석사 학위 논문

심방세동의 수술적 절연술에서 좌심방축소술식의 영향

The Impact of Left Atrial Reduction during Surgical Ablation of Atrial Fibrillation

울산대학교 대학원

의학과

최우석

심방세동의 수술적 절연술에서

좌심방축소술식의 영향

지도교수 김준범

이 논문을 석사학위 논문으로 제출함

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국문 요약

연구 목적

심방세동은 수술적 절연술을 통해 동율동의로의 전환을 효과적으로 시킬 수 있음이 증명되어왔다. 하지만 좌심방 비대는 수술적 절연술의 동율동전환 실패율을 높인다고 알려져 있다. 이를 해결하기 위해 수술적 절연술 도중에 좌심방을 절제하는 술식이 개발되었으나, 이것의 임상적 효과에 대한 검증은 제한적이었다. 이번 연구는 좌심방축소술식을 시행한 경우의 임상적 효과를 비교적 대단위의 환자군에서 검증하고자 하였다.

연구 방법

2001년 1월부터 2018년 8월까지 서울아산병원에서 주요심장수술과 함께 수술적 절연술을 시행 받은 환자 1,484명을 대상으로 하였다. 이를 좌심방축소술을 시행한 군(876명)과 좌심방축소술을 시행하지 않은 군(608명)으로 나누어 임상적 결과를 비교하였다. 두 군 간의 기저질환, 수술특성 등의 차이를 보정하기 위해서 Propensity score를 이용한 Inverse Probability of Treatment Weigting을 사용하였다.

연구 결과

보정 후 두 군 간에 조기사망, 조기 합병증, 만기사망 및 심방세동의 만기

재발율에는 통계적으로 유의한 차이가 없었다. 하지만 장기 결과에서 뇌경색의 발생률이, 좌심방축소술을 시행한 군에서 더 적었다. (위험비 0.54; 95% 신뢰수준 0.32-0.90; p=0.018) 이는 다변량검정에서도 유의하였다. 또한 좌심방축소술식 군에서는 수술후 심초음파상에서 좌심방의 크기가 더 작아진 것을 확인하였다. . (50.6±8.0 mm vs. 53.6±8.9 mm; p<0.001)

결론

좌심방이 50mm이상으로 커져있는 환자에서, 심방세동의 수술적 절연술을 시행할 때 좌심방 축소술식을 추가하는 것은 뇌경색의 위험을 낮추는 것으로 보인다..

차례

Glossary of Abbreviations

AF = atrial fibrillation

LA = left atrium

PPM = permanent pacemaker

PS = propensity score

IPTW = inverse probability of treatment weighting

SMD = standardized mean difference

TR = tricuspid regurgitation

HR = hazard ratio

CI = confidence interval

Introduction

First reported by Cox et al. in 1987, surgical ablation has been established as a standard treatment for atrial fibrillation (AF) during concomitant major cardiac surgery.[1,2] Thereafter, [3,4]modification of lesion sets and adoption of new energy sources have further improved clinical outcomes.[5] However, a dilated left atrium (LA) is a risk factor for ablation failure[6,7] and has been reported to increase the risk of thromboembolism.[8]

Several previous studies have reported that an aggressive approach in these high-risk patients by reducing the LA size along with the surgical ablation procedure is feasible. Although these studies reported a high rate (up to 90%) of conversion to sinus rhythm without further increasing the operative risk,[4,9] these studies were limited by small sample sizes and insufficient clinical endpoints that pertained only to AF recurrence or early mortality.[10] Therefore, we sought to evaluate the clinical impact of LA reduction on the early and long-term clinical outcomes in a large cohort of patients with enlarged LA who underwent concomitant surgical AF ablation during major cardiac surgery.

Materials and Methods

Patients

The study period was from January 2001 to August 2018. Patients who underwent concomitant surgical ablation for AF during major cardiac surgery were enrolled. Among these, patients with an enlarged LA (antero-posterior diameter≥50 mm)[11] were selected for the analysis. The patients were grouped into the "Reduction" group or the "Preservation" group according to the resection of the posterior LA free wall to reduce the LA size intraoperatively. The data was retrospectively collected from the institutional cardiac surgery database and

electronic medical records. Data included the baseline patient characteristics, echocardiographic data, and the early and long-term outcomes. The Institutional Review Board of Asan Medical Center approved this study (study number: 2020-0741). The need for informed consent was waived because of the retrospective design of this study.

Surgical Procedure and Postoperative Management

In this study, the LA reduction procedure was performed by a resection of the posteroinferior LA wall between the right inferior pulmonary veins and the mitral annulus so that the width of the wall remains <4 cm in this area (**Figure 1**).

The lesion sets for surgical ablation are described in a previous study.[12] In the LA, the lesion sets include a box lesion isolating the pulmonary veins, "a mitral line" from the box lesion to the mitral annulus, an additional line to the LA appendage (LAA), and epicardial ablation of the coronary sinus. In the right atrium, lesion sets included cavo-tricuspid isthmus lesion and a line to the superior vena cava. (**Figure 1**) The LAA was excluded by external resection or internal obliteration; more recently, this was achieved through external clipping in selective cases **(Supplementary Figure 3).**

Argon-based endocardial cryoablation was the main energy source; before 2006, nitrogen-based cryoablation was more popular, and radiofrequency ablation was performed in a few patients (Supplementary Table 1). All cases were operated on by multiple surgeons. The decision whether to perform LA reduction was made by the operating surgeon.

During the immediate postoperative period, electrocardiography (ECG) was obtained on a daily basis, and 24-hour Holter monitoring was performed before discharge. Any episodes of AF or atrial flutter lasting <30 seconds were considered as AF recurrence.[13] Electrical

cardioversion or class I or III antiarrhythmic drugs were used to restore sinus rhythm if AF recurrence was noted. After discharge, monitoring for AF recurrence was carried out in the outpatient clinic, usually with three regular visits at 3, 6, and 12 months. After the 3-month blanking period, electrocardiography (ECG), and 24-hour Holter monitoring was performed to confirm the restoration of the sinus rhythm according to the guidelines of the Heart Rhythm Society.[14] The rhythm status was monitored using ECG at every visit and 24-hour Holter monitoring every 6 months until 2 years after surgery. Follow-up beyond 2 years was performed using ECG and 24-hour Holter monitoring annually.

The patients in whom prosthetic devices were implanted received systemic anticoagulation. In those with mechanical prosthetic valves, lifelong anticoagulation with warfarin was indicated to achieve a target INR of 2.0 to 3.0. In patients who received a bioprosthetic valve and annuloplasty ring, anticoagulation was indicated for the first 3 months. Subsequent discontinuation of the warfarin was decided according to the patient's rhythm status and other indications for anticoagulation. If AF recurred, anticoagulation was reinitiated. Those with coronary artery bypass were treated with dual anti-platelet therapy for the first year, after which they were switched to aspirin.

Outcomes

The primary outcome of interest was the long-term clinical outcome including mortality, stroke, and AF recurrence. The recurrence of AF was documented using follow-up ECG and Holter monitoring data. Referring from the guideline,[14] AF recurrence occurring within 3 months after surgery was defined as early recurrence and was regarded as an event during the blanking period. All patients with newly developed neurologic symptoms were

evaluated by a neurologist and subsequently evaluated using brain imaging studies. The neurologic deficits validated on the imaging studies were defined as stroke.

Secondary outcomes were early postoperative complications (e.g., low cardiac output syndrome, sternal wound infection, and new-onset hemodialysis) and postoperative echocardiographic parameters, especially LA size, were also compared between both groups. Follow-up data was obtained until August 31, 2018. The patients who did not have AF recurrence or stroke were censored at the end of the follow-up. Vital status was checked through the institutional medical records and the National Population Registry of the Korea National Statistical Office.

The early outcome was defined clinical result within 90 days after the operation. Long term stroke and death included both the early and late clinical result, which can be stated as the overall outcome. However, AF recurrence only included those who had recurrence after the 3 months, as early recurrence is considered to be originated from different etiology of blanking period.

Statistical Analyses

All analyses were performed with R software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria. Continuous variables are presented as mean±standard deviation or median with interquartile range depending on their distribution, and categorical variables are presented as frequency (percentage). The comparison between the groups were conducted with independent-samples t tests or Mann-Whitney U test for continuous variables and chi-square tests or Fisher's exact tests for categorical variables, as appropriate.

Propensity scores (PS) were estimated to perform the inverse probability of treatment

weighting (IPTW) to yield well-balanced groups with and without LA reduction based on the preoperative characteristics. The PS model was built using logistic regression model based on the following covariates selected a priori: age, sex, body mass index, ejection fraction, diabetes, hypertension, chronic pulmonary disease, peripheral vascular disease, chronic kidney disease, dependency on dialysis, previous myocardial infarction, coronary artery disease, previous cerebrovascular accident, CHA DS -VASc Score, minimally invasive approach, LA size, left ventricle dimension, type of AF (long-standing/ persistent vs. others), pulmonary hypertension, the number of surgical procedures, anticoagulation drugs use, lesion sets (bi-atrial vs. left-only), and LA appendage treatment. The balance for all covariates in Table 1 was assessed using the standardized mean difference (SMD), for which a difference of <10% was deemed to indicate good balance.

After IPTW, early outcomes were evaluated using logistic regression analysis and robust estimator. For long-term time-related outcomes, Cox proportional hazard model with robust estimator and weighted log-rank analysis was used. Early outcomes are given as odds ratio (OR); Long-term outcomes are given as hazard ratio (HR). All reported p-values were 2-sided, and $p<0.05$ indicated statistical significance.

To assess the possible confounders, multivariable Cox regression analysis was additionally performed on the non-weighted (original) data. Moreover, to evaluate the difference in the effect of LA size on the clinical outcome across difference LA sizes, an interaction term was included in the model between the LA reduction and the LA size and plotted as a spline curve.

Results

During the study period, a total of 1,956 patients underwent surgical ablation during a major cardiac operation in this center. From which, the patients with a LA diameter ≥ 50 mm were selected for the analysis. (n=1,484) Of these, 876 (59%) patients underwent concomitant LA reduction (**Reduction group**), whereas the remaining 608 (41%) had the LA wall preserved (**Preservation group). (Figure 2)**

Patient Characteristics

Table 1 (left column) summarized the baseline characteristics of patients in each group. The Reduction group patients were relatively younger (57.2±12 vs. 60.0±11 years; p<0.001), and had fewer comorbidities than those of the Preservation group, such as hypertension (30.7% vs. 37.5%; p=0.008) and a history of cerebrovascular attack (12.0% vs. 17.3%; p=0.005). The Reduction group had a higher prevalence of rheumatic etiology (64.6% vs. 53.1%; p=<0.001), longer AF duration (5.7±7 vs. 4.0±; p<0.001), and had undergone multiple cardiac procedures more commonly than the Preservation group (70.8% vs. 60.7%; p<0.001).

On echocardiography data, the Reduction group showed a larger LA diameter than that observed in the Preservation group (62.3±8.6 vs. 56.5±5.8 mm; p<0.001). Additionally, left ventricular dimensions were larger in the Reduction group than in the Preservation group; however, as a surrogate for pulmonary hypertension, the tricuspid regurgitation pressure gradient showed no difference between both groups (Table 1).

The profiles of concomitant cardiac operations are demonstrated in **Supplementary Table 1.** The Reduction group had a higher proportion of mitral valve procedure, whereas the Preservation group showed a higher proportion of aortic valve procedure.

The Reduction group compared to the Preservation group had a higher proportion of

LAA treated (57.5% vs. 50.1%; p=0.01). The left-side only maze was less common in the Reduction group (29.6% vs. 50.2%; p<0.001) than in the Preservation group. The changes in the proportion of LAA treatment and the left-only maze per year are demonstrated in **Supplementary Figure 2**. In 2018, the proportion of patients who received LAA treatment increased to 72.6%. Recently, as the application of minimal invasive cardiac surgery increases, the use of external clip or internal obliteration is gaining popularity. Meanwhile, left-only lesion sets are widely used, approximately up to 60%.

Using the IPTW technique, significant differences in the baseline characteristics and echocardiography profiles were adjusted. The adjustment with PS resulted in a cohort that was well-balanced with all measurable baseline data, indicated by SMD <10% in all included variables (**Table 1, Supplementary Figure 1**).

Clinical Outcomes

The median follow-up period was 60.1 months (interquartile range: 26.7-112.7months). The early and long-term clinical outcomes are summarized in Table 2. Early mortality rates were comparable between both groups. (2.9% vs. 2.8%; p=0.947). There was no significant difference in the incidence of early recurrence of AF (67.1% vs. 69.1%; p=0.428) and perioperative adverse events. The results are similar after the IPTW-adjustment. (**Table 2**).

For the long-term outcomes, there were no significant differences in the rates of overall mortality and AF recurrence between both groups. However, the Reduction group revealed a significantly decreased risk of stroke (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.33-0.82; p=0.005), compared with that seen in the Preservation group. After adjustment with IPTW, the Reduction group still showed significant reduction in the risk of stroke (HR, 0.54;

95% CI, 0.32-0.90; p=0.018). The risk for mortality (HR, 1.25; 95% CI, 0.86-1.82; p=0.250) and AF recurrence (HR, 0.96; 95% CI, 0.71-1.28; p=0.767) showed no significant difference. (**Figure 3**)

The protective effect of LA reduction against stroke was further inspected using multivariable Cox regression analysis. In this model, LA reduction was still found to have a significant protective effect against stroke (HR 0.476, 95% CI 0.29-0.78, p=0.003). Older age, low hemoglobin level, increased LA size, and the presence of peripheral arterial occlusive disease were found to be independent contributors associated with stroke. The possible confounders, LA auricle treatment and left-side only ablation, showed no statistical significance on univariate analysis. The use of anticoagulation medication was a significant risk factor for stroke occurrence; however, it was not included in the model as anticoagulation is influenced by postoperative rhythm variables (**Table 3**). In addition, the AF recurrence was incorporated into the regression analysis, considered as a time-dependent covariate. It revealed that the effect of postoperative AF recurrence on the risk of stroke was not statistically significant.

The effect of LA size on stroke risk during LA reduction was tested using the interaction term. The protective effect of LA reduction against stroke was effective regardless of LA size; this was especially evident in the 50-70 mm range (p=0.5). A spline curve was plotted, which is demonstrated in **Figure 4**.

The median time to last follow-up echocardiography after surgery was 46.3 months (quartile 1-3, 19.9~89.0) months, which included the echocardiography performed after surgery. For the last follow-up echocardiography data of adjusted dataset, the LA dimension was smaller in the Reduction group (50.6±8.02 mm vs. 53.00±8.72mm; SMD=0.291) (**Table 4**). The

decrease in size was more evident in the Reduction group.

Discussion

In this study, the comparative clinical effect of LA reduction was inspected. In the long-term, the Reduction group showed no difference in the mortality and AF-free rate compared with the those of the Preservation group; however, the risk of stroke was significantly lower in the Reduction group. There was no additional peri-operative risk induced by LA reduction. In the follow-up echocardiography, the Reduction group showed an effective decrease in the LA size.

First described by Cox et al., surgical ablation for AF was designed to isolate triggers from the rest of the atrial tissues and interrupt the macro-reentrant circuits.[2] After subsequent modifications of lesion sets and adopting various energy sources, surgical ablation is now widely used. Recent studies have reported that the rate of conversion to sinus rhythm after the maze procedure is as high as 90%.[1,15] However, the outcomes of surgical ablation for patients with a large LA and persistent AF is known to be suboptimal. Failure to convert to sinus rhythm tends to occur frequently in patients with chronic (>6 months) AF, low-amplitude fibrillatory waves of <1 mm, and large atrial size >60 mm.[16] Therefore, the application of surgical ablation to such high-risk subgroups has been limited. In this regard, LA reduction has been attempted to improve the rate of sinus rhythm restoration in these high-risk subgroups.[17] LA resection is based on the assumption that in the enlarged and remodeled atrial wall, additional foci of fibrillation exist that may contribute to failure of surgical ablation in persistent AF.[18]

However, the difference in the AF recurrence rate in this study was not significant. Wang et al. demonstrated that the restoration of sinus rhythm was significantly higher in the

LA Reduction group.[19] Marui et al. also reported that during the follow-up until 36 months, the restoration of sinus rhythm was significantly better in the LA Reduction group.[20] However, these studies included relatively small numbers of patients, and the baseline characteristics were not balanced. It is noteworthy that in the original analysis, there was no significant change in the risk of AF recurrence. As the Reduction group had a larger LA diameter and a higher prevalence of persistent AF, comparable outcomes in the original analysis support the assumption that LA reduction may have a protective effect against AF recurrence.

In this study, the risk of stroke was lower in the Reduction group. The mechanism by which LA reduction was associated with stroke reduction remains to be elucidated. In a study conducted by Marui et al. using cardiac MRI after LA reduction concomitant with the maze procedure, it was found that LA reduction facilitates restoration of both the contraction and compliance of the LA, which improves its hemodynamic profile.[20] This may contribute to the reduction of blood stasis in the reduced LA. Moreover, in a microscopic review of the enlarged LA, increased infiltration of immune cells was noted.[21] This may represent the local inflammatory response of the atrium. It is known that thrombosis is associated with inflammatory processes.[22] In the Preservation group, the remnant diseased LA wall tissue may have formed a thrombogenic environment in addition to blood stasis. The decreased risk of stroke may therefore be attributable to the reduced portion of thrombogenic foci in the atrial wall and the improved hemodynamics after atrial wall reduction.

It is likely that LA reduction may increase the operating time and risk of bleeding. In this study, no additional risk was found in the Reduction group with respect to bleeding (HR 1.42, 95% CI 0.92-22, p=0.117) and low cardiac output syndrome (HR 1.06, 95% CI 0.56-2.10;

p=0.849). The cardiopulmonary bypass time showed no significant increase in the Reduction group.

The possible contributors to this study are the rhythm status of the patient at the occurrence of stroke, and oral anticoagulation after the operation. 1,077 patients (72.6%) received anticoagulation until the last follow-up: 464 (76.3%) in the Preservation group and 613 (70.0%) in the Reduction group. In the IPTW model, the proportion of oral anticoagulation was similar. However, oral anticoagulation showed significant risk in the univariate analysis. It is thought to be caused by the confounding variables such as PAOD and postoperative rhythm status.[23]

Setting a cut-off value for when to reduce the LA would be a good reference for real-world clinical practice. However, this study was a retrospective study and the indication of LA reduction in this data depended on the surgeon's discretion. Moreover, the data covers a long period and includes various surgical procedures. Therefore, it was difficult to set an entry point to reduce the LA size and exclude patients based on a certain standard.

The spline plotting method and interaction term were analyzed to evaluate the effect of LA reduction on the risk of stroke depending on baseline LA sizes. As results, baseline LA size did not seem to have any interaction in the protective effect of LA reduction against stroke in the present data (LA>50mm at baseline).

LA size measurement has changed over time.[24] Anteroposterior (AP) diameter is a traditional and reliable method of measuring the LA size. LA volumetry is a recent alternative option for measuring the LA size. In future studies, it would be preferable to study the effect of LA size based on newly developed tools for LA volume measurement.

Although the degree of reduction seemed only 2.5 mm in the weighted data, this is a

measurement from the AP diameter (short axis) of an ellipse-shaped LA. The actual reduction in the circumference would relatively be larger. For instance, if we assume that the LA is a complete circle, the reduced wall length would be π×radius, at least 3 times greater than measured reduction in AP diameter. The target of reduction was that "width of the wall remains less than 4 cm in this area". This would not be accurately reflected in the AP diameter.

Study Limitations

This study is limited by it retrospective, observational design. The relatively long time period of this cohort, the modification of the lesion sets, and the changes in the energy source may have affected the incidence of stroke. Moreover, no data were available regarding the prior use of antiarrhythmic drugs.

Conclusion

LA reduction effectively decreased LA size and appeared to decrease the stroke risk in patients with enlarged LA undergoing ablation for AF. Further studies are warranted to investigate the underlying mechanisms of the study findings. To obtain concrete evidence, randomized trials for LA reduction should be considered.

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Figure Legends

Figure 1. Schematic illustration of left atrial reduction procedure. Posteroinferior LA wall between the right inferior pulmonary veins and the mitral annulus was resected, width of the remaining wall <4 cm. SVC, Superior vena cava, IVC, Inferior vena cava; LAA, Left atrial appendage; PVs, Pulmonary veins; MV, Mitral valve; LA, Left atrium.

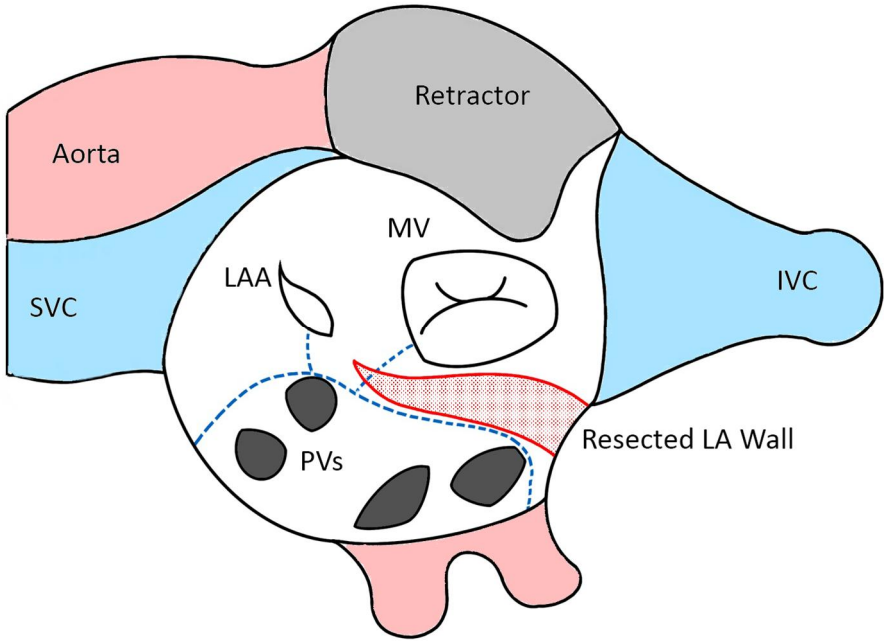


Figure 2. Patient flow diagram. AF, Atrial fibrillation; LA, Left atrium; PPM, Permanent pacemaker

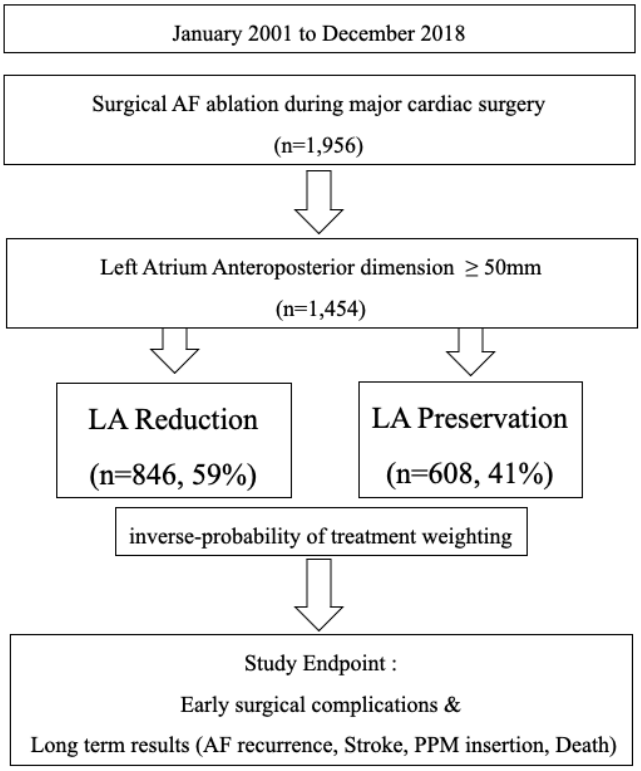


Figure 3. Kaplan-Meier survival plot for each clinical outcome. A. Overall survival before weighting, B. Overall Survival after inverse probability of treatment weighting (IPTW), C. Freedom from stroke before weighting, D; Freedom from stroke after IPTW, E. Freedom from atrial fibrillation recurrence before weighting, F. Freedom from atrial fibrillation recurrence after IPTW. HR[], Hazard Ratio; [95% Confidence Interval].

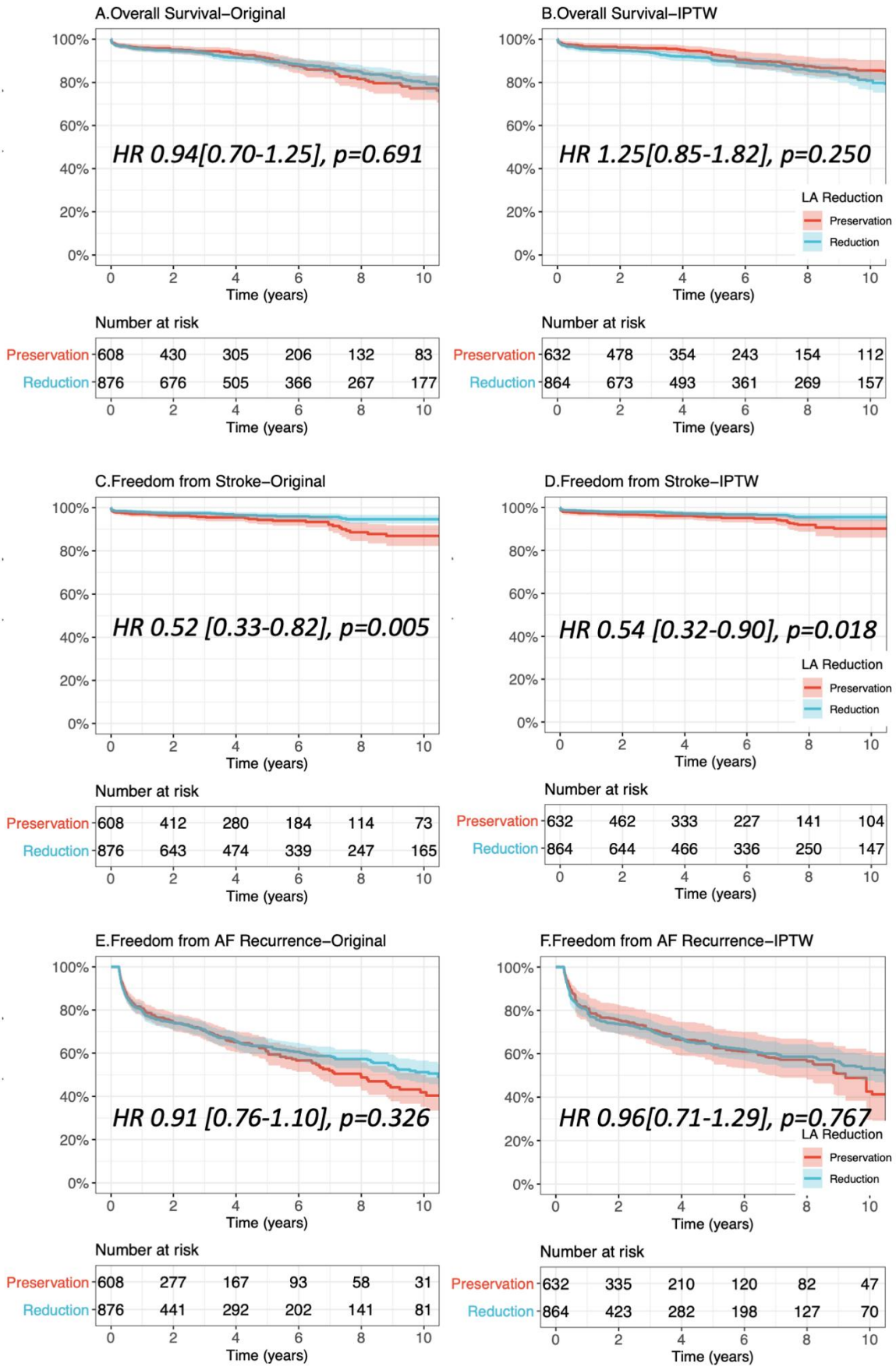

A.Overall Survival–Original
HR 0.94[0.70-1.25], p=0.691
B.Overall Survival–IPTW
HR 1.25[0.85-1.82], p=0.250
LA Reduction
Preservation
Reduction
Time (years)
Number at risk
Preservation 608 430 305 206 132 83
Reduction 876 676 505 366 267 177
Preservation 632 478 354 243 154 112
Reduction 864 673 493 361 269 157
C.Freedom from Stroke–Original
HR 0.52 [0.33-0.82], p=0.005
D.Freedom from Stroke–IPTW
HR 0.54 [0.32-0.90], p=0.018
Preservation 608 412 280 184 114 73
Reduction 876 643 474 339 247 165
Preservation 632 462 333 227 141 104
Reduction 864 644 466 336 250 147
E.Freedom from AF Recurrence–Original
HR 0.91 [0.76-1.10], p=0.326
F.Freedom from AF Recurrence–IPTW
HR 0.96[0.71-1.29], p=0.767
Preservation 608 277 167 93 58 31
Reduction 876 441 292 202 141 81
Preservation 632 335 210 120 82 47
Reduction 864 423 282 198 127 70

Figure 4. Spline curve for the relative hazard ratio of left atrial reduction on stroke by left atrial anteroposterior diameter

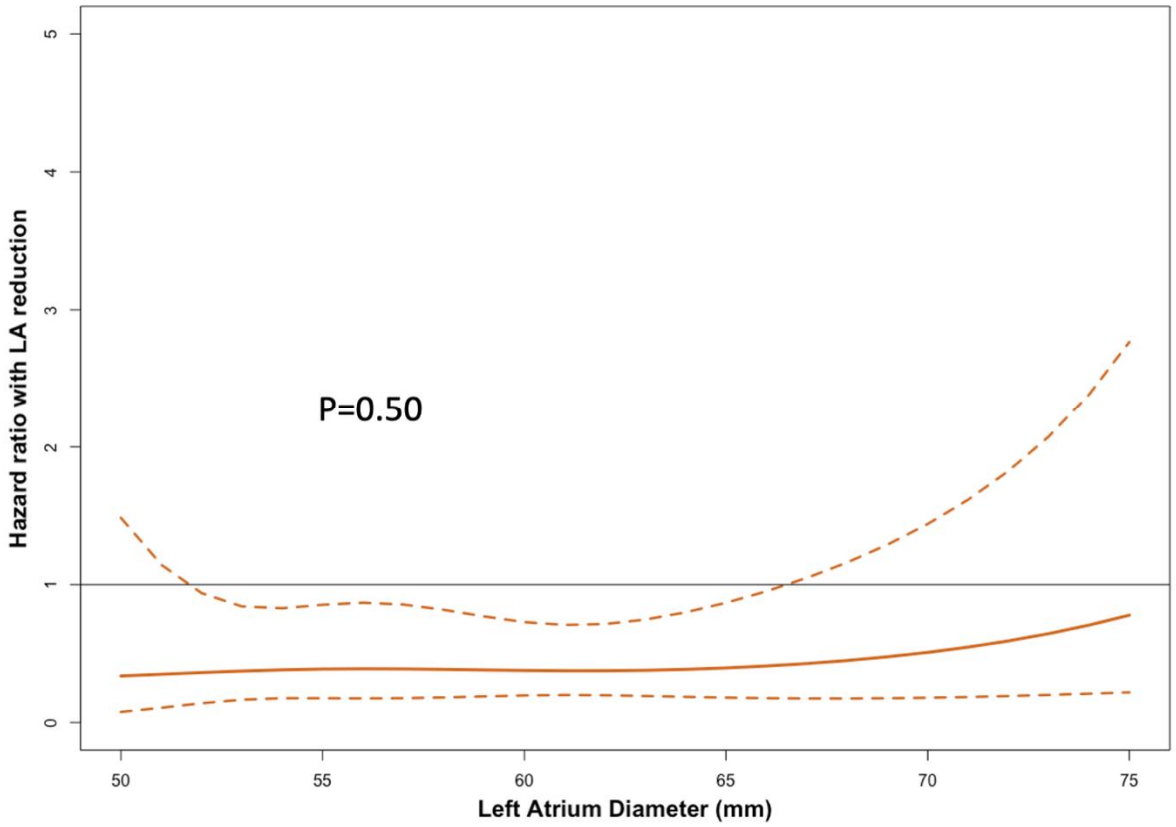
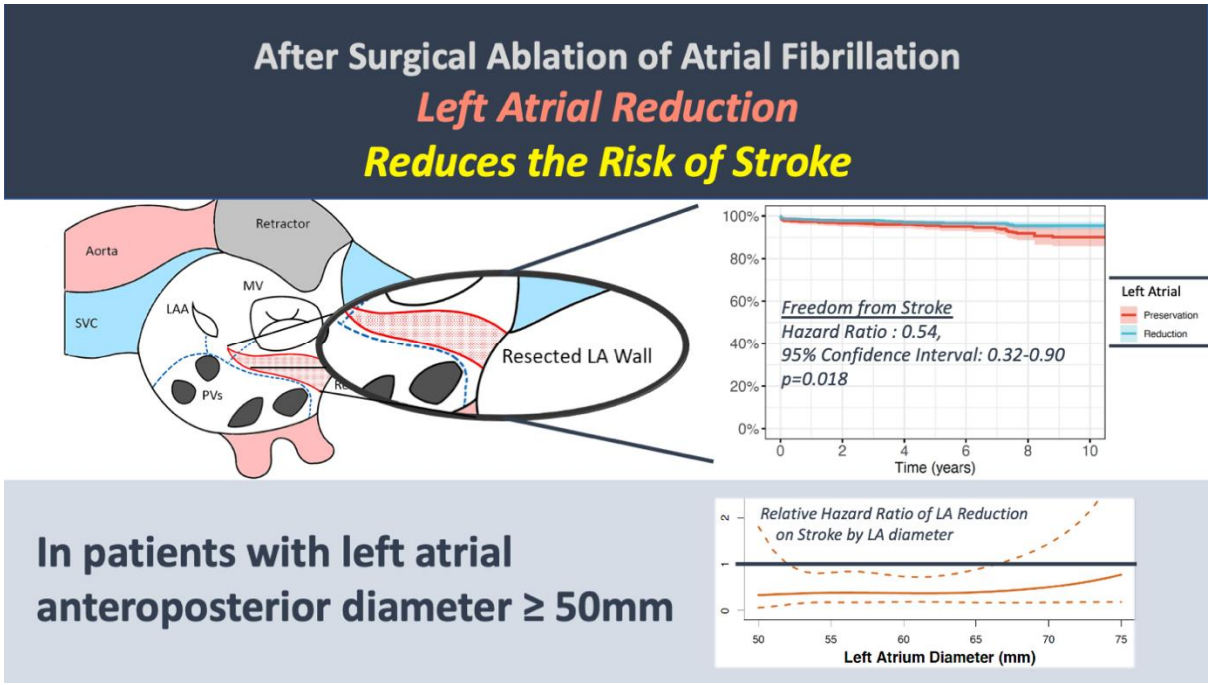
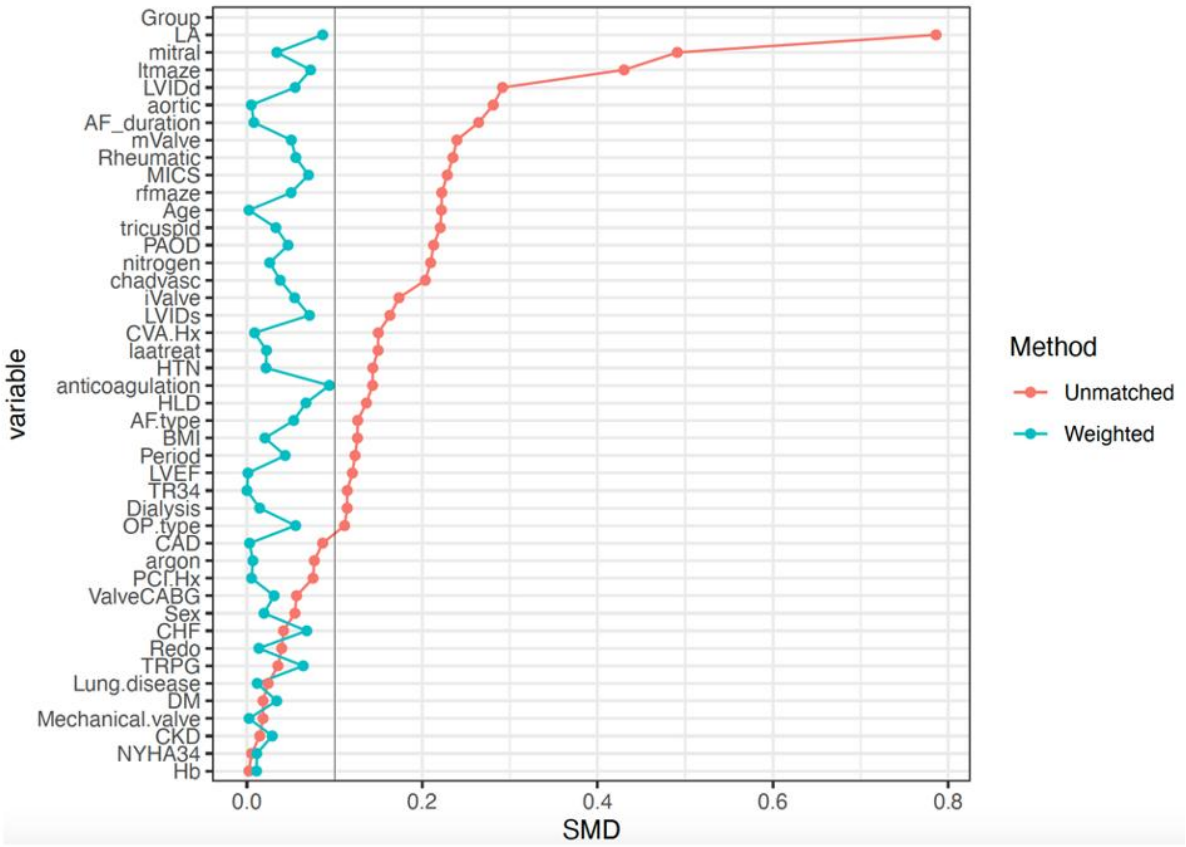


Figure 5. Graphical abstract

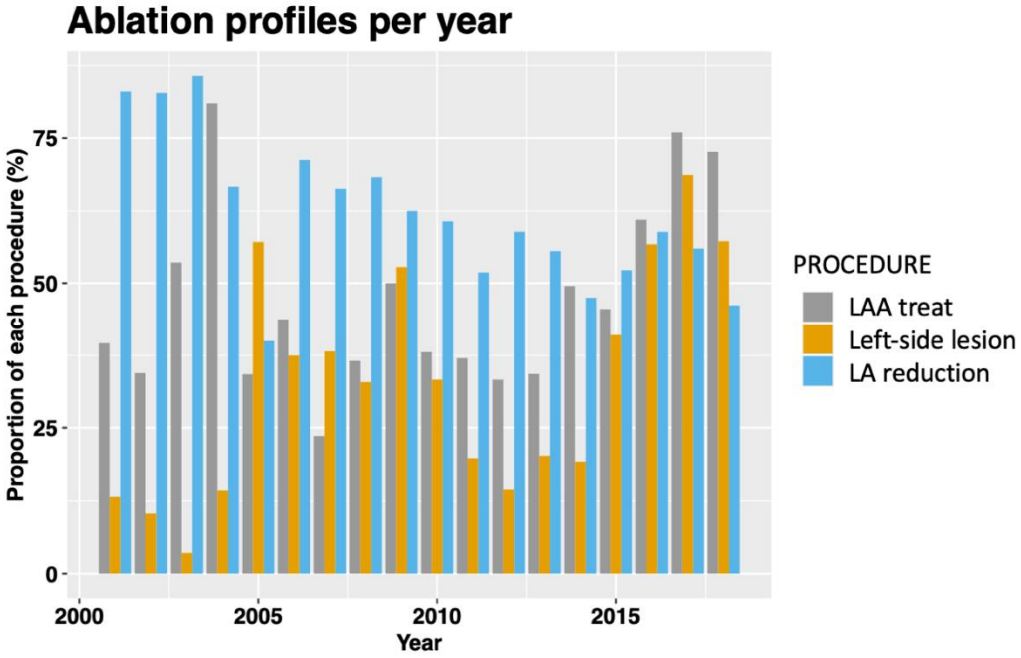
SVC, Superior vena cava, IVC, Inferior vena cava; LAA, Left atrial appendage; PVs, Pulmonary veins; MV, Mitral valve; LA, Left atrium.



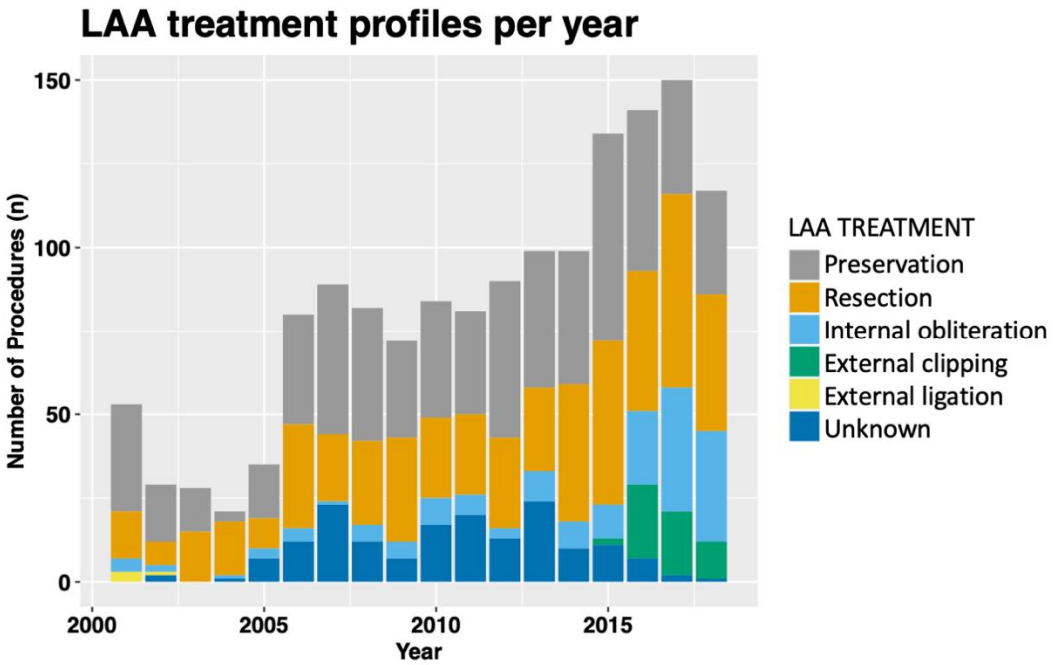
Supplementary Figure 1. Plot for the Standardized Mean Difference (SMD) before/after inverse probability of treatment weighting for each variable. Code is explained in the **Supplementary table 1**



Supplementary Figure 2. The profiles of surgical ablation per year from January 2001 to August 2018. LAA treat, Left atrial appendage treatment(details of LAA treatment are described in the supplementary figure 2), Left-side lesion, LA reduction; Left atrial reduction



Supplementary Figure 3. Left atrial appendage profiles per year from January 2001 to August 2018.



Tables

Table 1. Baseline characteristics of LA Reduction and preservation group, before and after IPTW* using PS**

Variables	Before weighting (Original)				After IPTW		
	Reduction (n = 876)	Preservation (n = 608)	p-value	SMD	Reduction (n=863.9)	Preservation (n=631.6)	SMD
Age, years	57.17 (11.53)	59.68 (11.02)	<0.001	0.222	57.66 (11.38)	57.63 (12.21)	0.002
Female	495 (56.5)	327 (53.8)	0.325	0.055	468.1 (54.2)	336.1 (53.2)	0.02
BMI	23.44 (3.26)	23.86 (3.36)	0.017	0.126	23.53 (3.32)	23.46 (3.45)	0.021
Hb	13.20 (1.96)	13.19 (1.81)	0.965	0.002	13.24 (1.95)	13.22 (1.78)	0.011
Comorbid conditions							
HTN	269 (30.7)	228 (37.5)	0.008	0.144	275.6 (31.9)	208.0 (32.9)	0.022
DM	124 (14.2)	90 (14.8)	0.784	0.018	114.6 (13.3)	91.2 (14.4)	0.034
HLD	200 (22.8)	175 (28.8)	0.011	0.136	205.7 (23.8)	132.7 (21.0)	0.067
CVA.Hx	105 (12.0)	105 (17.3)	0.005	0.15	111.8 (12.9)	83.6 (13.2)	0.009
CHF	87 (9.9)	53 (8.7)	0.486	0.042	73.3 (8.5)	66.2 (10.5)	0.068
CKD	162 (18.5)	109 (17.9)	0.834	0.015	160.2 (18.5)	110.1 (17.4)	0.029
Dialysis	5 (0.6)	11 (1.8)	0.044	0.114	11.4 (1.3)	7.3 (1.2)	0.015
Lung.disease	66 (7.5)	42 (6.9)	0.722	0.024	70.4 (8.2)	53.5 (8.5)	0.012
PCI.Hx	17 (1.9)	19 (3.1)	0.198	0.075	17.1 (2.0)	12.1 (1.9)	0.005
CAD	87 (9.9)	77 (12.7)	0.117	0.086	93.6 (10.8)	67.9 (10.7)	0.003

PAOD	64 (7.3)	84 (13.8)	<0.001	0.213	76.9 (8.9)	64.9 (10.3)	0.047
CHA_2 DS_2 -VASc	1.85 (1.49)	2.17 (1.61)	<0.001	0.204	1.88 (1.53)	1.93 (1.50)	0.038
Rheumatic	566 (64.6)	323 (53.1)	<0.001	0.235	519.0 (60.1)	362.2 (57.3)	0.056
AF duration, year	5.70 (6.94)	4.04 (5.56)	<0.001	0.264	4.99 (6.53)	5.03 (5.77)	0.008
NYHA34	182 (20.8)	125 (20.6)	0.971	0.005	174.0 (20.1)	124.3 (19.7)	0.011
Permanent Afib	815 (93.0)	544 (89.5)	0.020	0.126	792.2 (91.7)	588.1 (93.1)	0.053
Preoperative Echocardiography							
LVEF	56.55 (8.85)	55.43 (9.87)	0.021	0.120	56.19 (9.12)	56.20 (9.02)	0.001
LVIDs	38.12 (7.62)	36.84 (8.07)	0.002	0.163	37.38 (8.28)	37.95 (7.54)	0.071
LVIDd	56.46 (8.75)	53.90 (8.81)	<0.001	0.292	55.39 (8.82)	55.87 (8.80)	0.055
LA	62.26 (8.58)	56.51 (5.79)	<0.001	0.786	59.82 (8.21)	60.56 (8.99)	0.086
TRPG	37.87 (13.36)	37.37 (14.55)	0.499	0.035	37.44 (13.55)	38.35 (14.84)	0.064
TR34	439 (50.1)	270 (44.4)	0.035	0.114	409.0 (47.3)	299.0 (47.3)	<0.001
Operative Characteristics							
Single Valve	253 (28.9)	225 (37.0)	0.001	0.174	269.8 (31.2)	213.3 (33.8)	0.054
Multiple Valve	554 (63.2)	313 (51.5)	<0.001	0.24	508.9 (58.9)	356.3 (56.4)	0.051
Valve+CABG	53 (6.1)	29 (4.8)	0.344	0.057	47.4 (5.5)	39.3 (6.2)	0.031
Aortic Valve	163 (18.6)	186 (30.6)	<0.001	0.281	199.0 (23.0)	146.9 (23.3)	0.005
Mitral Valve	838 (95.7)	487 (80.1)	<0.001	0.491	785.7 (90.9)	568.1 (89.9)	0.034
Tricuspid Valve	560 (63.9)	323 (53.1)	<0.001	0.221	509.2 (58.9)	362.0 (57.3)	0.033

Emergency OP	7 (0.8)	13 (2.1)	0.049	0.111	7.9 (0.9)	9.6 (1.5)	0.056
Redo	36 (4.1)	30 (4.9)	0.529	0.04	40.1 (4.6)	27.5 (4.4)	0.014
MICS	323 (36.9)	160 (26.3)	<0.001	0.229	279.4 (32.3)	225.3 (35.7)	0.07
After 2016	221 (25.2)	187 (30.8)	0.022	0.123	239.8 (27.8)	163.1 (25.8)	0.044
Energy source							
RF ablation	0.01 (0.09)	0.04 (0.20)	<0.001	0.222	0.01 (0.11)	0.02 (0.14)	0.05
Nitrogen	0.14 (0.35)	0.08 (0.26)	<0.001	0.21	0.11 (0.32)	0.10 (0.31)	0.026
Argon	0.84 (0.37)	0.87 (0.34)	0.148	0.077	0.87 (0.34)	0.87 (0.34)	0.007
Ablation profile							
Left only lesion	259 (29.6)	305 (50.2)	<0.001	0.43	340.1 (39.4)	226.4 (35.8)	0.073
LAA treatment	458 (57.5)	260 (50.1)	0.01	0.15	414.7 (53.9)	307.4 (55.0)	0.022
Anticoagulaiton status (not matched)	613 (70.0)	464 (76.3)	0.008	0.143	583.3 (67.5)	453.8 (71.8)	0.094

*IPTW, Inverse-Probability of Treatment Weighting; **PS, Propensity Score. (PS model's Hosmer-Lemeshow goodness of fit test p-value = 0. 0.422, indicating adequate fit. PS model's c-index = 0.823) Values are n (%), or mean[median] ± standard deviation[Interquartile range], unless otherwise indicated. SMD, standardized mean difference; AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; CVA, cerebrovascular accident; PCI, percutaneous coronary intervention; NYHA, New York Heart Association classification of heart failure; LVEF, left ventricular ejection fraction; LVESD, LV end-systolic dimension; LVEDD, LV end-diastolic dimension; LA, left atrium; TR, tricuspid regurgitation; PG, pressure gradient; Complex operation: multi-valve surgery or a combined valvular and coronary procedure; MICS, Minimal Invasive Cardiac Surgery; LAA, Left atrial appendage

Table 2. Early and Long-term clinical outcomes of LA reduction and LA preservation groups adjusted by IPTW

	Before Weighting (Original)						After IPTW					
Early Outcomes	Reduction (n = 876)	Preservation (n = 608)	OR	95% CI		p-value	Reduction (n=863.9)	Preservation (n=631.6)	Group OR	95% CI		p-value*
				LB	UB					LB*	UB*	
Early Death	25 (2.9)	17 (2.8)	1.021	0.546	1.910	0.947	24.3 (2.8)	14.8 (2.3)	1.205	0.552	2.625	0.639
LCOS	23 (2.6)	15 (2.5)	1.066	0.551	2.062	0.850	17.5 (2.0)	15.6 (2.5)	0.814	0.321	2.059	0.663
Early Stroke	14 (1.6)	13 (2.1)	0.743	0.347	1.595	0.446	11.7 (1.4)	13.0 (2.1)	0.654	0.281	1.520	0.324
Bleeding	64 (7.3)	32 (5.3)	1.419	0.915	2.199	0.118	58.1 (6.7)	42.7 (6.8)	0.995	0.365	2.712	0.993
CRRT	38 (4.3)	30 (4.9)	0.874	0.535	1.427	0.590	35.6 (4.1)	47.4 (7.5)	0.530	0.201	1.394	0.198
SWI	6 (0.7)	6 (1.0)	0.692	0.222	2.159	0.526	4.3 (0.5)	5.0 (0.8)	0.623	0.183	2.116	0.449
Early PPM	30 (3.4)	26 (4.3)	0.794	0.464	1.357	0.399	28.4 (3.3)	21.9 (3.5)	0.944	0.518	1.721	0.852
Early recur	588 (67.1)	420 (69.1)	0.914	0.731	1.142	0.428	574.6 (66.5)	436.0 (69.0)	0.891	0.625	1.270	0.524
Long Term Outcomes	# patients (n/100*person-year)		HR	95% CI		p-value	# patients (n/100*person-year)		HR	95% CI		p-value*
				LB	UB					LB*	UB*	
Death	122 (2.38)	75 (2.50)	0.943	0.706	1.259	0.691	110.8 (2.24)	61.2 (1.78)	1.250	0.855	1.828	0.250
Stroke	**35 (0.72)**	**40 (1.44)**	**0.522**	**0.331**	**0.824**	**0.005**	**28.4 (0.61)**	**36.6 (1.12)**	**0.539**	**0.323**	**0.901**	**0.018**
PPM	55 (1.17)	46 (1.68)	0.763	0.515	1.129	0.176	49.4 (1.08)	48.2 (1.5)	0.736	0.463	1.171	0.196
Late.recur	296 (9.68)	195 (11.29)	0.913	0.761	1.095	0.326	276.4 (9.46)	211.1 (9.97)	0.956	0.710	1.287	0.767
Composite	189 (4.12)	145 (5.56)	0.801	0.645	0.996	0.046	170.6 (3.82)	129.7 (4.17)	0.933	0.705	1.235	0.629

*: Using sandwich estimator (=Huber estimator = Robust estimator)

Values are n (%), or median with inter-quartile range unless otherwise indicated. AF, atrial fibrillation; LCOS, low cardiac output syndrome; MCS, mechanical circulatory support; PPM, permanent pacemaker* χ^2 test for early outcomes and log-rank test for late outcomes

*Early outcomes are given as odds ratio (OR); Overall outcomes are given as hazard ratio (HR). CI, confidence interval; IPTW, inverse probability of treatment weighting; LCOS, low cardiac output syndrome; MCS, mechanical circulatory support; PPM, permanent pacemaker

Table 3. Univariate and multivariate risk analysis for stroke

Variables	Univariate				Multivariate			
	HR	95% CI		p-value	HR	95% CI		p-value
		LB	UB			LB	UB	
LA reduction	**0.522**	**0.331**	**0.824**	**0.005**	**0.476**	**0.290**	**0.779**	**0.003**
Age, years	1.039	1.017	1.063	0.001	1.026	1.000	1.053	0.049
Hb, g/dL	0.818	0.727	0.921	0.001	0.865	0.762	0.981	0.024
LA size, mm	1.023	0.997	1.048	0.079	1.033	1.007	1.061	0.014
CHA_2DS_2-VASc	1.258	1.099	1.440	0.001	1.012	0.834	1.229	0.902
PAOD	2.964	1.643	5.347	<0.001	2.037	1.006	4.122	0.048
Rheumatic	1.637	0.969	2.764	0.065				
Afib duration, years	1.012	0.980	1.045	0.463				
Anticoagulation*	**3.420**	**1.642**	**7.125**	**0.001**				
aspirin	1.562	0.961	2.541	0.072				
clopidogrel	0.726	0.264	1.994	0.535				
Left side maze	1.544	0.972	2.453	0.066				
LAA Resection	1.352	0.836	2.185	0.218				

*: violates proportional hazard assumption

Table 4. Follow up LA size after LA Reduction. Echo > 90days

Median follow-up 1,391 days, IQR 597-2,670 days

	LA reduction (n=765)	LA preservation (n=498)	P value
	LA size (mm)		
Pre-operative	62.12 (8.79)	56.47 (5.81)	<0.001
Post-operative	51.53 (8.37)	50.94 (7.35)	0.196
	IPTW-adjusted, n=761.6	IPTW-adjusted, n=501.9	SMD
Pre-operative	59.81 (8.29)	59.83 (8.36)	0.002
Post-operative	50.57 (8.02)	53.00 (8.72)	0.291

Supplementary Table 1. Codebook for the variables used in inverse probability of treatment weighting, (IPTW)

LA	Left atrial AP diameter (Numeric)
mitral	Involvement of mitral procedure (Factor)
ltmaze	Left side only ablation (Factor)
LVIDd	Diastolic Left Ventricular Internal Dimension (Numeric)
Aortic	Involvement of aortic valve procedure (Factor)
AF_duration	Duration of Atrial fibrillation, year (Numeric)
mValve	Valve involvement more than 2 (Factor)
Rheumatic	Rheumatic Heart Valve Disease
MICS	Minimal invasive cardiac surgery
Rfmaze	Radiofrequency ablation
Age	Age (numeric)
tricuspid	Involvement of tricuspid valve procedure (Factor)
PAOD	Peripheral Arterial Occlusive Disease
Nitrogen	Nitrogen based cryoablation (Factor)
Chadvasc	CHA2DS2-VASc Score (Numeric)
iValve	Single valve procedure (Factor)

LVIDs	Systolic Left Ventricular Internal Dimension
CVA.Hx	Cerebrovascular Accident History (Factor)
Laatreat	Left atrial appendage treatement(resection,obliteration,external clip) (Factor)
HTN	Hypertension
Anticoagulation	Anticoagulation (Factor)
HLD	Hyperlipidemia
AF.type	Persistent Atrial fibrillation
BMI	Body Mass Index (numeric)
Period	After year 2016
LVEF	Left Ventricular Ejection Fraction
TR34	Tricuspid regurgitation grade 3-4
Dialysis	History of dialysis
OP.type	Emergency operation
CAD	Coronary arterial disease
Argon	Use of Argon cryoablation
PCI.Hx	Percutaneous coronary intervention History
ValveCABG	Concomitant Valve and CABG
Sex	Sex

CHF	Congestive Heart Failure
Redo	Re-operation
TRPG	Tricuspid regurgitation Pressure Gradient
Lung.dieases	Either Asthma or COPD
DM	Diabetes Mellitus
Mechanical Valve	Use of Mechanical prosthesis
CKD	Chronic Kideny Disease
NYHA34	New York Heart Association class 3-4
Hb	Hemoglobin

Supplementary Table 2. Operative profiles of concomitant cardiac operation

Operation	LA Reduction (n=876)	LA Preservation (n=608)	p-value
Single Valve	**253 (28.9)**	**225 (37.0)**	**0.001**
AVR	**3 (0.3)**	**37 (6.1)**	**<0.001**
MVR	120 (13.7)	103 (16.9)	0.1
MVP	109 (12.4)	60 (9.9)	0.146
TVR	3 (0.3)	7 (1.2)	0.121
TVP	18 (2.1)	18 (3.0)	0.345
Multiple Valve	**554 (63.2)**	**313 (51.5)**	**<0.001**
DVR+TVR	5 (0.6)	1 (0.2)	0.425
DVR	49 (5.6)	46 (7.6)	0.156
DVR+TVP	78 (8.9)	61 (0.0)	0.52
MVR+TVP	**237 (27.1)**	**113 (18.6)**	**<0.001**
MVP+TVP	**153 (7.5)**	**52 (8.6)**	**<0.001**
ValveCABG	53 (6.1)	29 (4.8)	0.344

AVRCABG	10 (1.1)	7 (1.2)	1
MVRCABG	28 (3.2)	15 (2.5)	0.505
Isolated CABG	0 (0.0)	5 (0.8)	0.026
ASD Closure	2 (0.2)	4 (0.7)	0.386
Others	1 (0.1)	5 (0.8)	0.089
Ablation Profile			
Left only maze	**259 (29.6)**	**305 (50.2)**	**<0.001**
LA Auricle treatment	**458 (57.5)**	**260 (50.1)**	**0.01**
Preservation	338 (38.6)	259 (42.6)	
Resection	341 (38.9)	158 (26.0)	
Internal obliteration	71 (8.1)	90 (14.8)	
Clipping	43 (4.9)	11 (1.8)	
External ligation	3 (0.3)	1 (0.2)	
Unknown	80(9.1)	89(14.6)	
Energy Source			
Nitrogen base cryoablation	123 (14.0)	46 (7.6)	<0.001
Argon base cryoablation	737 (84.1)	528 (86.8)	0.17
Radiofrequency ablation	7 (0.8)	26 (4.3)	<0.001

AVR, Aortic Valve Replacement; MVR, Mitral Valve Replacement; MVP, Mitral Valvuloplasty; TVR, Tricuspid Valve Replacement; TVP,

Tricuspid Valvuloplasty; DVR, Double Valve Replacement (AVR+MVR),

Abstract

Objective: Enlarged left atrium (LA) is a risk factor for ablation failure after atrial fibrillation (AF) surgery. It predisposes patients to thromboembolic events, even in successful ablation; therefore, concomitant resection of the LA wall during surgical ablation was introduced. This study examined the clinical impacts of LA reduction in patients undergoing concomitant ablation for AF.

Methods: This study enrolled 1,484 patients with enlarged LA (≥50 mm) who underwent surgical AF ablation during major cardiac surgery between January 2001 and August 2018. Among them, 876 (59%) patients underwent concomitant LA reduction (Reduction group), whereas in the remaining 608 (41%), the LA wall was unresected (Preservation group). The primary outcome of interest was long-term mortality, stroke, and AF recurrence, and secondary outcomes were early postoperative complications and postoperative echocardiographic parameters. Outcomes were compared after adjusting baseline characteristics with inverse probability of treatment weighting (IPTW) using propensity score.

Results: The median follow-up was 60.1 months. After IPTW adjustment, long-term mortality (p=0.250) and AF-free rates (p=0.196) did not significantly differ between groups. However, the Reduction group showed a decreased risk of stroke (hazard ratio 0.54; 95% confidence interval 0.32-0.90; p=0.018). Early postoperative complications rate such as mortality or reoperation for bleeding, was not significantly different between the two groups. The Reduction group showed smaller LA diameter (50.6±8.0 mm vs. 53.6±8.9 mm; p<0.001) on follow-up echocardiography.

Conclusions: LA reduction effectively decreased LA size and appeared to decrease the stroke risk in patients with enlarged LA undergoing ablation for AF.