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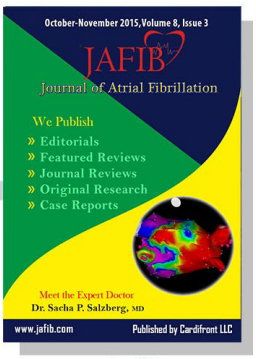

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Variations in Anticoagulation Practices Following the Maze Procedure

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Abstract

The current real-world anticoagulation practices following left atrial appendectomy in the context of the Maze procedure are unknown. This is a cohort study of all patients who underwent the Maze procedure with amputation of the left atrial appendage from June 2005 to November 2012. Data was prospectively collected at regular intervals with an interview and Holter monitoring. All patients received anticoagulation for 3 months. Those then kept on anticoagulation and those for whom anticoagulation was stopped were compared in terms of death, bleeding and incidence of stroke. In total, there were 113 patients, of whom 66 were treated with anticoagulation (Group A) and 47 were not (Group B). There were no significant baseline differences between the two groups, including the presence of atrial fibrillation (A:19.7%, B:10.6%, p=0.30), CHADS2 score (A:1.41±1.05, B:1.15±1.08, p=0.19), and left atrial size (A:48.3±7.1mm, B:47.6±7.8 mm, p=0.57). There were 275 patient-years of follow-up, with an average of 2.43 years per patient. Only two patients experienced strokes, both in Group A (p=0.27). Of the 5 bleeding events, 4 occurred in the first 3 months while on anticoagulation and the remaining event occurred in Group A at 3 years post-operatively (p=0.10). No standardized approach to anticoagulation after the Maze procedure is apparent in real-world practice in an urban Canadian setting. Patients who undergo the Maze procedure with amputation of the left atrial appendage are at a low risk of stroke, but the optimal anticoagulation strategy requires further investigation.

Introduction

Embolism secondary to atrial fibrillation, which accounts for 25% of all ischemic strokes, has a 60% rate of death and severe disability.[1, 2] Unfortunately, due to its risks and inconveniences, anticoagulation therapy is underused in real-world practice.[3] The surgical treatment of atrial fibrillation is the Cox-Maze procedure which produces transmural scars to interfere with abnormal electrical circuits. It has an 80% long-term success rate in maintaining patients in sinus rhythm and has been proposed as a method of avoiding anticoagulation.[4] A component of this procedure is exclusion of the left atrial appendage (LAA), the main culprit in cardiogenic emboli. Thus many believe that the procedure may obviate the need for long-term anticoagulation. Unfortunately, no randomized controlled trials exist to confirm the safety of stopping anticoagulation after the Maze procedure. Also, there are some conflicting reports regarding the efficacy of different techniques of surgical LAA exclusion on stroke risk, whether alone or as a component of the Maze procedure.[5, 6] Therefore, the best anticoagulation practices following such procedures are unclear and the real-world prescribing patterns are unknown.

In our setting, it has usually been the referring cardiologist who makes long-term anticoagulation decisions with the patient. By reviewing our centre's experience, our primary aim is to characterize real-world post-operative anticoagulation practices. Our secondary goal is to review stroke rates among patients with and without anticoagulation.

Material And Methods

The study was approved by the McGill University Health Centre's Institutional Review Board and need for patient consent was waived. This was an observational cohort study of a single centre, which is a major referral centre for mitral valve disease in an urban Canadian setting (Figure 1). A total of 123 patients who did not have an obligate reason to be on long-term oral anticoagulants underwent the Maze procedure from June 2005 to November 2012. After excluding 8 early post-operative deaths and 2 patients lost to follow-up, the remaining 113 patients were divided into two cohorts: 1) Group

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None.

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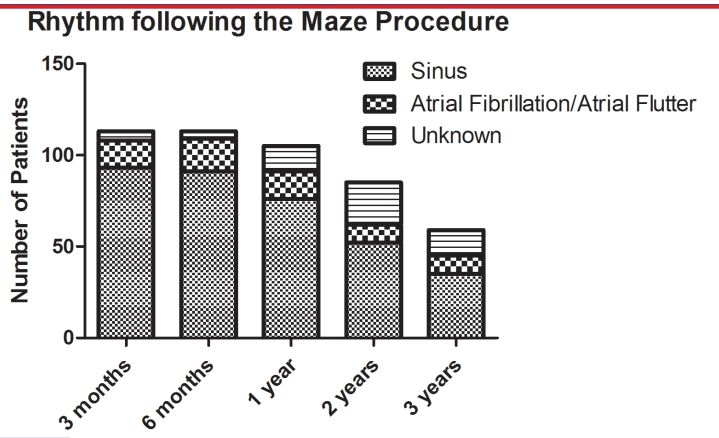

Figure:1 **Patient demographics.**

A - those who were on anticoagulants at the 6 month visit (65 patients), and 2) Group B - those who were off anticoagulants at the 6 month visit (48 patients). The 6 month time point was chosen as it is our practice to recommend anticoagulation for all patients following the Maze procedure for the first 3 months post-op. After 3 months, the decision for anticoagulation is based on the treating physician's preference (usually the referring cardiologist). The primary endpoints were mortality, stroke, bleeding events and the composite endpoint of death, stroke and bleeding, termed "major adverse events".

Surgical Technique

The Maze procedure was always performed with concomitant cardiac surgery, and in 111 of the 123 patients (90.2%), this included mitral valve surgery. The remaining patients underwent the following concomitant surgeries: 1 hemiarch repair, 1 tricuspid valve repair, 5 aortic valve replacements (AVR), 2 coronary artery bypass graftings (CABG), 2 AVR/CABG/replacement of the ascending aortas, and 1 AVR/replacement of the ascending aorta. Of note, the left atrial appendectomy was performed on cardiopulmonary bypass by complete amputation and oversewing in two layers. Obliteration of the stump was confirmed by direct visualization from within the left atrium and transesophageal echocardiography. The energy source used was radiofrequency in 89 patients and cryoablation in 8 patients. Laser ablation was used in 26 patients from the earliest part of this series. Sixty-eight patients (55.3%) underwent the full bi-atrial Maze procedure (Cox-Maze IV), while the remaining patients underwent the left atrial Maze.

Database

Data was prospectively collected by a research nurse at 3 months, 6 months, 1 year, 2 years and 3 years after the surgery. At each visit, an interview was conducted including a review of the patient's medications, and a 12-lead electrocardiogram as well as a 24-hour Holter monitor was performed. If Holter monitoring was not possible, the patient's rhythm status was extracted from the electrocardiogram, echocardiography or pacemaker interrogations. Strokes were defined as documented complications during hospitalization, or as self-reported events at time of follow-up. Major bleeding events were defined as events requiring hospitalization, blood transfusions or intracranial bleeds. The charts of all patients were reviewed with a focus on past medical history and left atrial parameters on echocardiography.

Data analysis

Incidence of stroke or bleeding events were represented as number of events per 100 patient-years. When comparing baseline patient characteristics, the Fischer's exact test was used for dichotomous variables and the Wilcoxon rank sum tests used for continuous variables. The primary outcomes of freedom from death, stroke, bleeding and major adverse events were compared using the Log-rank test. All statistics were performed with GraphPad Prism 5.01 (GraphPad Software, Inc, CA, USA).

Results

Our results with the Maze procedure are comparable to reported literature with 72 to 86 % of patients converted to sinus rhythm at 1 year post-op (Figure 2). The procedure appears to be safe and does not add to the operative risk. Of the 123 patients, 8 patients suffered early post-operative deaths and none were directly related to the addition of the Maze procedure. The causes of death were as follows: pulmonary embolism, ischemic bowel, uremia from dialysis refusal, 3 respiratory failures, and 2 heart failures. The overall mortality rate for this cohort was 6.5%, which is lower than the mortality risk predicted by the average Parsonet score of 9.9%.

At the 6 month time point, 66 patients were continued on anticoagulation (Group A) while 47 patients were taken off anticoagulation (Group B). The average follow-up was 2.74 years per patient in Group A and 2.03 years per patient in Group B. Overall, this series represents 275 patient-years of follow-up, with an average of 2.43 years per patient.

Many patient characteristics were compared between Group A and Group B, in an attempt to elucidate the real-world decision-making process with respect to anticoagulation following the Maze procedure (Table 1). Presence of atrial fibrillation at 6 months, the CHADS2 and the CHA2DS2-Vasc scores (including their individual components), and the HASBLED scores, were compared. Additionally, left atrial size and pre-operative duration of atrial fibrillation were examined. There were no statistically significant differences between the two groups in any of the patient characteristics.

When comparing outcomes, risk of death, stroke, major bleeding or major adverse events were not statistically different regardless of whether patients were treated with anticoagulation (Table 2). Interestingly, both stroke events occurred in Group A. One stroke was fatal, occurring 2 years post-operatively. The other stroke was noted immediately post-operatively after awakening from anesthesia. Four

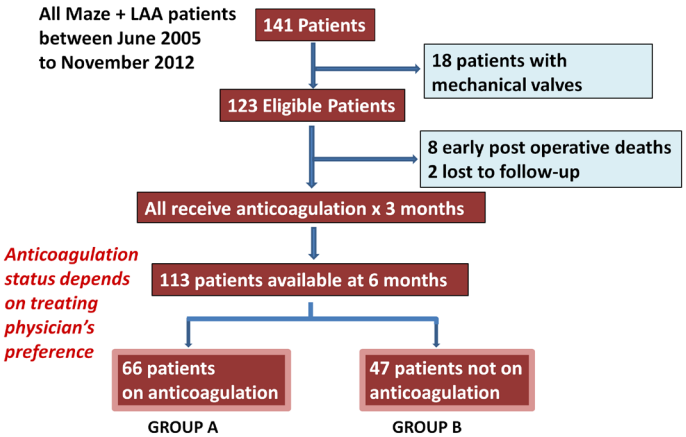

Figure:2 **Majority of rhythm established by 24-hour Holter monitoring.**

Table 1: Comparison of patient characteristics for patients on and off of anticoagulation.

	On Anticoagulation N=66 (%)	Off Anticoagulation N=47 (%)		P-value	
Presence of atrial fibrillation	13 (19.7)	5 (10.6)		0.30	
CHADS2 score Score of 3 or greater	1.41 ± 1.05 5 (7.6)	1.15 ± 1.08 (10.6)	5	0.19	0.74
CHA2DS2-Vasc score	2.53 ± 1.53	2.82 ± 1.47		0.40	
Congestive HF (EF<35%)	5 (7.6)	4 (8.5)		1.0	
Hypertension	41 (62.1)	28 (59.6)		0.85	
Age > 65 > 75	47 (71.2) 15 (24.6)	32 (68.1) (28.6)	10	0.83	0.83
Female sex	25 (37.9)	20 (42.6)		0.70	
Diabetes	15 (22.7)	5 (10.6)		0.13	
Previous stroke	8 (12.1)	2 (4.3)		0.19	
Vascular disease	21 (31.8)	13 (27.7)		0.68	
HASBLED score Score of 3 or greater	2.11 ± 1.04 21 (31.8)	2.21 ± 1.21 (38.3)	18	0.68	0.55
Left atrial size (mm) Left atrium ≥ 5 cm	48.3 ± 7.1 19 (28.8)	47.6 ± 7.8 (38.3)	18	0.57	0.31
Duration of atrial fibrillation (months)	31± 5	64 ± 16		0.47	

of the 5 bleeding events occurred in the first 3 months during which all patients were on oral anticoagulation.

While the majority of patients taking oral anticoagulants were prescribed warfarin, a handful of patients were prescribed dabigatran. One patient was switched from warfarin to dabigatran after 3 years, and 1 patient was taking dabigatran from the beginning and remains on the novel oral anticoagulant. Two patients who were not initially anticoagulated at 6 months were initiated on dabigatran at 2 years of follow up. Similar proportion of patients were taking aspirin (p=0.13) whether they were on oral anticoagulants (39.4%) or not (55.3%).

Patients' anticoagulation status was tracked at each visit, and therefore our database captured the frequency with which patients switched anticoagulation strategies. Ten of the 47 patients not on anticoagulation at the 6 month visit (21%), were placed back on anticoagulation according to their most recent follow up visit. On the other hand, 20 of the 66 patients on anticoagulation at the 6 month visit (30%), were taken off anticoagulation according to their most recent follow up visit. Our analysis was conducted using an "intent-to-treat" strategy based on the anticoagulation strategy chosen at the 6 month time point.

Discussion

Patients undergoing the Maze procedure with LAA exclusion, and without other indications for anticoagulation, experience variable anticoagulation treatment. Interestingly, although surgeons may believe that long-term anticoagulation is unnecessary following the Maze procedure, we found that almost 60% of our patients were actually kept on long-term anticoagulation. Our study of over 100 patients, with a cumulative follow-up of 275 patient-years, found no patient factor that can identify post-Maze patients who are prescribed long-term anticoagulation. Moreover, a significant proportion of patients in both groups crossed over during follow-up. These results suggest that in real-world practice, in an urban Canadian setting, prescribing patterns are somewhat arbitrary. With only 2 strokes in 113 patients, both occurring in anticoagulated patients, our study supports the notion that optimal LAA exclusion technique and the Maze procedure

Table 2: Primary outcomes for patients on and off of anticoagulation

	On Anticoagulation N=66 (per 100 patient-years)	Off Anticoagulation N=47 (per 100 patient-years)	P-value
Death	4 (2.2)	1 (1.0)	0.51
Stroke	2 (1.1)	0	0.27
Major bleeding	2 (1.1)	3 (3.1)	0.36
Major Adverse Events	8 (4.5)	4 (4.1)	0.79

can achieve low embolic rates regardless of anticoagulation strategy.

The arbitrary anticoagulation practices reflect a paucity of evidence and guidance. Current Canadian guidelines suggest using the CHADS2 schematic to aid anticoagulation decision-making in this population of post-Maze patients.[7] This is despite the prominence of valvular atrial fibrillation in Maze patients (90% of our cohort), to which the CHADS2 is not typically applied. Moreover, a previous study found no association between the CHADS2 score and embolic risk in this population.[8]

Confusion over the effectiveness of the Maze procedure leaves many clinicians wary of discontinuing oral anticoagulation in Maze patients who no longer have their LAA, limiting the usefulness of undergoing the procedure. In fact, the original Cox series did not advocate any long-term anticoagulation and demonstrated a remarkable 0.8% stroke rate in long-term follow-up.[9] A recent study from a major American referral centre also reinforced this concept and demonstrated low stroke rates (5.1 cases per 1,000 person-years) with a higher anticoagulation discontinuation rate than we have reported.[10] In that study the majority of those continuing on anticoagulation had other indications such as deep vein thrombosis. However, hesitation remains amongst cardiologists due to the lack of widespread standardized follow-up protocols with respect to rhythm analysis and anticoagulation, and contradictory stroke protection data regarding surgical LAA exclusion. When deciding on anticoagulation, it is important to acknowledge that oral anticoagulation does not eliminate stroke risk, and carries a significant side-effect profile.

A major strength of our study is the consistent prospective protocolized follow-up provided by a dedicated research nurse who is able to enforce Holter studies and medication reviews. Our consistency extends to operative technique with respect to the left atrial appendectomy: the amputation and oversewing technique. Although it is logical that excluding the LAA should provide powerful stroke protection (as seen in the PROTECT-AF trial), this has been difficult to prove in the surgical literature.[11] This is likely due to data contamination by combining results from a variety of surgical techniques. It is now known that high residual flow rates are associated with certain techniques, such as loop and snare or purse-stringing.[12, 13] With evidence that incomplete closure may increase thromboembolic risk, this can be quite dangerous.[14, 15] By consistently using the amputation and oversewing technique, we eliminate the risk of residual flow.

Our study is limited by sample size. This is a prevailing difficulty in this area of surgical literature, where even the largest centres can take many years to amass one to two hundred patients.[16, 17] The variability in follow-up and operative protocols as mentioned above hamper the ability to combine multiple centres.

Our research identifies a gap between guidelines and real-world practice, highlighting the need for rigorous study in anticoagulation practices following the Maze procedure. Standardization of operative and post-operative practices would move the field forward by

facilitating multicentre studies, and providing the groundwork for a randomized controlled trial.

Conclusion

Examination of anticoagulation practices following the Maze procedure found that majority of patients were kept on long-term anticoagulation. We found no consistent prescribing patterns by referring cardiologists, thus identifying a major gap between guidelines and real-world practice. Although we demonstrated a very low stroke rate, the optimal anticoagulation practice after the Maze procedure requires further investigation.

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