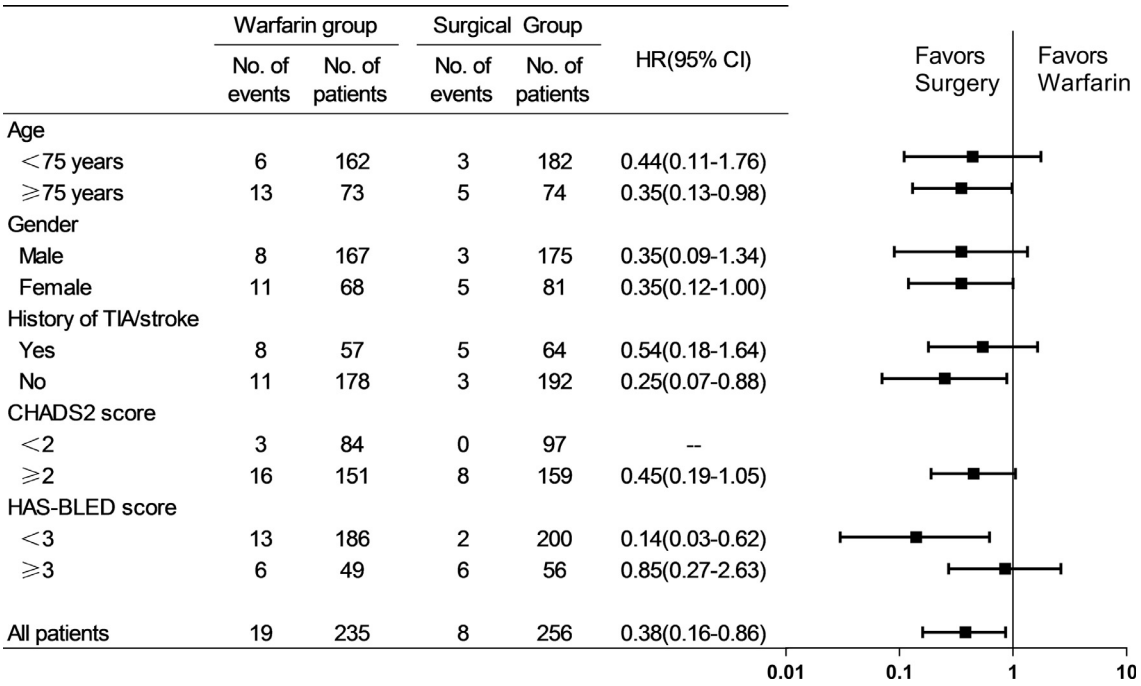

Figure 2. Primary efficacy results beyond 7 days postoperation to 2 years according to subgroup.

Table 4
Primary safety results

	Long-term warfarin (n = 235)		Thoracoscopic LAA occlusion (n = 257)		HR (Surgical group/Warfarin group)	95% CI	p
	Events/Patient-Years	Observed rate: Events per 100 Patient-Years (95% CI)	Events/Patient-Years	Observed rate: Events per 100 Patient-Years (95% CI)			
Total hemorrhage events	19/436.0	4.4 (2.4−6.3)	8/489.1	1.6 (0.5−2.8)	0.38	0.17−0.87	0.022
Surgery−unrelated bleeding	19/436.0	4.4 (2.4−6.3)	6/496.1	1.2 (0.2−2.2)	0.28	0.11−0.70	0.007
Digestive tract hemorrhage	12/446.0	2.7 (1.2−4.2)	3/498.3	0.6 (0.0−1.3)	0.22	0.06−0.80	0.021
Hematuria	2/465.5	0.4 (0.0−1.0)	1/499.6	0.2 (0.0−0.6)	0.46	0.04−5.05	0.523
Intracranial hemorrhage	2/455.9	0.4 (0.0−1.0)	0/501.5	0	–		
Nasal bleeding	2/4557.7	0.4 (0.0−1.0)	1/500.0	0.2 (0.0−0.6)	0.46	0.04−5.05	0.524
Other bleeding	1/457.6	0.2 (0.0−0.6)	1/499.5	0.2 (0.0−0.6)	0.92	0.06−14.65	0.951
Surgery−related bleeding	0//459.5	0	2/497.5	0.4 (0.0−1.0)	–		

bleeding risk. (4) The incidence of surgical complications associated with LAA removal was low, and all of them occurred in the hospital without causing serious outcomes.

The relationship between AF and stroke is well proved in many researches. Stroke in AF patients was mainly caused by thrombosis in LAA, which required continuous anticoagulant. Warfarin has its limitations, which leads to underutilization and frequent discontinuation. Therefore, nonpharmaceutical therapies that prevent thrombosis in LAA and lower incidence of stroke in AF patients increasingly attract attention. Although the comparison of transcatheter LAA closure and warfarin has been the subject of sufficient study,[7−8] long-term follow-up of this study has confirmed the efficacy and safety of thoracoscopic LAA occlusion.

In the control warfarin group, warfarin was generally well managed, with INR levels in the therapeutic range 65% of the time. This value was 64% in the RE-LY trial and less in the ROCKET-AF study.[9−10] INR was monitored every 4 weeks after it was stable up to standard, and only 5.1% of INR measurements were separated by >4 weeks. Therefore, the management of warfarin in this study was effective.

In the surgical group, using surgical staplers and positioning them right in place are the guarantee of expected surgical benefit. Ohtsuka[11] reported on his experience with 32 LAA resections using a stapler and no complications were reported. If the LAA were not completely resected and permanently closed, the surgical procedure won't protect the patient from thrombus and stroke as it means to. So

Table 5
Bleeding events beyond 3 months postoperation to 2-year follow-up

	Long-term warfarin (n = 232)		Thoracoscopic LAA occlusion (n = 252)		HR (Surgical group/Warfarin group)	95% CI	p
	Events/Patient-Years	Observed rate: Events per 100 Patient-Years (95% CrI)	Events/Patient-Years	Observed rate: Events per 100 Patient-Years (95% CrI)			
Surgery-unrelated bleeding	16/435.5	3.7 (1.9−5.4)	3/491.8	0.6 (0.0−1.3)	0.17	0.05−0.57	0.004
Digestive tract hemorrhage	11/441.9	2.5 (1.0−3.9)	2/490.2	0.4 (0.0−1.0)	0.16	0.04−0.74	0.019
Hematuria	2/450.5	0.4 (0.0−1.1)	0/491.5	0	–		
Intracranial hemorrhage	1/451.8	0.2 (0.0−0.7)	0/491.5	0	–		
Nasal bleeding	2/451.7	0.4 (0.0−1.1)	1/490.5	0.2 (0.0−0.6)	0.46	0.04−5.09	0.527
Other bleeding	0/453.5	0	0/491.5	0	–		

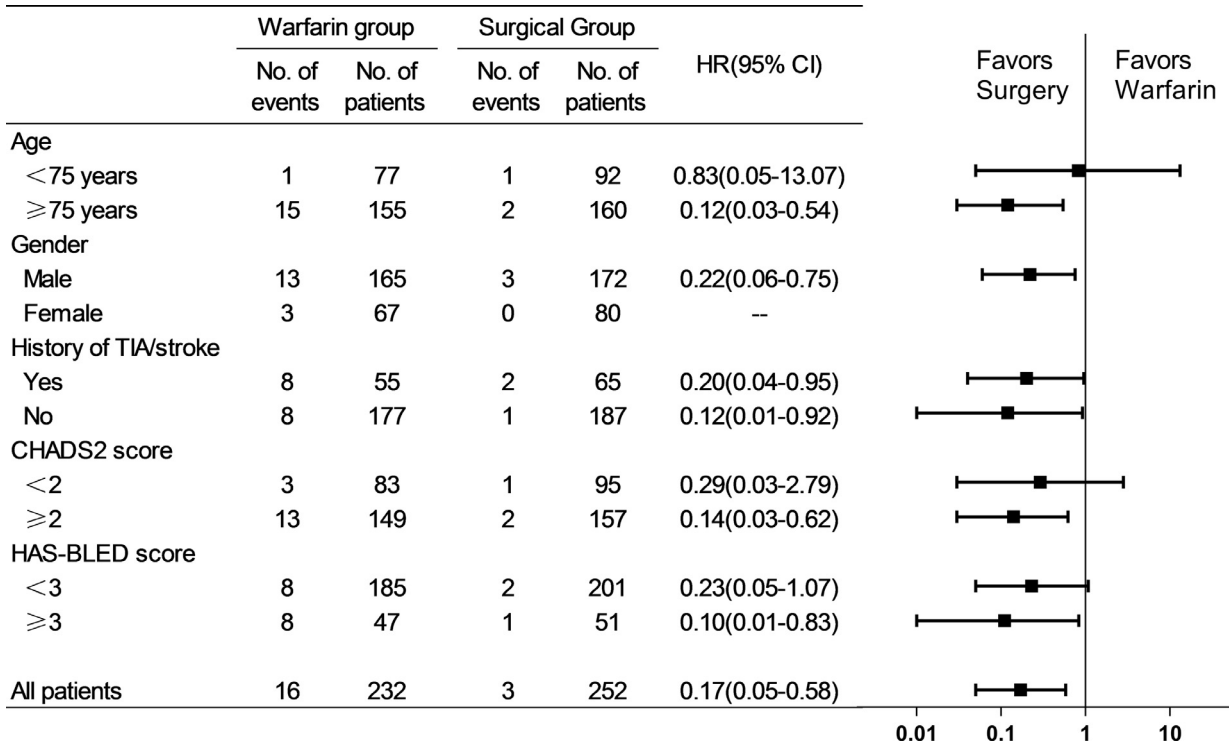

Figure 3. Primary safety results beyond 3 months postoperation to 2 years according to subgroup.

we ensured every LAA completely resected by a team of experienced cardiovascular surgeons who have performed more than 500 LAA resection procedures. This number of this operation in authors' unit is reported to be in the leading position in the Asia Pacific Region.

Follow-up of 24 months has confirmed the efficacy of thoracoscopic LAA occlusion. The event rates with warfarin for the primary composite efficacy endpoint were significantly higher than the surgical group (p = 0.033). The event rates with warfarin were lower than the expected stroke rate based on the CHA_2DS_2-VASc score[12] (0.025 vs 0.035), indicating a relative stroke risk reduction of 28.6%. The stroke/TIA rates of the surgical group were significantly lower than expected (0.008 vs 0.033), indicating a relative stroke risk reduction of 75.8%.

The results of the second efficacy endpoint showed that the rate of composite stroke or systemic embolism in the surgical group was obviously lower than that in the warfarin group (p = 0.019), supporting the deduction that thoracoscopic LAA occlusion can prevent longer-term ischemic events in the absence of chronic anticoagulation.

The total hemorrhage events in surgical group were significantly less than those in the warfarin chronic group in the 2-year follow-up (p = 0.022). Taking the first three months as time node, for the surgical group, surgery-related bleeding events accounted for 40% (2/5), which all happened in hospital during the perioperative period (≤7 day). The patients could get effective treatment in time and no adverse consequences had occurred. However, the bleeding events in the warfarin group all happened outside the hospital, which was a

disadvantage for the timeliness of treatment. After the first 3 months, the risk of hemorrhage was obviously lower in the surgical group than the warfarin group due to the discontinuation of warfarin in the surgical group, indicating a relative reduction of 83.8%. As time went on, the benefit would last a lifetime. Subgroup analyses suggested that in the high risk subgroup (HASBLED score ≥ 3), thoracoscopic LAA occlusion had significantly fewer bleeding events than the warfarin group. It was proved that high bleeding risk patients received more benefit from the thoracoscopic LAA occlusion strategy because of the discontinuation of warfarin.

Overall, the findings support that the thoracoscopic LAA occlusion is a reasonable alternative to chronic long-term warfarin therapy for stroke/systemic embolization prevention in patients with NVAF.

Disclosures

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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