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The impact of $CHADS_2$ score on late stroke after the Cox maze procedure

Mitchell Pet, MD, **Jason O. Robertson, MD, MS**, **Marci Bailey, RN, MSN**, **Tracey J. Guthrie, RN, BSN**, **Marc R. Moon, MD**, **Jennifer S. Lawton, MD**, **Andrew Rinne, MD**, **Ralph J. Damiano Jr, MD**, and **Hersh S. Maniar, MD**

Division of Cardiothoracic Surgery, Barnes-Jewish Hospital, Washington University School of Medicine, St Louis, Mo.

Abstract

Objective—The Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society jointly recommend indefinite warfarin anticoagulation in patients with $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, and stroke) score of at least 2 who have undergone ablation for atrial fibrillation. This study determined the impact of $CHADS_2$ score on risk of late stroke or transient ischemic attack after the performance of a surgical Cox maze procedure.

Methods—A retrospective review of 433 patients who underwent a Cox maze procedure at our institution was conducted. Three months after surgery, warfarin was discontinued regardless of $CHADS_2$ score if the patient showed no evidence of atrial fibrillation, was off antiarrhythmic medications, and had no other indication for anticoagulation. A follow-up questionnaire was used to determine whether any neurologic event had occurred since surgery.

Results—Follow-up was obtained for 90% of the study group (389/433) at a mean of 6.6 ± 5.0 years. Among these patients, 32% (125/389) had a $CHADS_2$ score of at least 2, of whom only 40% (51/125) remained on long-term warfarin after surgery. Six patients had late neurologic events (annualized risk of 0.2%). Neither $CHADS_2$ score nor warfarin anticoagulation was significantly associated with the occurrence of late neurologic events. Among the individual $CHADS_2$ criteria, both diabetes mellitus and previous stroke or transient ischemic attack were predictive of late neurologic events.

Conclusions—The risk of stroke or transient ischemic attack in patients after a surgical Cox maze procedure was low and not associated with $CHADS_2$ score or warfarin use. Given the known risks of warfarin, we recommend discontinuation of anticoagulation 3 months after the procedure if the patient has no evidence of atrial fibrillation, has discontinued antiarrhythmic medications, and is without any other indication for systemic anticoagulation.

Address for reprints: Hersh S. Maniar MD, Washington University School of Medicine, Barnes-Jewish Hospital, One Barnes-Jewish Plaza, Queeny Tower Suite 3108, St Louis, MO 63108 (maniarh@wudosis.wustl.edu).

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Atrial fibrillation (AF) is a common cardiac arrhythmia that currently affects more than 2 million adults in the United States and is projected to increase in prevalence approximately 2.5-fold by the year 2050.[1] The most feared consequence of AF is the increased risk of thromboembolic complications, particularly stroke.[2] The annualized risk of stroke for patients with AF has been quantified by Gage and colleagues[3] according to the $CHADS_2$ score, a multifaceted index that is based on the presence of congestive heart failure, hypertension, age of at least 75 years, diabetes mellitus, and stroke or transient ischemic attack (TIA) history. To mitigate the risk of thromboembolic disease, current Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), and European Cardiac Arrhythmia Society (ECAS) joint guidelines recommend lifetime warfarin anticoagulation to an international normalized ratio of 2.0 to 3.0 for all patients with AF and a $CHADS_2$ score of at least 2.[4]

Although controversial, the restoration of normal sinus rhythm remains a goal by many clinicians in the treatment of their patients with AF. Because of the limited efficacy of antiarrhythmic drugs, both catheter-based and surgical procedures have been introduced to treat AF.[5,6] The Cox maze procedure (CMP) is the criterion standard for the surgical treatment of AF, offering more than 90% freedom from AF[5] and an annualized risk of late stroke of less than 1% in several series.[6–8] The efficacy of the CMP for decreasing stroke risk has been attributed to both its success at restoring sinus rhythm and the amputation or exclusion of the left atrial appendage (LAA).[9]

The HRS, EHRA, and ECAS have cooperatively established guidelines regarding the use or discontinuation of warfarin in patients undergoing catheter-based procedures for AF.[4] Their consensus statement recommends that (1) decisions regarding the use of warfarin for more than 2 months after ablation should be based on the patient's risk factors for stroke and not on the presence or type of AF and (2) discontinuation of warfarin therapy after ablation generally not be advised at any point for patients who have a $CHADS_2$ score of at least 2.

Because of the important differences that exist between catheter-based and surgical techniques, it is unclear whether patients undergoing the CMP should be treated according to the same algorithm. The purpose of this study was to examine the impacts of the $CHADS_2$ score and warfarin therapy on the risk of stroke and TIA in patients who have undergone a CMP.

MATERIALS AND METHODS

Surgical Management

Between September 1987 and March 2008, a total of 450 patients underwent the CMP for AF at our institution as either a stand-alone procedure (n = 226) or concomitantly with other cardiac surgery (n = 224). The CMP has undergone several modifications since its inception. Patients underwent either the CMP I (n = 33), CMP II (n = 16), CMP III (n = 197), or the most recent iteration, the CMP IV (n = 204) (5). All versions of the CMP included amputation or exclusion of the LAA.

Postoperatively, all patients were anticoagulated with warfarin for 3 months unless contraindicated. After 3 months, warfarin therapy was discontinued for patients who were off all antiarrhythmic drugs and in normal sinus rhythm, as determined by electrocardiography (1987–2002) or 24-hour Holter monitoring (2002–2008). Patients who did not meet these criteria were instructed to continue warfarin anticoagulation. Warfarin was also continued for patients with mechanical valves, left atrial stasis, or thrombus as shown by the postoperative echocardiogram. Left atrial stasis was defined as either the absence of an A wave or the presence of "smoke" within the left atrium. Longitudinal follow-up with evaluation of rhythm was subsequently completed at 3 months, 6 months, 12 months, and annually thereafter. This algorithm was followed without regard to the patient's $CHADS_2$ score.

Long-Term Follow-up

A follow-up questionnaire and telephone script were composed and approved by the institutional review board, and all patients gave oral or written consent before follow-up. This questionnaire asked whether the patient had had a late stroke or TIA (defined as later than 90 days postoperatively) and whether the patient was on a warfarin regimen at the time of follow-up. Stroke and TIA were each defined as loss of neurologic function that was abrupt in onset and lasted longer or shorter than 24 hours, respectively.

Follow-up was performed for all cases in which at least 90 days had elapsed from the date of surgery (n = 433). Follow-up was completed by patient interview (n = 372) or by review of the most recent clinical record when the patient could not be contacted (n = 17). All neurologic events reported by patients were confirmed by acquiring medical records from the physicians who had treated the patient at the time of the event. Records included documentation of the patient's anticoagulation and rhythm status.

Assignment of $CHADS_2$ Scores

A computerized, prospective database was retrospectively queried to determine the preoperative $CHADS_2$ score for all patients.[3]

Statistical Analysis

Continuous variables are expressed as mean ± SD unless otherwise specified. Categorical data are expressed as counts and proportions. Comparisons were performed with paired, 2-tailed *t* tests for means of normally distributed continuous variables and with Wilcoxon rank sum tests for skewed data. Either χ^2 or Fisher exact tests were used to compare categoric data. Univariate binary logistic regression was used to determine predictors of late neurologic complications. All data analyses were done with SPSS statistical software (SPSS 11.0 for Windows; IBM Corporation, Armonk, NY). Annual risk in this study was calculated as events per patient in the subgroup divided by the mean follow-up within the subgroup.

RESULTS

Follow-up

Seventeen patients died within 90 days of the procedure and were excluded. Of the 433 patients remaining, follow-up was achieved for 90% (n = 389), with a mean duration of 6.6 ± 5.0 years. These patients were subsequently divided into high (≥2) and low (<2) $CHADS_2$ score groups. The follow-up was similarly complete for patients in both the low $CHADS_2$ score (91%; 264/291) and high $CHADS_2$ score (88%; 125/142) groups (P = .38).

Patient Demographic Characteristics

The patients in the high $CHADS_2$ score group were older and had a significantly higher prevalence of congestive heart failure, hypertension, diabetes mellitus, and stroke or TIA history than did those in the low $CHADS_2$ score group (Table 1). Furthermore, patients in the high $CHADS_2$ score group were more likely to have had persistent AF and larger left atria, despite a shorter preoperative duration of AF. Finally, other concomitant cardiac surgery was more commonly performed for patients in the high $CHADS_2$ score group.

Neurologic Events

There were 6 neurologic events (stroke, n = 4; TIA, n = 2) during the 21-year study period (2400 patient-years), for an overall neurologic event risk of 0.2% per year. The time to occurrence of a neurologic event ranged from 0.3 to 12.5 years, with a mean of 4.8 ± 4.6 years. No neurologic events were hemorrhagic in nature, as documented by computed tomographic scanning.

The clinical details of each case are shown in Table 2. Of the 6 neurologic events, half occurred in the low $CHADS_2$ score group. Half of the events occurred in patients who had undergone concomitant cardiac surgical procedures. Two thirds of the events (4/6) occurred while the patient was in normal sinus rhythm, and a third (2/6) occurred while therapeutically anticoagulated with warfarin. Of note, case 6 is a patient, who despite a therapeutic international normalized ratio, had an intracardiac thrombus associated with his prosthetic mitral valve and was subsequently diagnosed with a hypercoagulable disorder (antiphospholipid antibody syndrome).

Impact of Warfarin and $CHADS_2$ on Risk of Late Neurologic Events

Univariate analysis (Table 3) and univariate binary logistic regression (Table 4) showed no association between either a $CHADS_2$ score ≥2 or warfarin use and the development of a late stroke or TIA. Univariate analysis identified previous stroke or TIA as the only variable to be significantly more common (P = .04) in the group with late neurologic events. Logistic regression analysis demonstrated that diabetes mellitus (odds ratio, 6.6; P = .03) and previous stroke or TIA (odds ratio, 2.5; P = .03) were associated with increased risks of late neurological event. No association was found between the remaining $CHADS_2$ criteria (congestive heart failure, hypertension, age ≥75 years) and the development of late stroke or TIA. The annualized risks of a neurologic event, stratified by both $CHADS_2$ score and warfarin use, are illustrated in Table 5. The event rate was low (≤0.9%) in all groups.

DISCUSSION

Neurologic Outcomes After a Cox Maze Procedure

A notable strength of this study is its size and completeness of long-term follow-up. The follow-up in this study was more extensive than previously performed for any CMP population[8] and exceeds what has been documented for catheter-based and other percutaneous stroke-reduction procedures.[10–13]

The overall annual risk of late stroke or TIA for patients who underwent the CMP was 0.2%. The striking rarity of these events after a CMP is not isolated to our particular series and has been similarly reported by other investigators in separate CMP cohorts.[8] The low risk of postoperative neurologic events among patients who underwent a CMP is actually more similar to that of the general population[14] than to patients with untreated AF. For example, patients not receiving warfarin had an annual stroke risk less than 1%, regardless of $CHADS_2$ score group. This rate compares favorably with the corresponding stroke rates per 100 patient-years of 2.8 and 4.0 to 5.9 per 100 patient-years that would be predicted by Gage and colleagues[3] for these same patients without warfarin. This disparity is thought to be related both to the high rate of restoration of sinus rhythm after the CMP[15,16] and to the fact that amputation of the LAA is likely a critical mechanism of stroke prevention. Numerous studies have shown that the LAA is an important source of potential emboli.[9,17] Moreover, the latest iteration of the CMP (the CMP IV), as well as previous iterations of the CMP, have been shown to achieve drug-free freedom from AF of at least 84% of patients at 2 years postoperatively.[18]

Impact of Warfarin and $CHADS_2$ Score on Risk of Late Neurologic Events

There was no association between $CHADS_2$ score or warfarin status and the development of late neurologic events in this series. Although the composite $CHADS_2$ score itself did not have predictive value in this series, 2 of its individual components (diabetes mellitus and stroke or TIA history) were significantly associated with an increased risk of late neurologic events. This is perhaps not surprising because both diabetes and a history of stroke have been found to be highly predictive of stroke in several studies among a wide range of populations, with or without the presence of AF.[14,19,20]

Although warfarin anticoagulation was not associated with a decrease in the incidence of late neurological events in this series (odds ratio, 2.2; $P = .35$), it is possible that warfarin may have some undetected protective effect against the future development of neurologic events. The low incidence of events in this surgical series precludes the demonstration of any significant association during a mean follow-up period of 7 years. It is likely that the establishment of any incremental benefit of warfarin in CMP patients will require a larger cohort size and longer follow-up duration, approaching the scale of the warfarin trials in the nonsurgical literature.[21,22] However, it may be justified to forego warfarin use after successful CMP given the low postoperative embolic risk, and because any undetected benefit of warfarin would be outstripped by the 0.58% to 4.2% annual risk of major bleeding associated with long-term anticoagulation.[21–23]

Applicability of the HRS, EHRA, and ECAS Guidelines for Cox Maze

The HRS, EHRA, and ECAS have jointly developed guidelines for the management of anticoagulation in patients who have undergone catheter-based ablation for AF. These guidelines place a strong emphasis on the preoperative $CHADS_2$ score, to the extent that patients with a $CHADS_2$ score of at least 2 are not to be offered the discontinuation of warfarin therapy regardless of the outcome of the procedure. Although these guidelines may be appropriate for catheter-based procedures, the relevance of these guidelines to surgical patients undergoing a CMP is unknown and cannot be assumed.

In this study, when patients met our defined criteria, warfarin therapy was discontinued, regardless of preoperative $CHADS_2$ score. The incidence of late neurologic events in this series was extremely low (0.2% annually), and there was no association with either $CHADS_2$ score or warfarin use. On the basis of these findings, we discontinue warfarin 3 months after the CMP if there is no evidence of AF on prolonged monitoring, the patient is off all antiarrhythmic drugs, and there is no other indication for anticoagulation.

Study Limitations

Although the follow-up in this study was 90%, it was limited by our inability to contact some patients. It is also possible that some neurologic events were missed because of their omission from patient reporting. A few studies, however, have suggested that self-reporting is reliable, even among elderly individuals, and may actually overestimate the incidence of stroke.[24,25] Furthermore, mean follow-up was significantly shorter in the high $CHADS_2$ score group ($P < .001$). This reflects a trend in recent years toward offering surgical therapy to patients at higher risk with proportionately higher $CHADS_2$ scores. This inconsistency notwithstanding, our mean follow-up of 4.6 years in the high $CHADS_2$ score group should be sufficient given the high risk of predicted stroke in this group.

The inclusion of patients who underwent concomitant surgery at the time of their CMP increases the heterogeneity of our study group; however, this study group is a good approximation of patients undergoing a CMP in the current era. Most centers perform the CMP in the setting of concomitant cardiac surgery. Studying this mixed population is thus important in developing practice guidelines that are applicable to the current practice environment.

The neurologic event rate was very low in all groups. Although this low incidence during the course of 2400 patient-years speaks well for the overall efficacy of the CMP, the low number of events limits the inferences that can be made from statistical comparisons between groups and restricts our ability to perform multivariate logistic regression. As a consequence, the most important finding in this study is the low overall incidence of stroke or TIA in this population. The statistical significances of individual clinical predictors of stroke or TIA are instructive but are certainly not conclusive evidence.

CONCLUSIONS

It seems prudent to develop anticoagulation guidelines specifically for patients who have undergone surgical ablation of AF with exclusion of the LAA. The presented findings

warrant consideration with respect to the management of anticoagulation. Although further validation of these results will be required, our data suggest that anticoagulation may be discontinued in patients who have undergone a CMP, regardless of their preoperative $CHADS_2$ scores.

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Abbreviations and Acronyms

AF	atrial fibrillation
CMP	Cox maze procedure
ECAS	European Cardiac Arrhythmia Society
EHRA	European Heart Rhythm Association
HRS	Heart Rhythm Society
LAA	left atrial appendage
TIA	transient ischemic attack

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TABLE 1

Patient characteristics stratified by $CHADS_2$ score

	$CHADS_2$ <2 (n = 264)	**$CHADS_2$ ≥2 (n = 125)**	***P* value**
Preoperative variables			
Congestive heart failure	32 (12%)	80 (64%)	<.001
Hypertension	73 (28%)	94 (75%)	<.001
Age (y, mean ± SD)	54 ± 11	64 ± 11	<.001
Diabetes mellitus	5 (2%)	24 (19%)	<.001
Stroke or TIA history	0	57 (46%)	<.001
AF variables			
Paroxysmal AF	167 (64%)	57 (46%)	<.001
Median AF duration (y, IQR)	5.0 (2.5–10)	2.9 (0.8–7)	.04
Mean left atrial diameter* (cm, mean ± SD)	5.0 ± 1.3	5.4 ± 1.3	.03
Procedural variables			
Concomitant surgery	101 (38%)	91 (73%)	<.001
Follow-up (y)			
Mean ± SD	7.5 ± 5.1	4.6 ± 4.2	<.001
Median and IQR	7.1 (2.4–11.8)	3.0 (1.3–6.5)	<.001

Data are numbers and percentages of patients unless otherwise stated. *AF*, Atrial fibrillation; *IQR*, interquartile range; *TIA*, transient ischemic attack; *SD*, standard deviation.

*Variable available since February 2002 for 172 patients.

TABLE 2

Clinical data for neurologic events

Case	Event	Procedures	$CHADS_2$ score	Warfarin	Rhythm	Time to event (y)
1	TIA	CMP III, CABG	0	No	AF	12.5
2	TIA	CMP IV, CABG	0	No	NSR	1.3
3	Stroke	CMP III	1	No	NSR	0.8
4	Stroke	CMP II	4	No	NSR	1.8
5	Stroke	CMP III	3	Yes	NSR	11.8
6	Stroke	CMP IV, MVR	5	Yes	Atrial flutter	0.3

AF, Atrial fibrillation; *CABG*, coronary artery bypass grafting; *CMP*, Cox maze procedure; *MVR*, mitral valve replacement; *NSR*, normal sinus rhythm; *TIA*, transient ischemic attack.

TABLE 3

Univariate analysis for the occurrence of a late neurological event

Variables	Event free (n = 383)	Late TIA or stroke (n = 6)	*P* value
$CHADS_2$ variables			
Congestive heart failure	111 (29%)	1 (17%)	.68
Hypertension	163 (43%)	4 (67%)	.41
Age ≥75 y	28 (7%)	0	>.999
Diabetes mellitus	27 (7%)	2 (33%)	.07
Stroke or TIA history	54 (14%)	3 (50%)	.04
$CHADS_2$ score ≥2	122 (32%)	3 (50%)	.39
Warfarin use at follow-up	121 (32%)	3 (50%)	.39
Follow-up (y)			
Mean ± SD	6.6 ± 5.0	7.9 ± 6.4	.59
Median and interquartile range	5.5 (2.0–10.6)	9.1 (1.0–13.7)	.68

Data are numbers and percentages of patients unless otherwise stated. *TIA*, Transient ischemic attack; *SD*, standard deviation.

TABLE 4

Univariate binary logistic regression with a dependent outcome of late stroke or transient ischemic attack

Variables	Odds ratio	95% CI	*P* value
$CHADS_2$ variables			
Congestive heart failure	0.5	0.06–4.2	.52
Hypertension	2.7	0.49–14.9	.26
Age*	1.0	0.96–1.1	.39
Diabetes	6.6	1.2–37.6	.03
Stroke or TIA history	2.5	1.1–5.6	.03
CHADS ≥2	2.1	0.43–10.8	.36
Warfarin	2.2	0.43–10.9	.35

CI, Confidence interval; *TIA*, transient ischemic attack.

*In this analysis, age was treated as a continuous variable for the calculation of an odds ratio because no patients aged 75 years or older had a late stroke or TIA.

TABLE 5

Risk of neurologic event by warfarin status and $CHADS_2$ score

	$CHADS_2$ <2	**$CHADS_2$ ≥2**	***P* value***
Off warfarin			>.999
Patients	191	74	
Events	3	1	
Follow-up (y, mean ± SD)	7.6 ± 5.1	4.9 ± 4.4	
Annual risk	0.2%	0.3%	
On warfarin			.17
Patients	73	51	
Events	0	2	
Follow-up	7.4 ± 5.3	4.2 ± 3.7	
Annual risk	0%	0.9%	
P value†	.56	.57	

SD, Standard deviation.

*Comparison of stroke off warfarin between the low and high $CHADS_2$ score groups.

†Comparison of stroke in all patients between on and off warfarin statuses.