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Clinical Benefits of Concomitant Surgical Ablation For Atrial Fibrillation Undergoing Mitral Valve Surgery: National Cohort Study

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Title: Clinical Benefits of Concomitant Surgical Ablation For Atrial Fibrillation Undergoing Mitral Valve Surgery: National Cohort Study

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Short title: Maze surgery in mitral valve surgery

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Abstract

Background: The maze procedure is the dominant concomitant surgery performed with mitral valve (MV) surgery in patients with atrial fibrillation (AF). Most clinical recommendation regarding the maze procedure depends on individual maze expert centers.

Objective:

The current study aimed to evaluate the clinical benefits of the maze procedure during MV surgery with national cohort.

Methods: Using the National Health Insurance Data Sharing Service of South Korea, subjects with AF who underwent MV surgery from 2009 to 2017 were reviewed. The outcomes of interest were mortality; occurrence of ischemic or hemorrhagic stroke; hospitalization for bleeding events; and the composite of death, cerebrovascular accident, and major bleeding. Propensity score (PS) matching was performed for baseline adjustment.

Results: Among 9,501 subjects, the maze procedure was performed in 5,508 subjects(58.0%). In the PS-matched cohort(3,376 pairs), the risk of the composite event was significantly lower in the maze group (hazard ratio 0.799; 95% confidence interval, 0.731–0.873) than in the non-maze group. The superiority of the maze was similar for individual clinical events, including death (0.795, 0.711–0.889), ischemic stroke (0.788, 0.67–0.926), and major bleeding (0.749, 0.627–0.895), but not hemorrhagic stroke (0.984, 0.768–1.262). In the subgroup analyses, concerning the composite events, these benefits were consistent in subjects aged ≥70 years or less, surgery types (replacement vs. repair), MV pathologies, and subjects with a CHA_2DS_2-VASc score of ≥4 or less.

Conclusion: The adding maze procedure during MV surgery provided protective effects in the composite outcome of interest.

Keywords: atrial fibrillation; mitral valve; death; stroke; big data

Introduction

Atrial fibrillation (AF) is the most common arrhythmia with a high prevalence among the aged population. [1,2] Surgical treatment for AF was introduced by Cox et al. [3] in 1987, with excellent long-term results, while medical treatment to restore and maintain sinus rhythm was unsuccessful in a considerable number of patients with permanent AF. Despite meaningful improvements in surgical ablation devices and growing evidence to support the positive effect of surgical ablation on the clinical outcomes of patients, surgical ablation for AF is still underperformed during cardiac surgery. [4,5] Recent guidelines support the performance of concomitant surgical ablation for AF when indicated. [6,7] It is therefore correct to assume that if AF is left untreated during cardiac surgery, it may be associated with increased long-term mortality and morbidity in patients undergoing valve surgery.

Despite extensive efforts to prove the efficacy of the maze procedure, there are limitations in the level of evidence of research and in real-world practice. Most studies have been conducted at expert cardiac centers; however, many studies have been retrospective with small cohorts. Moreover, the invasiveness of additional cardiac incision and the prolonged cardiac ischemic time are additional obstacles to implementation of the maze procedure by non-expert groups. In real-world practice, changes in medical behavior are important issues in the field of arrythmia. Non-warfarin anti-coagulation agents (NOACs) effectively reduce cerebrovascular accidents in subjects with AF with fewer complications and restrictions than warfarin. Administration of NOACs to patients after cardiac surgery is not uncommon.

However, there are still unsolved questions regarding the effect of the maze procedure on hard endpoints related to AF during MV surgery, and updates to recent clinical circumstances are required. To understand real-world practice, we used the largest Korean database of national cohort data to investigate the impact of the maze procedure on various clinical outcomes in subjects with preoperative AF who underwent MV surgery.

Methods

Data source and study population

Subjects were retrieved from the national health claims database established by the National Health Insurance Service (NHIS) of Korea. The NHIS is the insurance service provided by the Korean government. Citizens of Korea are mandatorily registered to the NHIS and covered for medical services. Claims data, including claimants' demographic information, diagnoses, procedures, and prescription records from inpatient and outpatient services, were obtained for this study. Diagnoses were recorded using International Classification of Disease 10th Revision (ICD-10) codes.

We identified subjects who were diagnosed with AF from January 2009 to December 2017 (N = 1,052,040). Among them, subjects who underwent MV surgery (replacement or repair) and who were older than 20 years were included in this study (N = 9,504). Subjects who had undergone prior cardiac surgery were excluded from the study cohort (N = 1,368). Those with missing data were also excluded (N = 3). This study was approved by the institutional review board of the institution at which the study was performed.

Cardiovascular risk factors and study outcomes

We obtained subjects' baseline characteristics, including age, sex, and comorbidities such as hypertension, diabetes mellitus, dyslipidemia, chronic renal failure, congestive heart failure, peripheral artery disease, history of myocardial infarction, and history of hemorrhagic or ischemic stroke. CHA_2DS_2-VASc scores were also calculated for analysis. AF duration was the number of years from the first AF diagnosis to the indexed day (admission for MV surgery). The major MV pathologies were categorized into mitral stenosis (MS), mitral regurgitation (MR), and infective endocarditis (IE). The type of MV surgery was divided into mitral valve replacement (MVR) and mitral valvuloplasty (MVP). The definition of each variable is described in the Supplementary Table 1.

To evaluate the effect of the maze procedure on AF-related clinical outcomes, we identified the risks of death, cerebrovascular accident (hemorrhage + ischemia), major bleeding, and the composite outcome (death + ischemic stroke + hemorrhagic stroke + major bleeding) in the control group (subjects who did

not undergo the maze procedure) and the maze group. Each outcome was defined as hospitalization with the corresponding ICD code. The detailed ICD codes used for diagnosis are described in the Supplementary Table 1.

Subgroup analyses

To investigate the effects of the maze procedure, subjects were analyzed in composite, mortality, ischemic stroke, hemorrhagic stroke, and major bleeding by age (<70 years vs. ≥70 years), sex, MV pathology (MS vs. non-MS; MR vs. non-MR), MV surgery type (replacement vs. repair), and CHA_2DS_2-VASc score (<4 vs. ≥4). A multivariable analysis was performed by adjusting for covariates, including age, sex, MS, MR, IE, coronary artery bypass grafting, aortic valve(AV) surgery, tricuspid valve(TV) surgery, mechanical prosthesis, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, transient ischemic attack/thromboembolism, history of myocardial infarction, peripheral artery disease, hemorrhage and ischemic stroke, AF duration, and CHA_2DS_2-VASc score. In each subgroup analysis, statistically significant interactions ($p < 0.05$) between two groups were analyzed and described.

Statistical analysis

Categorical variables are presented as frequency and percentage and were compared using the chi-square test. Continuous variables are presented as mean ± standard deviation or median with range and were compared using Student's *t*-test.

To reduce the effect of selection bias, the PS was used to adjust subjects' baseline characteristics. The PS that was used to indicate whether the maze procedure should be performed was estimated using multiple logistic regression based on age, sex, MV pathology, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, congestive heart failure, transient ischemic attack/thromboembolism, peripheral artery disease, previous myocardial infarction, hemorrhagic stroke, ischemic stroke, CHA_2DS_2-VASc score, AF duration, concomitant surgery (MVR, MVP, coronary artery bypass grafting, AV surgery, and TV surgery), and use of a mechanical valve prosthesis. The PS-

matched pairs were created by 1:1 matching between the maze group and the control group. We set a caliper for nearest-neighbor matching within the first four to eight digits; for example, two patients with propensity scores of 0.12345678 and 0.12347123 matches on the first four digits (0.1234). The macro makes the "best" matches first and the "next-best" matches next in a hierarchical sequence until no more matches can be made. If no maze patient has a propensity score that lies within a four-digit width of an non-maze patient's propensity score, then that maze patient is left unmatched and is not used in subsequent analyses. The difference in the covariates after PS matching was evaluated using the absolute standardized difference (ASD) for balance assessment. An ASD of <0.1 indicated a negligible difference between the two study groups.(Supplemental Figure 1) For the clinical outcome analysis, the incidence rates were estimated using the total number of clinical outcomes during the follow-up period divided by 1,000 person-years at risk. The risk of outcomes in the maze group compared with the control group (reference) was analyzed using the Kaplan–Meier method and the log-rank test for the univariable analysis, and the Cox proportional hazards regression model was used for the multivariable analysis. The results are expressed as hazard ratio (HR) with 95% confidence interval (CI). A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

Population

A total of 9,501 subjects with AF who underwent MV surgery were retrieved from the Korea NHIS database from 2009 to 2017. At index surgery, paroxysmal AF was observed in 46.4% (n=4412) The mean age of subjects was 60.77 ± 11.85 years, and 44.3% of subjects were male. MVR was performed in 64.8% of subjects (n = 6,161). A mechanical prosthesis was implanted in 66.6% of subjects who underwent MVR. The maze procedure was performed in 57.9% of the total cohort (n = 5,508). The proportion of maze procedures in those receiving MV surgery was stationary at about 57% during the

study period. Yearly the number of maze procedures was described in figure 1.

Subjects who underwent the maze procedure were more likely to be younger, have MS, have undergone concomitant tricuspid valve surgery, have a longer AF duration, and have myocardial ischemia. A statistically significant difference was not observed in CHA_2DS_2-VASc score between the non-maze group and the maze group. The follow-up duration was 4.64 ± 2.87 years.

PS matching was performed to reduce bias from the difference in subjects' characteristics. Subjects' baseline characteristics before and after PS matching are described in Table 1. After matching, 3,376 pairs were retrieved, and all baseline profiles in the matched cohort were well balanced (all covariates: ASD < 0.1). The crude incidence rate between the maze and non-maze group was described in table 2.

Incidence of the composite outcome, death, ischemic stroke, hemorrhagic stroke, and major bleeding

In the PS-matched cohort, the incidence rate of death was 44.5 per 1,000 person-years in the control group and 35.3 per 1,000 person-years in the maze group. The maze group showed a lower risk of death than the control group (HR, 0.795; 95% CI, 0.711–0.889; P < 0.001). The incidence rate of ischemic stroke in the control group and the maze group was 22.5 and 17.7, respectively. The maze group showed a lower risk of incident ischemic stroke than the control group (HR, 0.788; CI, 0.67–0.926; P = 0.004). The incidence rate of hemorrhagic stroke in the control group and the maze group was 8.16 and 8.03, respectively. There was no significant difference in the incidence rate of hemorrhagic stroke between the two groups (HR, 0.984; CI, 0.768–1.262; P = 0.902). The incidence rate of major bleeding in the control group and the maze group was 18.7 and 13.9, respectively. The maze group showed a lower risk of incident major bleeding than the control group (HR, 0.749; CI, 0.627–0.895; P = 0.002). The incidence rate of the composite outcome in the control group and the maze group was 77.6 and 61.4, respectively. The maze group showed a lower risk of the composite outcome than the control group (HR, 0.799; CI, 0.731–0.873; P < 0.001). The maze procedure reduced the risk of the composite outcome, death, ischemic stroke, and major bleeding when performed during MV surgery. The maze group showed comparable outcomes to the control group in terms of hemorrhagic stroke (Table 3).

The cumulative incidence of the composite outcome, death, cerebrovascular accident (ischemic stroke + hemorrhagic stroke), and major bleeding in the PS-matched cohort is depicted in Figure 2 and was calculated using the log-rank test.

Anticoagulation medication in patients with bio-prosthesis or repaired MV

The maze procedure was associated with a lower prescription rate of warfarin compared to non-maze group at 6 and 12 months after surgery. (P=0.038 at 6 months, P < 0.001 at 12 months) (Table 4)

Subgroup analysis

An explanatory subgroup analysis adjusted for covariates was performed by age (<70 vs. ≥70 years), sex, MV pathology, MV surgery type, and CHA_2DS_2-VASc score (<4 vs. ≥4). The maze procedure was beneficial in all subgroups in terms of the incidence rate of the composite outcome, ischemic stroke, major bleeding, and death. A comparable outcome was observed between the subgroups in terms of hemorrhagic stroke. There was a significant interaction on the specific subgroups concerning ischemic stroke and major bleeding. In terms of ischemic stroke, the maze procedure showed a significant interaction between subjects with MS pathologies (HR, 0.653; CI, 0.519–0.82) and those with non-MS pathologies (HR, 0.901; CI, 0.712–1.14) (P for interaction = 0.044) and between subjects who underwent MVR (HR, 0.664; CI, 0.545–0.81) and those who underwent MVP (HR, 1.012; CI, 0.756–1.355) (P for interaction = 0.015). In terms of major bleeding, the maze procedure showed a significant interaction between subjects with a CHA_2DS_2-VASc score of <4 (HR, 0.587; CI, 0.446–0.749) and those with a CHA_2DS_2-VASc score of ≥4 (HR, 0.972; CI, 0.755–1.251) (P for interaction = 0.005). The maze procedure reduced the risk of ischemic stroke in subjects with MS and in subjects who underwent MVR, as well as the risk of major bleeding in subjects with a CHA_2DS_2-VASc score of <4. However, a comparable outcome was observed in subjects with non-MS pathologies, who underwent MVP, and who had a CHA_2DS_2-VASc score of ≥4 (Figure 3)(Supplementary Table 2)

Discussion

This study using the national cohort data investigates the effect of the maze procedure during MV surgery on long-term outcomes related to AF, including death, ischemic stroke, hemorrhagic stroke, and major bleeding. The addition of the maze procedure during MV surgery was associated with a lower risk of the composite outcome, death, ischemic stroke, and major bleeding. However, there was no difference between the two groups in terms of the risk of hemorrhagic stroke. The benefit of the maze procedure in terms of the incidence of the composite outcome was consistently observed in all subgroups stratified by age, sex, MV pathology, MV surgery type, and CHA_2DS_2-VASc score. The maze procedure was associated with a lower prescription rate of warfarin compared to non-maze group at 6 and 12 months after surgery.

As a concomitant procedure during cardiac surgery, the maze procedure has a low risk of perioperative and long-term morbidity and mortality.[8-11] Ad et al.[9] reported that perioperative mortality and morbidity are acceptable with the maze procedure, with a low observed-to-expected ratio of 0.55 for mortality. Long-term follow-up of such subjects should focus on the success of AF ablation, thromboembolic rate, anticoagulation, and survival. Cox reported a trend in the surgical ablation of AF in the US using PS matching. From July 2011 to June 2014, 86,941 subjects with AF underwent primary non-emergent cardiac operations and were recorded in the Society of Thoracic Surgeons (STS) database.[8] The risk of concomitant surgical ablation was analyzed by PS matching of 28,739 patient-pairs with and without surgical ablation by AF type, primary operation, and STS comorbid risk variables using the greedy 1:1 matching algorithm. After PS matching, surgical ablation was associated with a reduction in the relative risk (RR) of 30-day mortality (RR, 0.92; 95% CI, 0.85–0.99) and stroke (RR, 0.84; 95% CI, 0.74–0.94), but an increase in renal failure (RR, 1.12; 95% CI, 1.03–1.22) and pacemaker implantation (RR, 1.33; 95% CI, 1.24–1.43). There is no evidence on the risk of bleeding events in subjects undergoing the maze procedure, contrary to ischemic stroke or thromboembolic risk. Our study showed a lower risk of major bleeding in the maze group than in the control group. We investigated the anticoagulation

prescription after MV surgery except for those with implantation of the mechanical prosthesis. At 6 months and 12 months after surgery, the warfarin prescription was significantly lower in the maze group compared to the non-maze group. Papers showed that warfarin prescription is associated with a higher risk of bleeding. Based on our results, the maze procedure was associated with a lower prescription of warfarin. It might be associated with a lower risk of major bleeding.

Decision-making on whether to perform surgical ablation with concomitant surgery is still evolving. Currently, there is clear variability among surgeons in terms of the degree and type of surgical ablation performed. [5] Previous studies have demonstrated that surgical ablation with concomitant surgery is not associated with an increased operative risk. [12,13] Moreover, recent guidelines have clearly recommended concomitant surgical ablation to improve perioperative morbidity and mortality. [14] In Asia cardiothoracic surgery society, until now, there was no specific recommendation for AF ablation during concomitant surgery, so we followed STS or American Heart Association (AHA)/American College of Cardiology (ACC) guidelines. [14] This study was conducted with the largest AF database and with complete follow-up data from the Korea NHIS database. Therefore, this study provided the current status and clinical outcomes of surgical ablation for AF in the patient receiving MV surgery.

We conducted a specific subgroup analysis to evaluate the effect of the maze procedure based on older age (age ≥ 70 years), MS pathology, MV surgery type, and high CHA_2DS_2-VASc score. The maze procedure provided protective effects in all subgroups in terms of the composite outcome. Therefore, the indications to concomitantly perform the maze procedure might be extended to high-risk subjects, regardless of MV pathology and surgical type. Older age has been shown to predict AF recurrence after the maze procedure in previous studies. [15,16] Despite concerns regarding the efficacy of sinus restoration, our study showed that the addition of the maze procedure was associated with a lower risk of the composite outcome. The maze procedure consistently reduced the risk of the composite outcome in specific subgroups, including the MS, MR, MVP, MVR, and high CHA_2DS_2-VASc score subgroups. Kim et al. [15] demonstrated that the maze procedure is acceptable regardless of MV surgery type. Moreover, Anders et al. [17] demonstrated that the Cox-maze III procedure reduces the incidence of

ischemic stroke compared with the predicted risk using the CHA_2DS_2-VASc score. However, subjects with a CHA_2DS_2-VASc score of ≥2 showed a higher risk of ischemic stroke than subjects with a CHA_2DS_2-VASc score of 0 or 1. In our subgroup analysis, subjects with a CHA_2DS_2-VASc score of ≥4 showed a greater reduction in the risk of ischemic stroke than subjects with a lower CHA_2DS_2-VASc score (<4: HR, 0.852; CI, 0.675–1.074; ≥4: HR, 0.683; CI, 0.543–0.858). Therefore, the addition of the maze procedure during MV surgery showed benefits in various subgroups.

Limitations

This study was conducted with data from the Korean NHIS database, which is the largest database of medical procedures and medical issues in South Korea. However, the lack of detailed clinical data, including data on echocardiographic factors, such as left ventricular ejection fraction and chamber dimensions, and information on the surgical technique used for the maze procedure and left atrial appendage procedure, was a major limitation of this study. Diagnosis and events were defined using ICD-10 codes and hospitalization records. Thus, there is a possibility that clinical events were over- or underestimated. Finally, postoperative AF status could not be investigated using the claims database. Because AF status after surgery may be an important determinant for clinical outcomes, absence of AF status is major limitation of this study to understand a cause of adverse event.

Selection and confounding bias may have been generated due to the limitation of the study design and the given cohort, despite rigorous statistical adjustment.

Conclusions

In this large cohort study, we reported the efficacy of the concomitant maze procedure for subjects who underwent MV surgery in terms of AF-related outcomes. Addition of the maze procedure during MV surgery reduced the incidence of the composite outcome, death, ischemic stroke, hemorrhagic stroke, and major bleeding. This benefit was consistently observed in specific subgroups stratified by age, MV pathology, MV surgery type, and CHA_2DS_2-VASc score. These findings and the supporting data from recent guidelines should be considered by surgeons when operating on subjects with AF during MV

surgery.

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References

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982;306:1018-1022.
2. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. J Am Coll Cardiol 2000;36:1303-1309.
3. Cox JL, Schuessler RB, D'Agostino HJ, Jr., et al. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg 1991;101:569-583.
4. Ad N, Damiano RJ, Jr., Badhwar V, et al. Expert consensus guidelines: Examining surgical ablation for atrial fibrillation. J Thorac Cardiovasc Surg 2017;153:1330-1354 e1331.
5. Ad N, Suri RM, Gammie JS, Sheng S, O'Brien SM, Henry L. Surgical ablation of atrial fibrillation trends and outcomes in North America. J Thorac Cardiovasc Surg 2012;144:1051-1060.
6. Ad N, Damiano RJ, Jr., Badhwar V, et al. Expert consensus guidelines: Examining surgical ablation for atrial fibrillation. J Thorac Cardiovasc Surg 2017;153:1330-1354.e1331.
7. Bando K, Kasegawa H, Okada Y, et al. Impact of preoperative and postoperative atrial fibrillation on outcome after mitral valvuloplasty for nonischemic mitral regurgitation. J Thorac Cardiovasc Surg 2005;129:1032-1040.
8. Badhwar V, Rankin JS, Ad N, et al. Surgical Ablation of Atrial Fibrillation in the United States: Trends and Propensity Matched Outcomes. Ann Thorac Surg 2017;104:493-500.
9. Ad N, Holmes SD, Massimiano PS, Rongione AJ, Fornaresio LM. Long-term outcome following concomitant mitral valve surgery and Cox maze procedure for atrial fibrillation. J Thorac Cardiovasc Surg 2018;155:983-994.
10. Iribarne A, DiScipio AW, McCullough JN, et al. Surgical Atrial Fibrillation Ablation Improves

Long-Term Survival: A Multicenter Analysis. Ann Thorac Surg 2019;107:135-142.

11. Gillinov AM, Gelijns AC, Parides MK, et al. Surgical ablation of atrial fibrillation during mitral-valve surgery. N Engl J Med 2015;372:1399-1409.

12. Ad N, Henry LL, Holmes SD, Hunt SL. The impact of surgical ablation for atrial fibrillation in high-risk patients. Ann Thorac Surg 2012;93:1897-1903; discussion 1903-1894.

13. Ad N, Holmes SD, Pritchard G, Shuman DJ. Association of operative risk with the outcome of concomitant Cox Maze procedure: a comparison of results across risk groups. J Thorac Cardiovasc Surg 2014;148:3027-3033.

14. Badhwar V, Rankin JS, Damiano RJ, Jr., et al. The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial Fibrillation. Ann Thorac Surg 2017;103:329-341.

15. Kim JB, Yun TJ, Chung CH, Choo SJ, Song H, Lee JW. Long-term outcome of modified maze procedure combined with mitral valve surgery: analysis of outcomes according to type of mitral valve surgery. J Thorac Cardiovasc Surg 2010;139:111-117.

16. Kuh JH, Song JY, Kim TY, Kim JH, Choi JB. Treatment of Atrial Fibrillation in Elderly Patients with the Cox Maze Procedure Concurrently with Other Cardiac Operations. Korean J Thorac Cardiovasc Surg 2017;50:171-176.

17. Albage A, Sartipy U, Kenneback G, et al. Long-Term Risk of Ischemic Stroke After the Cox-Maze III Procedure for Atrial Fibrillation. Ann Thorac Surg 2017;104:523-529.

Figure Legends

Figure 1. The number of mitral valve surgery according to concomitant maze procedure by year

Figure 2. Cumulative incidence rate plots for composite events (death + ischemic stroke + hemorrhagic stroke + major bleeding), death, cerebrovascular accident (ischemic + hemorrhagic) and, major bleeding between control and maze group. (Propensity score matched cohort)

Figure 3. Hazard ratio of composite events (death + ischemic stroke + hemorrhagic stroke + major bleeding), death, ischemic stroke, and major bleeding according to subgroups including age, sex, mitral valve pathology, mitral valve surgery type, and CHA2-DS2-VASc score between the control and the maze group in propensity score matched cohort.

* Adjusted with covariates age, sex, mitral stenosis, mitral regurgitation, infective endocarditis, coronary artery bypass grafting, aortic valve surgery, tricuspid valve surgery, mechanical heart valve prosthesis, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, TIA/TE, transient ischemic attack, or thromboembolism; PAD, peripheral artery disease, hemorrhage stroke, ischemic stroke, atrial fibrillation duration, CHA2-DS2-VASc score.

Table 1. Baseline characteristics of study cohort before and after propensity score matching(PSM)

		Before PSM			After PSM		
Variables	Total (9501)	Non-Maze (3993)	Maze (5508)	ASD	Non-Maze (3376)	Maze (3376)	ASD
Sex, male	4209 (44.3)	1861 (46.61)	2348 (42.63)	0.08	1534 (45.44)	1492 (44.19)	0.025
Age, years	60.77 ± 11.85	61.6 ± 12.9	60.18 ± 11	0.119	60.85 ± 12.52	61.06 ± 11.57	0.018
20 - 64	5515 (58.05)	2136 (53.49)	3379 (61.35)	0.159	1921 (56.9)	1865 (55.24)	0.033
65 - 74	2889 (30.41)	1220 (30.55)	1669 (30.3)	0.006	1034 (30.63)	1113 (32.97)	0.050
75 -	1097 (11.55)	637 (15.95)	460 (8.35)	0.234	421 (12.47)	398 (11.79)	0.021
Mitral valve pathology							
Mitral stenosis	4829 (50.83)	1636 (40.97)	3193 (57.97)	0.345	1593 (47.19)	1612 (47.75)	0.011
Mitral regurgitation	6822 (71.8)	2940 (73.63)	3882 (70.48)	0.07	2468 (73.1)	2461 (72.9)	0.005
Infective endocarditis	1297 (13.65)	724 (18.13)	573 (10.4)	0.222	431 (12.77)	458 (13.57)	0.024
Comorbidity							
Hypertension	7921 (83.37)	3321 (83.17)	4600 (83.51)	0.009	2807 (83.15)	2798 (82.88)	0.007
Diabetes mellitus	3395 (35.73)	1476 (36.96)	1919 (34.84)	0.044	1196 (35.43)	1207 (35.75)	0.007
Dyslipidemia	3732 (39.28)	1611 (40.35)	2121 (38.51)	0.038	1331 (39.43)	1329 (39.37)	0.001
Chronic kidney disease	1722 (18.12)	729 (18.26)	993 (18.03)	0.006	599 (17.74)	606 (17.95)	0.005
Congestive heart failure	5967 (62.8)	2411 (60.38)	3556 (64.56)	0.086	2098 (62.14)	2099 (62.17)	0.001
TIA/TE	396 (4.17)	161 (4.03)	235 (4.27)	0.012	138 (4.09)	129 (3.82)	0.014
Myocardial infarction	582 (6.13)	340 (8.51)	242 (4.39)	0.168	206 (6.1)	204 (6.04)	0.003
PAD	1407 (14.81)	635 (15.9)	772 (14.02)	0.053	495 (14.66)	508 (15.05)	0.01
Hemorrhage stroke	249 (2.62)	119 (2.98)	130 (2.36)	0.039	75 (2.22)	96 (2.84)	0.04
Ischemic stroke	1722 (18.12)	729 (18.26)	993 (18.03)	0.006	599 (17.74)	606 (17.95)	0.005
CHA2-DS2-VASc score	3.22 ± 1.64	3.3 ± 1.74	3.16 ± 1.56	0.087	3.21 ± 1.67	3.21 ± 1.63	<0.001
Score ≥ 4	3643 (38.34)	1637 (41)	2006 (36.42)	0.094	1292 (38.27)	1306 (38.68)	0.009
AF duration, years	3.3 ± 4.23	2.89 ± 4.25	3.6 ± 4.2	0.168	3.18 ± 4.38	3.24 ± 4.05	0.015
Operation profile							

Mitral valve replacement	6161 (64.85)	2551 (63.89)	3610 (65.54)	0.035	2131 (63.12)	2123 (62.89)	0.005
Mitral valvuloplasty	3340 (35.15)	1442 (36.11)	1898 (34.46)	0.035	1245 (36.88)	1253 (37.11)	0.005
Concomitant CABG	372 (3.92)	189 (4.73)	183 (3.32)	0.072	144 (4.27)	142 (4.21)	0.003
Concomitant Aortic valve surgery	2223 (23.4)	1040 (26.05)	1183 (21.48)	0.108	813 (24.08)	840 (24.88)	0.019
Concomitant Tricuspid valve surgery	4393 (46.24)	1427 (35.74)	2966 (53.85)	0.37	1395 (41.32)	1425 (42.21)	0.018
Mechanical prosthesis	4105 (43.21)	1630 (40.82)	2475 (44.93)	0.083	1414 (41.88)	1409 (41.74)	0.003
F/U duration, years	4.64 ± 2.87	4.51 ± 2.92	4.73 ± 2.83	0.076	4.63 ± 2.92	4.65 ± 2.84	0.009

Numeric values are mean and standard deviation. Categorized variables are number and percent (%).

Abbreviations- ASD, absolute standardized difference; AF, atrial fibrillation; MV, mitral valve; TIA/TE, transient ischemic attack, or thromboembolism; PAD, peripheral artery disease

Table 2. Crude incidence rate and hazard ratio of clinical outcomes between control and Maze group with crude study cohort

Group	N	Event	Duration	IR	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
CVA (ischemic + hemorrhagic stroke)								
Control	3993	509	16654.19	30.5629	1 (ref.)	<0.001	1 (ref.)	<0.001
MAZE	5508	518	24681.81	20.9871	0.695 (0.615, 0.785)		0.742 (0.653, 0.844)	
Hemorrhagic stroke								
Control	3993	155	17632.86	8.7904	1 (ref.)	0.114	1 (ref.)	0.257
MAZE	5508	188	25625.64	7.3364	0.842 (0.681, 1.042)		0.879 (0.704, 1.098)	
Ischemic stroke								
Control	3993	411	16906.54	24.3101	1 (ref.)	<0.001	1 (ref.)	<0.001
MAZE	5508	392	24985.11	15.6893	0.652 (0.567, 0.748)		0.697 (0.603, 0.806)	
Major bleeding								
Control	3993	327	17229.44	18.9791	1 (ref.)	<0.001	1 (ref.)	<0.001
MAZE	5508	318	25338.51	12.5501	0.668 (0.572, 0.779)		0.714 (0.608, 0.839)	
Death								
Control	3993	874	18014.48	48.5165	1 (ref.)	<0.001	1 (ref.)	<0.001
MAZE	5508	779	26052.99	29.9006	0.624 (0.566, 0.687)		0.74 (0.669, 0.819)	
Composite events (death + ischemic stroke+ hemorrhagic stroke + major bleeding)								
Control	3993	1338	15996.82	83.6416	1 (ref.)	<0.001	1 (ref.)	<0.001
MAZE	5508	1293	24086.39	53.6818	0.656 (0.608, 0.708)		0.734 (0.677, 0.795)	

IR, incidence rate; HR, hazard ratio; CVA, cerebrovascular accident

Incidence rate presented as per 1000 person-years.

Adjusted by age, sex, mitral stenosis, mitral regurgitation, infective endocarditis, coronary artery bypass grafting, aortic valve surgery, tricuspid valve surgery, mechanical heart valve prosthesis, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, TIA/TE, transient ischemic attack, or thromboembolism; PAD, peripheral artery disease, hemorrhage stroke, ischemic stroke, atrial fibrillation duration, CHA2-DS2-VASc score

Table 3. Incidence rate and hazard ratio of clinical outcomes between control and Maze group with propensity score matched cohort

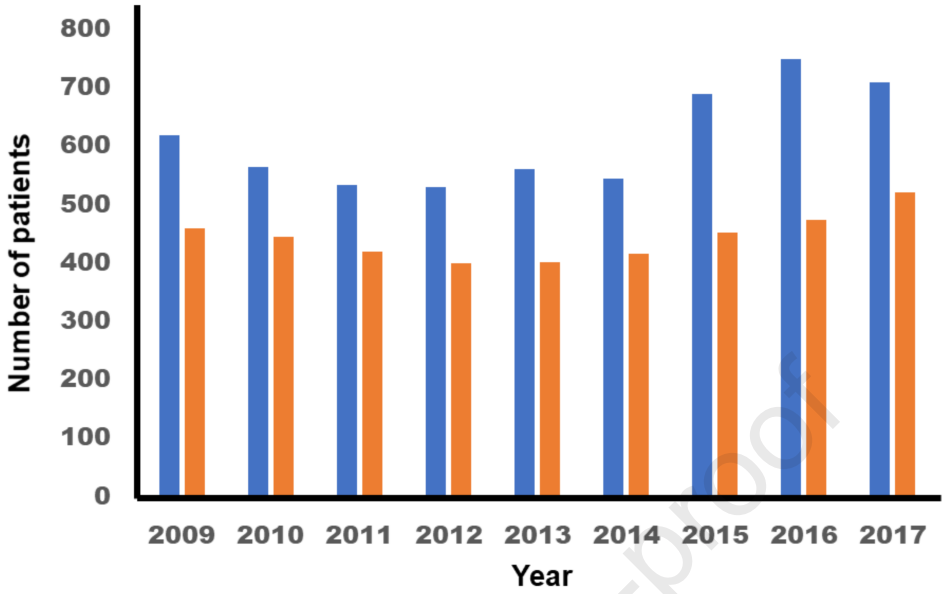
Group	N	Event	Duration	IR (per 1,000)	Unadjusted HR	P-value
CVA (ischemic + hemorrhagic stroke)						
Control	3376	408	14532.45	28.0751	1 (ref.)	0.013
MAZE	3376	346	14836.14	23.3214	0.833 (0.722, 0.962)	
Hemorrhagic stroke						
Control	3376	125	15315.32	8.16176	1 (ref.)	0.902
MAZE	3376	124	15432.03	8.03524	0.984 (0.768, 1.262)	
Ischemic stroke						
Control	3376	332	14729.18	22.5403	1 (ref.)	0.004
MAZE	3376	266	15022.99	17.7062	0.788 (0.67, 0.926)	
Major bleeding						
Control	3376	280	14930.26	18.7539	1 (ref.)	0.002
MAZE	3376	213	15220.69	13.9941	0.749 (0.627, 0.895)	
Death						
Control	3376	696	15622.12	44.5522	1 (ref.)	<0.001
MAZE	3376	555	15708.91	35.3303	0.795 (0.711, 0.889)	
Composite events (death + ischemic stroke+ hemorrhagic stroke + major bleeding)						
Control	3376	1081	13936.96	77.5636	1 (ref.)	<0.001
MAZE	3376	886	14424.05	61.4252	0.799 (0.731, 0.873)	

Incidence rate presented as per 1000 person-years.

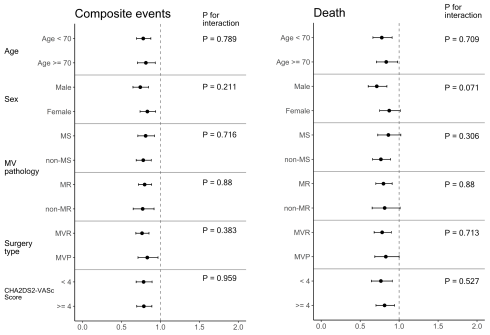
Abbreviations: IR, incidence rate; HR, hazard ratio

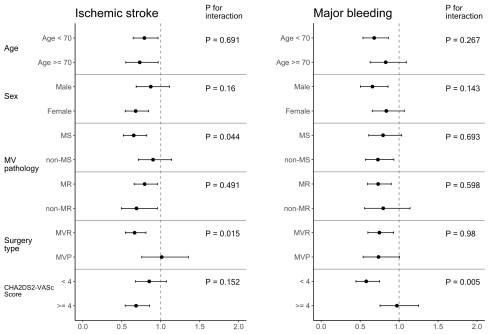
Table 4. Postoperative anticoagulation prescription according to surgical ablation surgery in patients with bio-prosthesis or repaired mitral valve.

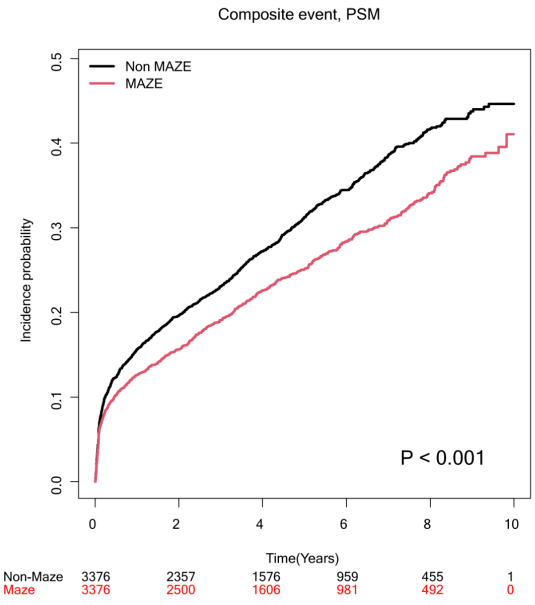
Period	Anticoagulation	Total	Maze group	Non-maze group	P
30 days	Anti-platelet	2222 (39.81)	1186 (38.21)	1036 (41.81)	0.006
	Warfarin	5115 (91.63)	2902 (93.49)	2213 (89.31)	<0.001
	NOAC	101 (1.81)	53 (1.71)	48 (1.94)	0.523
165-195 days	Anti-platelet	1030 (20.38)	601 (21.04)	429 (19.52)	0.184
	Warfarin	1146 (22.67)	617 (21.6)	529 (24.07)	0.038
	NOAC	37 (0.73)	16 (0.56)	21 (0.96)	0.102
350-380 days	Anti-platelet	885 (17.85)	502 (17.84)	383 (17.86)	0.982
	Warfarin	839 (16.92)	424 (15.07)	415 (19.36)	<0.001
	NOAC	43 (0.87)	27 (0.96)	16 (0.75)	0.423

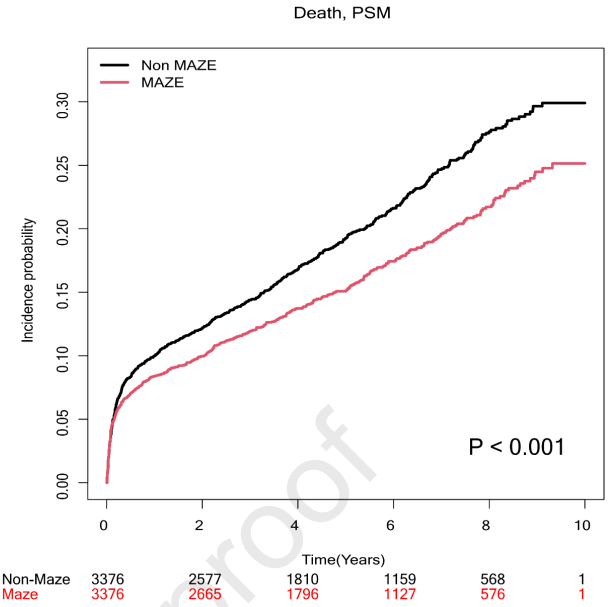


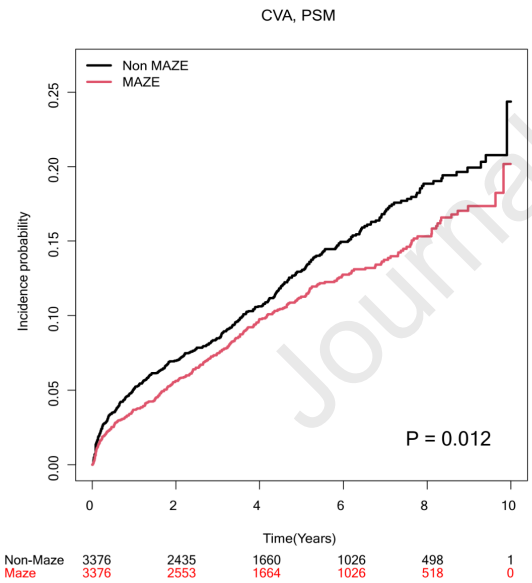
MAZE	620	565	534	531	561	546	690	750	711
Non-MAZE	461	445	421	400	402	416	453	474	521

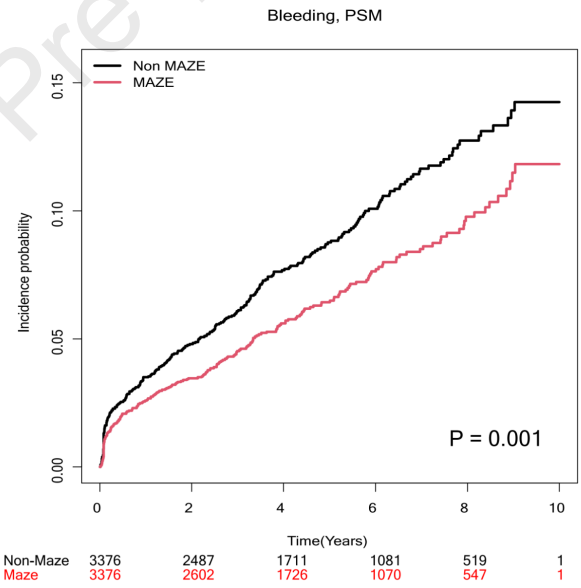










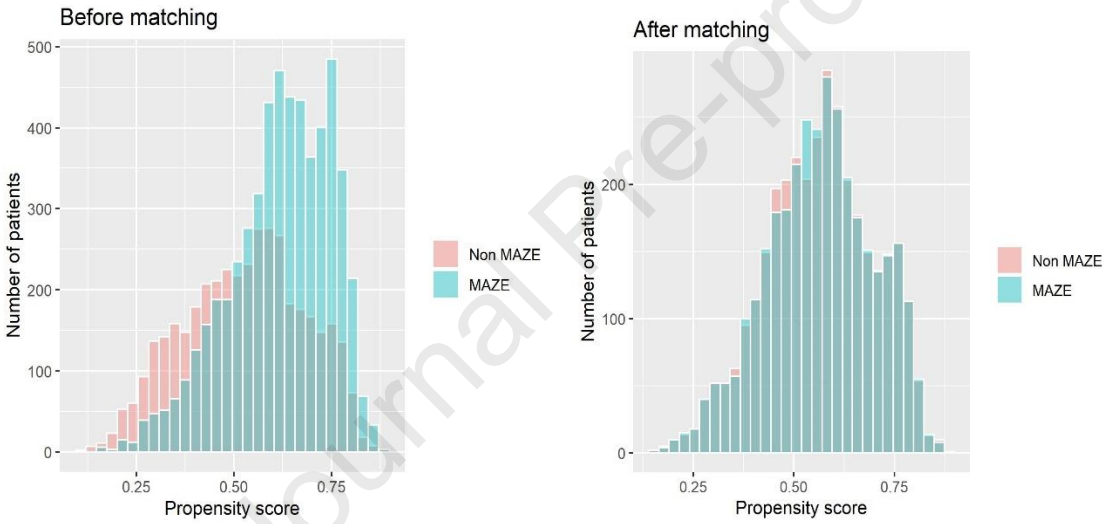


Supplementary table 1. Definition of comorbidity or outcome

Variables	ICD code or procedure code	Detailed definition
Atrial fibrillation	I48	Hospitalization ≥ 1 or Outpatient visit ≥ 2
Baseline characteristics		
Hypertension	I10-I13, I15	Hospitalization ≥ 1 or Outpatient visit ≥ 2 with medication
Diabetes mellitus	E11-14	Hospitalization ≥ 1 or Outpatient visit ≥ 2 with medication
Dyslipidemia	E78	Hospitalization or outpatient visit ≥ 2, with medication
Chronic kidney disease	I12.0, I12.9,I13.1,I13.2,N17, N18, N19	Hospitalization or outpatient visit ≥ 2 or Dialysis (V001, V003)
Congestive heart failure	I50	Hospitalization or outpatient visit ≥ 2
Myocardial infarction	I21, I22	Hospitalization or outpatient visit ≥ 2
Peripheral artery disease	I70, I73	Hospitalization ≥ 1 or Outpatient visit ≥ 2
TIA	G458, G4599	Hospitalization or outpatient visit ≥ 2
Liver cirrhosis	K70.2, K70.3, K74	Hospitalization or outpatient visit ≥ 2
Ischemic stroke	I63, I64	Hospitalization or outpatient visit ≥ 2
Hemorrhagic stroke	I60-62	Hospitalization or outpatient visit ≥ 2
Mitral stenosis	I05.0, I05.2, I34.2	Hospitalization or outpatient visit ≥ 2
Mitral regurgitation	I05.1, I05.2, I34.0, I34.1	Hospitalization or outpatient visit ≥ 2
Infective endocarditis	I33, I38, I39.8	Hospitalization or outpatient visit ≥ 2
Surgery code		
Mitral valve replacement	O1792	Single prescription
Mitral valve repair	O1782	Single prescription
Coronary artery bypass grafting	O164x, OA64x	Single prescription
Aortic valve surgery	O1793 O1799 O1783	Single prescription
Tricuspid valve surgery	O1781, O1791	
Mechanical heart valve prosthesis	G20310xx	Single prescription
Maze operation	O2006	Single prescription
Outcome of interest		
Ischemic stroke	I63, I64	Hospitalization and computed tomography, magnetic

		resonance imaging
Hemorrhagic stroke	I60-62	Hospitalization and computed tomography, magnetic resonance imaging
Major bleeding	I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K552, K625, K633, K649, K920, K921, K922	Hospitalization and transfusion of red blood cell

Supplementary figure. Histograms of propensity score distribution before and after propensity score matching.



Supplementary table 2. Incidence rate and hazard ratio of clinical outcomes according to specific subgroups of Maze group compared to control group. (Propensity score matched cohort)

	Composite events		Death		Ischemic stroke		Hemorrhagic stroke		Major bleeding	
Subgroup	IR	HR	IR	HR	IR	HR	IR	HR	IR	HR
Age		P = 0.789		P = 0.709		P = 0.692		P = 0.976		P = 0.267
< 70	55.8	0.779 (0.693, 0.877)	22.7	0.777 (0.663, 0.91)	15.0	0.79 (0.646, 0.965)	7.0	0.948 (0.7, 1.284)	9.8	0.68 (0.536, 0.863)
≥ 70	44.9	0.813 (0.707, 0.934)	81.0	0.834 (0.71, 0.981)	27.6	0.73 (0.551, 0.967)	11.6	0.936 (0.595, 1.474)	29.7	0.828 (0.628, 1.093)
Sex		P = 0.211		P = 0.071		P = 0.16		P = 0.914		P = 0.143
Male	59.3	0.741 (0.647, 0.847)	33.9	0.713 (0.603, 0.843)	18.9	0.872 (0.684, 1.112)	6.9	0.929 (0.621, 1.391)	13.5	0.658 (0.504, 0.858)
Female	63.2	0.832 (0.738, 0.938)	36.5	0.873 (0.75, 1.015)	16.8	0.678 (0.544, 0.844)	8.9	0.966 (0.701, 1.333)	14.4	0.836 (0.655, 1.067)
MV pathology		P = 0.716		P = 0.306		P = 0.044		P = 0.413		P = 0.693
MS	56.9	0.81 (0.71, 0.923)	30.7	0.862 (0.726, 1.022)	16.8	0.653 (0.519, 0.82)	8.4	1.096 (0.769, 1.563)	12.9	0.794 (0.61, 1.033)
Non-MS	65.9	0.779 (0.689, 0.882)	39.9	0.766 (0.659, 0.89)	18.6	0.901 (0.712, 1.14)	7.6	0.821 (0.573, 1.178)	15.1	0.728 (0.568, 0.933)
MV pathology		P = 0.88		P = 0.89		0.491		P = 0.264		P = 0.598
MR	62	0.797 (0.718, 0.886)	35.9	0.799 (0.7, 0.911)	18.6	0.793 (0.658, 0.957)	8.5	1.03 (0.767, 1.382)	14.3	0.731 (0.593, 0.899)
Non-MR	60	0.772 (0.65, 0.918)	33.8	0.814 (0.654, 1.013)	15.3	0.688 (0.495, 0.957)	6.7	0.765 (0.467, 1.252)	13.2	0.796 (0.556, 1.14)
Surgery type		P = 0.383		P = 0.714		P = 0.015		P = 0.409		P = 0.98
Mitral valve replacement	63.3	0.764 (0.684, 0.853)	35.0	0.782 (0.679, 0.9)	18.0	0.664 (0.545, 0.81)	9.4	1.006 (0.746, 1.357)	14.6	0.747 (0.599, 0.931)
Mitral valvuloplasty	58.5	0.831 (0.712, 0.969)	35.9	0.829 (0.687, 1)	17.2	1.012 (0.756, 1.355)	5.9	0.83 (0.52, 1.326)	13.1	0.736 (0.538, 1.006)
CHA2DS2-VASc		P = 0.959		P = 0.527		P = 0.152		P = 0.348		P = 0.005

< 4	43.5	0.784 (0.688, 0.893)	22.2	0.766 (0.643, 0.912)	13.9	0.852 (0.675, 1.074)	6.8	1.043 (0.735, 1.48)	9.2	0.578 (0.446, 0.749)
≥ 4	96.5	0.787 (0.696, 0.89)	60.1	0.813 (0.702, 0.941)	25.0	0.683 (0.543, 0.858)	10.4	0.827 (0.576, 1.189)	23.2	0.972 (0.755, 1.251)

Abbreviations: IR, incidence rate; HR, hazard ratio

Incidence rate presented as per 1000 person-years.

Adjusted by age, sex, mitral stenosis, mitral regurgitation, infective endocarditis, coronary artery bypass grafting, aortic valve surgery, tricuspid valve surgery, mechanical heart valve prosthesis, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, TIA/TE, transient ischemic attack, or thromboembolism; PAD, peripheral artery disease, hemorrhage stroke, ischemic stroke, atrial fibrillation duration, CHA2-DS2-VASc score