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The long-term efficacy of concomitant maze IV surgery in patients with atrial fibrillation

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia, and associated with increased risk of morbidity and mortality. AF surgery is widely used for rhythm control of AF, but previous studies have shown varying results. This study sought to investigate the long-term efficacy of concomitant maze IV (CMIV) surgery in an unselected AF population and identify predictors of late AF recurrence.

Methods: In total 144 consecutive patients, who underwent CMIV between January 2006 and December 2010 were enrolled. By data from electronic medical records, registers, and rhythm prints, late AF recurrences and heart rhythm at latest follow-up were retrospectively registered. All patients still alive were invited to an ambulant follow-up to update rhythm status.

Results: During a median (IQR) follow-up of 7.39 (2.67) years, 114 (79.2%) patients had recurrence. The cumulative incidence of sinus rhythm (SR) without antiarrhythmic drugs (AADs) was 52.3% after 1 year. Long-term results after 2, 5 and 7 years were 47.9%, 32.6% and 25.1%, respectively. At latest follow-up 34.7% were in SR off AADs. No difference in 10-year event-free survival stratified by recurrence were found ($p = 0.678$). Contrary, time to death (5.40 vs. 3.43 years, $p = 0.004$) revealed death as competing risk event. The Fine-Gray model identified preoperative sustained AF (SAF) (SHR 3.54, 95%CI [2.35;5.32], $p < 0.001$), AF duration (1.08, [1.05;1.11], $p < 0.001$), and postoperative atrial tachyarrhythmia (ATA) (2.29, [1.21;4.35], $p = 0.011$) as predictors.

Conclusion: CMIV in the present cohort provided limited long-term success in obtaining SR. SAF, longer AF duration, and postoperative ATA were associated with late AF recurrence.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, more frequently affecting men and elderly, and associated with increased morbidity and mortality,[1,2], especially due to heart failure or stroke, [1,3]. AF management comprises oral anticoagulation for stroke prevention and rate and/or rhythm control to improve symptoms and preserve left ventricular function. Rhythm control modalities include antiarrhythmic drugs (AADs), cardioversion, catheter ablation, and AF surgery,[1].

Present evidence shows that AADs and ablation procedures, mostly catheter-based pulmonary vein (PV) isolation, reduce rather than eliminate AF,[1,4,5]. Cox-maze surgery aims to create an electrical labyrinth of functional atrial myocardium via biatrial incisions obstructing potential macro re-entry circuits to prevent fibrillatory conduction. The procedure also includes left atrial (LA) appendage exclusion for prevention of thromboembolism,[6]. The lesion sets of maze IV are performed using radiofrequency energy and/or freezing, diminishing complications and technical complexity without reducing efficacy compared to maze III,[7]. Therefore, the use of AF surgery has expanded during recent years,[1]. Several studies have demonstrated that maze III/IV lesions are successful in obtaining sinus rhythm (SR),[8–13] regardless of whether they were performed as a stand-alone or concomitant procedure,[14–16]. However, studies investigating the efficacy of maze IV differ in terms of study design and settings leading to heterogeneous short- and long-term rates of freedom from AF recurrence between 47 and 94%,[8,12,17–20] and 56–91%,[9,18,21–24], respectively. Consequently, predictors of recurrence also are inconsistent.

Therefore, the aim of this retrospective cohort study was to investigate the long-term efficacy of concomitant maze IV (CMIV) surgery in an unselected population of AF patients during a long follow-up and identify possible predictors of late AF recurrence.

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2. Methods

2.1. Study design

We retrospectively identified consecutive patients, who underwent maze IV surgery between January 2006 and December 2010 at a tertiary Danish university center, from the Western Denmark Heart Registry. Patients were included, if they had AF confirmed by preoperative electrocardiogram (ECG) or long-term monitoring,[1], AF as ablation indication, and survived the first 3 months after CMIV. Patients with catheter-based, surgical stand-alone, or incomplete maze IV procedures were excluded. Incompleteness was defined as lacking or insufficient lesions confer surgical standards,[25].

2.2. Data acquisition

Baseline and follow-up data were obtained from health care registries, electronic medical records, and during ambulant follow-up visits in patients still alive, when the study was performed. Data on prior hospital admissions, treatments and diagnoses were retrieved from the Danish National Patient Registry, and perioperative data from the Western Denmark Heart Registry. Date and cause of death during follow-up were recorded from the Danish National Patient and Cause-of-Death Registry. The Danish National Prescription Database provided data on medications. Echocardiographic parameters were retrospectively measured on preoperative transthoracic echocardiograms (TTEs) by a cardiologist, blinded for other study data. All data were independently adjudicated by two experienced cardiologists.

2.3. Surgical procedure and postoperative management

CMIV was performed after decision by a heart team,[1]. Main procedures included mitral and aortic valve surgery (i.e. repair, replacement) and/or coronary artery bypass grafting (CABG). All patients underwent median sternotomy, following standard cardiopulmonary bypass with bicaval cannulation and cardioplegic arrest. A biatrial maze IV procedure was accomplished with a left and right atriotomy enabling ablation close to the mitral and tricuspid valve. Remaining lesions were performed using a bipolar radiofrequency clamp (AtriCure Inc., USA) and cryoprobe (Frigitronics, CCS200, USA). The right atrial lesion set consisted of a cavo-tricuspid isthmus line connected to the superior vena cava. After cardioplegic arrest, left atrial lesions were performed; a circumferential PV isolation, left- and right-sided PVs separately with a superior and inferior interconnecting line (i.e. box lesion set), a lesion from the left upper PV to the rim of left atrial appendage and from the right lower PV to the mitral annulus. Enclosing lines around the coronary sinus and the tricuspid and mitral annuli were made by cryoablation. Electrical isolation of the box lesion set was documented by assessing exit block via bipolar pacing in all patients. LA appendage was ligated by stapling and excised.

Early postoperative care was similar to other open-heart surgery including continuous rhythm monitoring. Patients received prophylactic AADs. Complications within 30 postoperative days were heart failure (admission to heart failure clinic and initiation/intensification of anticongestive treatment), stroke, major bleeding (Bleeding Academic Research Consortium type 3–5), re-operation, myocardial infarction, renal failure requiring dialysis, and mortality. Furthermore, implantation of pacemaker or implantable cardioverter defibrillator (ICD), was documented.

Routine clinical follow-up visits occurred at 1, 3, 6 and 12 months postoperatively. A 12 lead ECG, TTE, and 48-h Holter monitoring were routinely performed at 1 and 3 months. Between hospital visits, patients were followed with routine ECGs by the referring physician. In case of suspected atrial tachyarrhythmia (ATA), additional Holter monitoring was performed. Cardioversion was recommended during a postoperative 3-months blanking period.

2.4. Long-term follow-up

Follow-up was defined as the time from the end of the blanking period to August 1st, 2016 or death, whichever came first. Long-term rhythm evaluation beyond routine follow-ups was done by available ECGs, Holter monitorings, and/or device interrogations. A12 lead ECG (MAC 5500, GE Healthcare, UK) and 48-h Holter monitoring (Lifecard CF, Spacelabs Healthcare, USA) were performed to update rhythm data in all patients attending the ambulant follow-up visit. Holter recordings were analysed by trained staff using dedicated software (Pathfinder SL, Spacelabs Healthcare, USA). All ECGs and Holter analyses were reviewed by an experienced electrophysiologist blinded for other study data.

2.5. Definition of arrhythmias and events

Preoperative AF duration was defined from the first date of AF documentation to CMIV and AF subtype comprised paroxysmal (PAF) and sustained (i.e. persistent, long-standing persistent, permanent) AF (SAF),[1]. Definitions of remaining baseline characteristics are presented in Online Table 1. Postoperative ATA during the blanking period was defined as monitoring-documented AF, atrial flutter, or atrial tachycardia lasting ≥30 s. The primary efficacy endpoint was freedom from late AF recurrence without AADs. Recurrence of AF was defined as the first monitoring-documented episode of AF, atrial flutter, or atrial tachycardia lasting ≥30 s after the blanking period,[1]. Secondary efficacy endpoints were freedom from recurrence on AADs, need of additional arrhythmia interventions (i.e. catheter ablation, pacemaker/ICD implantation), stroke, all-cause and cardiovascular mortality.

2.6. Ethics

The study was performed in accordance with the Declaration of Helsinki II and approved by the Danish Data Protection Agency (15/49691) and Regional Scientific Ethical Committees for Southern Denmark (S-20150209). All patients alive gave written informed consent before ambulant follow-up.

2.7. Statistical analysis

Descriptive statistics of baseline characteristics were stratified by late recurrence. Taking the possibility of differing individual follow-up times into account, pre-, peri-, and postoperative parameters were evaluated in a univariate Fine-Gray proportional subdistribution hazard analysis allowing for death during follow-up as a competing risk event to identify predictors of recurrence. Subsequently, the effect estimates (i.e. sub-hazard ratios (SHRs)) of the given covariates were adjusted for age and gender,[1]. Hereafter, statistically significant and insignificant covariates deemed clinically relevant were entered into a multivariate Fine-Gray regression by forced entry. Model comparisons were mediated by Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) incorporating the trade-off between fit and complexity. Because of missing echocardiographic observations (i.e. LA diameter (LAd), LA volume indexed for body surface area (LAvI)) to some degree, evaluation of model prediction was further based on AIC/BIC relative to Wald's χ^2 test for raw data and multiple imputed. The model with the lowest AIC/BIC relative to highest Wald's index was chosen. Precondition of independence between the event of interest and the competing risk event was ensured by the consecutive study inclusion mediating a homogeneous cardiac risk group, and model assumption of proportional sub-hazards was validated by checking insignificance of time-varying covariates.

For graphically representation, Kaplan-Meier estimates were used to depict the event-free survival, and rates of death and stroke were compared, separately, using Log-rank test. Implementing death as competing risk event, cumulative incidence functions (CIFs) of late AF

recurrence were generated for the total cohort and stratified by identified categorical predictors. Pepe and Mori test was used to compare CIFs across subgroups.

A two-tailed p-value <0.05 was considered statistically significant. Analyses were performed using STATA 14 (StataCorp LP, College Station, USA).

3. Results

3.1. Baseline characteristics

A total of 171 patients were eligible, of which 144 patients (mean age 69.2 ± 8.79 years, 71.5% males) were included (Online Fig. 1).

Table 1
Baseline characteristics.

Preoperative parameter	Total, n = 144	Late AF recurrence, n = 114 (79.2)	Freedom from late AF recurrence, n = 30 (20.8)	*P* Value
Age, y	69.2 ± 8.79	70.0 ± 8.14	66.3 ± 10.6	0.038[a]
Male gender, n (%)	103 (71.5)	78 (68.4)	25 (83.3)	0.107
AF-disposing comorbidity, n (%)				
Heart failure	31 (21.5)	26 (22.8)	5 (16.7)	0.467
Cardiac valve disease	110 (76.4)	90 (78.9)	20 (66.7)	0.159
Mitral valve insuffi-ciency/stenosis	61 (42.4)	46 (40.4)	15 (50.0)	0.341
Aortic valve insufficiency/stenosis	56 (38.9)	48 (42.1)	8 (26.7)	0.123
Ischemic heart disease	72 (50.0)	53 (46.5)	19 (63.3)	0.101
Congenital heart disease	10 (6.94)	9 (7.89)	1 (3.33)	0.688
Hypertension	90 (62.5)	73 (64.0)	17 (56.7)	0.458
Obesity	38 (26.4)	33 (28.9)	5 (16.7)	0.174
Chronic kidney disease	25 (17.4)	19 (16.7)	6 (20.0)	0.668
Chronic obstructive pulmonary disease	17 (11.8)	14 (12.3)	3 (10.0)	1.00
Hyperthyroidism	4 (2.78)	4 (3.51)	0 (0)	0.580
Sleep apnea	3 (2.08)	3 (2.63)	0 (0)	1.00
Cardiovascular risk factors, n (%)				
Diabetes mellitus type 2	21 (14.6)	18 (15.8)	3 (10.0)	0.567
Hypercholesterolemia	86 (59.7)	68 (59.6)	18 (60.0)	0.972
Smoking status				0.775
Ex-smoker	77 (53.5)	61 (53.5)	16 (53.3)	
Smoker	19 (13.2)	14 (12.3)	5 (16.7)	
Thromboembolic event, n (%)	12 (8.33)	9 (7.89)	3 (10.0)	0.714
Catheter ablation, n (%)	6 (4.17)	5 (4.39)	1 (3.33)	1.00
Pacemaker/ICD implantation, n (%)	5 (3.47)	4 (3.51)	1 (3.33)	1.00
CHA_2DS_2VASc, n (%)				0.048[a]
Score 1	12 (8.33)	9 (7.89)	3 (10.0)	
Score ≥ 2	119 (82.6)	98 (86.0)	21 (70.0)	
Logistic EuroSCORE, %	5.35 (6.27)	5.52 (6.09)	4.45 (7.88)	0.560
Intermediate risk (3–5), n (%)	46 (31.9)	37 (32.5)	9 (30.0)	0.578
High risk (≥ 6), n (%)	65 (45.1)	53 (46.5)	12 (40.0)	
Echocardiographic parameters				
LAd, cm	4.91 ± 0.74	4.91 ± 0.85	4.89 ± 0.72	0.894
LAvI, mL/m^2	52.1 (26.3)	53.1 (24.5)	41.0 (38.2)	0.218
LVEF, %	53.3 ± 8.60	53.3 ± 8.06	53.4 ± 10.6	0.985
AF characteristics				
AF subtype, n (%)				<0.001[a]
PAF	73 (50.7)	46 (40.4)	27 (90.0)	
SAF	71 (49.3)	68 (59.6)	3 (10.0)	
AF duration, y	0.60 (4.30)	0.82 (4.92)	0.19 (1.11)	0.002[a]

Perioperative Parameter	Total, n = 144	Late AF recurrence, n = 114 (79.2)	Freedom from late AF recurrence, n = 30 (20.8)	*P* Value
Cardiac surgery, n (%)	42 (29.2)	35 (30.7)	7 (23.3)	0.430
Maze IV + Mitral valve procedure	40 (27.8)	33 (28.9)	7 (23.3)	0.541
Maze IV + Aortic valve procedure	34 (23.6)	23 (20.2)	11 (36.7)	0.058
Maze IV + CABG	26 (18.1)	21 (18.4)	5 (16.7)	0.824
Maze IV + CABG + Valve procedure	2 (1.39)	2 (1.75)	0 (0)	1.00
Maze IV + Congenital correction	41 (28.5)	32 (28.1)	9 (30.0)	0.835

Postoperative parameter	Total, n = 144	Late AF recurrence, n = 114 (79.2)	Freedom from late AF recurrence, n = 30 (20.8)	*P* Value
30-day surgery complication, n (%)	49 (34.0)	39 (34.2)	10 (33.3)	0.928
Major bleeding	16 (11.1)	12 (10.5)	4 (13.3)	0.744
Re-operation	4 (2.78)	3 (2.63)	1 (3.33)	1.00
Stroke	3 (2.08)	2 (1.75)	1 (3.33)	0.507
Myocardial infarction	5 (3.47)	5 (4.39)	0 (0)	0.584
Renal failure requiring dialysis	13 (9.03)	10 (8.77)	3 (10.0)	0.734
Heart failure	9 (6.25)	8 (7.02)	1 (3.33)	0.685
Pacemaker/ICD implantation	9 (6.25)	8 (7.02)	1 (3.33)	1.00
Postoperative ATA, n (%)	121 (84.0)	102 (89.5)	19(63.3)	0.001[a]

Pre-, peri- and postoperative parameters for the total study cohort. A normally distributed continuous variable is represented as mean ± SD, a non-normally distributed as median (IQR), and a categorical variable as number (percentage). Besides main cardiac surgeries, other procedures could be performed, hereunder tricuspidal valve repair, septal myectomy, aorta ascendens repair and excision of pathological tissue in the left atrium.

AF, atrial fibrillation; ICD, implantable cardioverter defibrillator; LAd, left atrial diameter; LAvI, left atrial volume index; LVEF, left ventricular ejection fraction; PAF, paroxysmal AF; SAF, sustained AF; CABG, coronary artery bypass grafting; ATA, atrial tachyarrhythmia.

[a] Comparisons by appropriate statistical tests with a $p < 0.05$ considered statistically significant.

Baseline characteristics are presented in Table 1. The proportion of patients with PAF and SAF were almost equal with a median duration of 7 months and only a minority had previous thromboembolic events, although 82.6% were at high risk ($CHA2DS_2$ VASc score ≥ 2). Most patients had valvular and/or ischemic heart disease equaling main surgical indications. Besides extensive cardiac morbidity, preoperative mean left ventricular ejection fraction was only mildly depressed (53.3 ± 8.60%). Almost one third had procedural complications consistent with the fact that nearly half of the cohort were high risk patients (logistic EuroSCORE ≥6). Main complications were major bleeding and renal failure, and 84.0% had a monitoring-documented ATA during the blanking period.

3.2. Long-term follow-up

During a median follow-up of 7.39 (2.67) years, 48 patients (33.3%) died. Cause of death was presumed cardiovascular in 56.3%. Ischemic stroke was reported in 20 patients (13.9%), of which 30.0% were fatal. The cumulative 10-year event-free survival was irrespective of recurrence for stroke ($p = 0.525$) and death ($p = 0.678$) (Online Fig. 2), but median time to death in patients with and without recurrence differed significantly (5.41 vs. 2.23 years, $p = 0.004$) underlining death being a competing risk event.

At 3-month postoperatively, 78.5%/71.5% of the patients were in SR on/off AADs. This prevalence was 87.5%/77.6% at 6 months and 83.2%/79.0% at 1 year. During long-term follow-up, 114 patients (79.2%) had recurrence, of which 61.4% ($n = 70$) were AF and the remaining atrial flutter ($n = 41$) and atrial tachycardia ($n = 3$). Fig. 1A shows the cumulative incidence of late AF recurrence for the total cohort. Cumulative freedom from recurrence on/off AADs was 64.6%/54.9% and 56.9%/52.3% at 6 and 12 months, and 49.3%/47.9%, 32.6%/32.6% and 25.1%/25.1% after 2, 5 and 7 years, respectively. Along with the high recurrence rate, a considerable proportion of the cohort needed catheter ablation ($n = 12$) and/or pacemaker/ICD implantation ($n = 21$). Nevertheless, only 37.4%/34.7% of the patients were in SR on/off AADs at latest follow-up with a median time to latest follow-up of 6.99 (3.17) years. By looking at the group of patients with late AF reccurence, it appeared that most of these patients still had an ATA ($n = 81$, 71.1%), of which 48.2% ($n = 55$) were AF and the remaining atrial flutter ($n = 22$) and atrial tachycardia ($n = 4$).

3.3. Predictors of late AF recurrence

From the initial predictor analysis of baseline parameters deemed clinically relevant, significant associations were found for SAF subtype, AF duration and postoperative ATA (Table 2). Comparable findings for hyperthyroidism and diabetes were regarded as statistically random. A corresponding analysis of all parameters is presented in Online Table 2. Subsequently, these possible predictors were integrated in the multivariate analysis along with the variable cardiac valve disease requiring treatment to introduce the clinically reasoning of worsening of cardiac function as a predictor (Table 3). SAF posed a 3.5-fold increased risk of recurrence compared to PAF ([2.35;5.32], $p < 0.001$). Additionally, one-year increase in AF duration (1.08 [1.05;1.11], $p < 0.001$) and

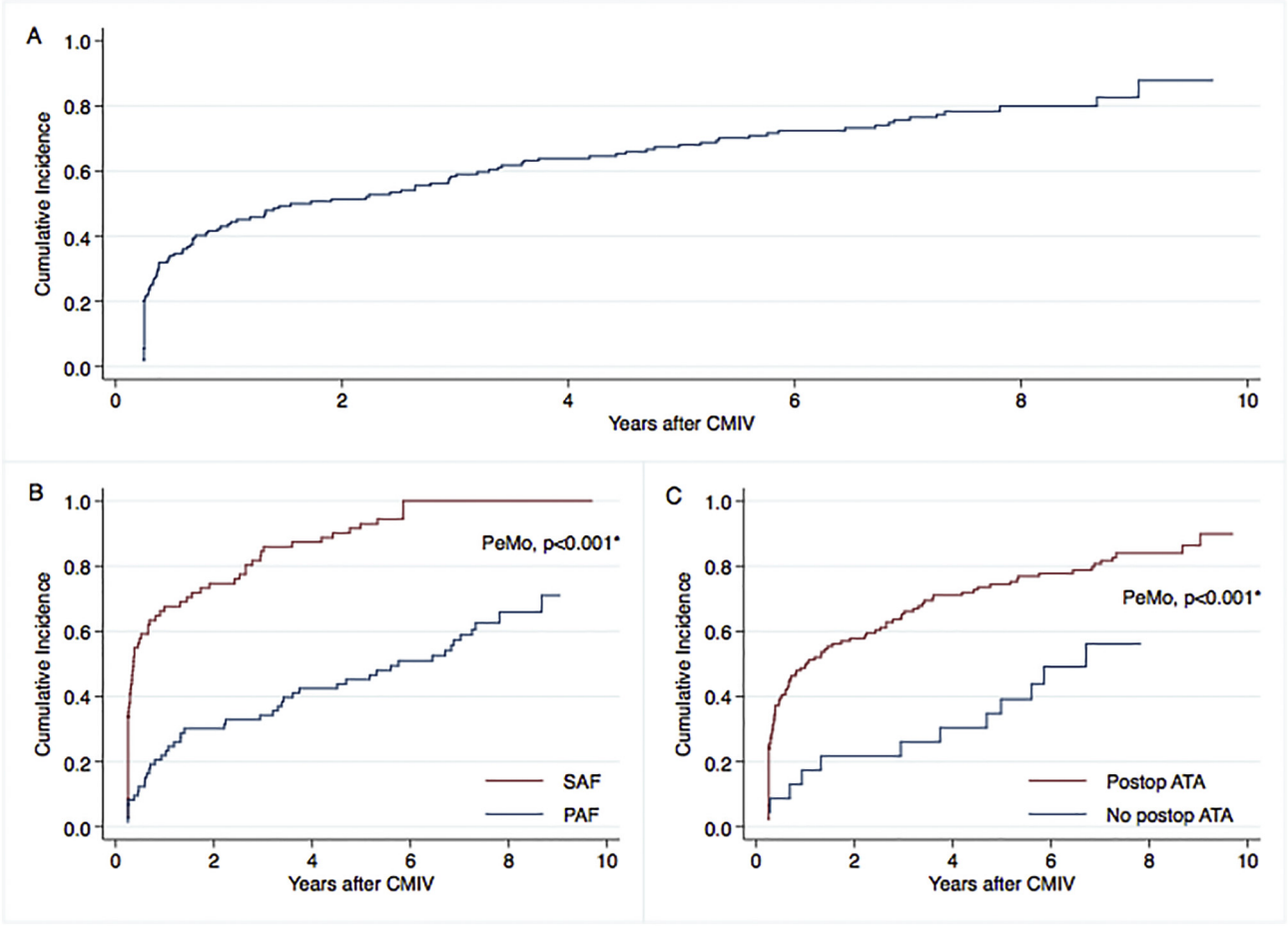

Fig. 1. Cumulative incidence function of late AF recurrence for the total cohort and stratified by independent categorical predictors. A. The cumulative incidence of recurrence for the total cohort during follow-up. In total, 35.4% 95%CI [27.7;43.2] of the cohort had recurrence after 6 months corresponding 43.1% [34.9;51.0], 50.7 [42.3;58.5], 67.4 [59.0;74.4], 74.9 [66.8;81.2] after 1, 2, 5 and 7 years, respectively; B. Statification by preoperative AF subtype; C. Statification by postoperative atrial tachyarrhythmia (ATA); Equality between subgroups was evaluated by the Pepe and Mori test (PeMo). AF, atrial fibrillation; CMIV, concomitant maze IV; ECG, electrocardiogram.

Table 2
Univariate predictor analysis.

Parameter	Univariate analysis		Adjusted† analysis	
	SHR [95% CI]	*P* value	SHR [95% CI]	*P* value
Age, y	1.03 [1.01;1.06]	0.008*	1.03 [1.01;1.06]	0.011*
Male gender	0.74 [0.51–1.09]	0.132	0.81 [0.54;1.21]	0.305
AF-disposing comorbidity				
Heart failure	1.23 [0.80;1.88]	0.342	1.22 [0.76;1.96]	0.414
Cardiac valve disease	1.54 [1.00;2.37]	0.051	1.51 [0.97;2.36]	0.068
Ischemic heart disease	0.81 [0.56;1.16]	0.242	0.71 [0.48;1.05]	0.089
Congenital heart disease	1.28 [0.69;2.37]	0.441	1.72 [0.97;3.03]	0.062
Hypertension	1.20 [0.82;1.74]	0.345	1.06 [0.71;1.57]	0.774
Obesity	1.26 [0.86;1.82]	0.233	1.38 [0.94;2.03]	0.096
Chronic kidney disease	0.85 [0.52;1.37]	0.504	0.75 [0.44;1.27]	0.277
Chronic obstructive Pulmonary disease	1.13 [0.64;1.99]	0.679	0.93 [0.51;1.71]	0.827
Hyperthyroidism	2.61 [1.21;5.65]	0.015*	2.43 [1.18;5.02]	0.016*
Sleep apnea	1.97 [0.85;4.56]	0.114	2.11 [0.84;5.30]	0.113
Cardiovascular risk factors				
Diabetes mellitus type 2	1.85 [1.05;3.27]	0.034*	1.94 [1.10;3.43]	0.023*
Hypercholesterolemia	1.08 [0.75;1.55]	0.689	1.00 [0.68;1.47]	0.992
Smoking status	1.00 [0.78;1.30]	0.981	1.05 [0.79;1.39]	0.745
CHA_2DS_2VASc score	1.55 [1.15;2.11]	0.004*	1.27 [0.90;1.80]	0.169
Echocardiographic parameters				
LAd, cm	1.16 [0.88;1.53]	0.294	1.22 [0.92;1.62]	0.169
LAvI, mL/m^2	1.00 [0.99;1.01]	0.460	1.00 [0.99;1.01]	0.406
LVEF, %	1.00 [0.97;1.02]	0.837	1.00 [0.98;1.03]	0.989
AF characteristics				
SAF subtype	3.65 [2.43;5.47]	<0.001*	3.63 [2.43;5.41]	<0.001*
AF duration, y	1.08 [1.05;1.11]	<0.001*	1.08 [1.05;1.11]	<0.001*
Cardiac surgery				
Maze IV + CABG	0.63 [0.40;1.01]	0.057	0.64 [0.40;1.04]	0.071
Maze IV + Cardiac valve procedure	1.51 [0.97;2.33]	0.066	1.49 [0.96;2.33]	0.076
Postoperative ATA	2.70 [1.58;4.60]	<0.001*	2.40 [1.40;4.11]	0.001*

Univariate predictor analysis of pre-, peri- and postoperative parameters deemed clinically relevant. Parameters were evaluated in a univariate Fine-Gray model incorporating the possibility of differing individual follow-up times and allowing for death during follow-up as a competing risk event. Subsequently, the covariates were adjusted for age and gender as well-known risk factors for AF.
SHR, sub-hazard ratio; CI, confidence interval; other abbreviations as in Table 1.
* A $p < 0.05$ were considered statistically significant.
† Adjusted for age and gender.

presence of postoperative ATA (2.29 [1.21;4.35], $p = 0.011$) were associated with increased risk of recurrence. Neither valve disease requiring treatment (1.37 [0.88;2.13], $p = 0.160$), nor the addition of LA size provided further predictive information (LAd: 1.23 [0.93;1.63], $p = 0.141$, LAvI: 1.01 [1.00;1.02], $p = 0.216$). To account for missing echocardiographic observations (LAd = 11.8%, LAvI = 38.2%), multiple imputed data was implemented in the analysis showing similar insignificant results with no improvement in model prediction (Online Table 3).

Fig. 1B–C shows the cumulative incidence of late AF recurrence stratified by the independent categorical predictors. Comparing CIFs with regard to subtype (Fig. 1B), a significantly higher incidence appeared in SAF patients ($p < 0.001$). Already at 1-year follow-up, 66.2% [53.9;75.9] with SAF vs. 20.5% [12.2;30.4] with PAF had recurrence. These figures increased to >90% of the SAF patients after 5 years (91.5% [82.2;96.1]). A similar difference in CIFs according to postoperative ATA is shown in Fig. 1C (48.8% [39.6;57.3] vs. 13.0 [3.30;29.7] at 1-year, $p < 0.001$). All time-specific CIFs are shown in Online Table 4.

4. Discussion

To the best of our knowledge, this is the first retrospective cohort study cumulatively evaluating the long-term efficacy of maze IV surgery in an unselected AF population, which is representative for clinical practice by being older and having significant co-morbidity. We found a relatively low short- and long-term rate of freedom from late AF recurrence without AADs, and at latest follow-up only approximately one third of the cohort was in SR off AADs. Furthermore, we identified an association between preoperative SAF, AF duration and postoperative ATA and a higher risk of recurrence.

4.1. The long-term efficacy of maze IV surgery

CMIV is recommended in current guidelines of AF management,[1] and recently, a systematic review of eight randomized trials (RCTs) has shown high success rates after concomitant AF surgery,[13]. However, the procedure efficacy is still under debate given considerable heterogeneity regarding several study aspects; the AF populations investigated, extent of maze IV lesions, use of ablation technologies, follow-up time and methodology.

When comparing the cumulative freedom from AF recurrence and the estimated short- and long-term prevalence of SR without AADs at certain time points in the present study, one of the reporting problems regarding efficacy of CMIV becomes evident, in that the time-dependent SR prevalence was higher, thus overestimating procedure efficacy. A similar tendency is seen when comparing our results with previous studies using the prevalence of freedom from recurrence as efficacy endpoint,[12,14–18,21,24]. Five cohort studies,[12,14–17] estimated the short-term success rate at 77–94% after 1 year with the lowest rate found in a study of mainly SAF patients undergoing uni−/bipolar radiofrequency energy CMIV,[17]. Gillinov et al.,[8] randomized SAF patients to surgical ablation (49.6% biatrial CMIV) or no ablation. After 1 year, 66.0% in the CMIV-group were in SR off AADs. Other RCTs showed similar results,[13], but with even lower success rates after only left-sided lesions,[19].

Only a few long-term follow-up studies exist, and even fewer use cumulative CMIV evaluations. The overall prevalence of SR was 56–91%

Table 3
Multivariate predictor analysis.

Parameter	Multivariate analysis 1		Multivariate analysis 2		Multivariate analysis 3		AIC/BIC†	Wald's χ^2 test†
	SHR [95% CI]	*P* value	SHR [95% CI]	*P* value	SHR [95% CI]	*P* value		
Age, y	1.03 [1.00;1.05]	0.034*	1.02 [1.00;1.05]	0.091	1.02 [0.99;1.05]	0.170		
Male gender	0.73 [0.51;1.07]	0.106	0.70 [0.49;1.00]	0.047*	0.74 [0.52;1.06]	0.102	985.73/991.67‡	7.75‡
Cardiac valve procedure	1.38 [0.89;2.15]	0.154	1.42 [0.90;2.24]	0.128	1.37 [0.88;2.13]	0.160	984.38/993.29	11.36
SAF subtype	3.57 [2.38;5.34]	<0.001*	3.69 [2.44;5.56]	<0.001*	3.54 [2.35;5.32]	<0.001*	946.74/958.62	51.46
AF duration, y			1.07 [1.05;1.10]	<0.001*	1.08 [1.05;1.11]	<0.001*	924.30/939.11	75.87
Postoperative ATA					2.29 [1.21;4.35]	0.011*	917.98/935.76	86.44

Multivariate predictor analysis of pre-, peri- and postoperative parameters deemed clinically relevant. Parameters were evaluated in a confounder-adjusted Fine-Gray model. Improvement of model prediction was evaluated by comparing the estimates of AIC/BIC in analysis 1, 2 and 3 relative to Wald's χ^2 test with last-mentioned having the best predictive effect. The addition of LAd (1.23 [0.93;1.63], $p = 0.141$, AIC/BIC = 808.36/828.21, Wald's test = 68.27) and LAvI (1.01 [1.00;1.02], $p = 0.216$, AIC/BIC = 508.06/525.40, Wald's test = 80.19) did not improve model prediction.
AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; other abbreviations as in Tables 1 and 2.
* A $p < 0.05$ were considered statistically significant.
† The estimates of AIC/BIC and Wald's index correlated to the multivariate analysis including the following parameter in the given table row and the preceding parameters.
‡ The basic multivariate model included age and gender.

and 61–85% after 2 and 5 years, respectively, with a lower success in patients off AADs,[18,21,23,24]. Studies either including PAF/SAF patients equally and using bipolar radiofrequency energy,[18,24] or excluding all patients with incomplete 5-year follow-up data,[21] found the highest prevalence. The discrepancy to our results additionally indicates that success rates may be largely overestimated when excluding the deceased patients. Two cohort studies cumulatively estimated the incidence of recurrence without reporting AAD treatment in SAF patients undergoing CMIV (52.7%) or no ablation,[22] and PAF/SAF patients receiving left-sided CMIV,[20]. Freedom from recurrence was 75.4% and 65.4–68.9% after 2 and 5 years, respectively. Although performing cumulative procedure evaluation, the success rates reported in these studies may still be overestimated due to lacking competing risk implementation, especially when taking into account that both studies included elderly, multi-morbid patients, of which more than half were females with higher risk of death. Competing risk models were only used in two recent studies,[9,23]. Gelsomino et al.,[23] retrospectively investigated SAF patients undergoing bipolar radiofrequency energy CMIV (45.8% biatrial). Maintenance of SR on/off AADs after 7 years was 26.5%/15.3%. On the contrary, a multicenter study,[9] found a high 8-year freedom from AF off AADs (60%) in SAF-patients. The highest success rate occurred when performing biatrial lesions by bipolar radiofrequency energy. Compared to our cohort, the diverging long-term success rates in the two studies might be due to a different 30 days and 6 months blanking period, respectively, not in line with current guidelines, and the fact that approximately one third of recurrences in our study occurred between 3 and 6 months postoperatively,[1]. Additionally, the extremely low long-term success in Gelsomino et al.,[23] might be due to the lack of right atrial lesions stated crucial especially in SAF patients,[9,23,26–28].

Moreover, it is unclear, whether CMIV prevents stroke and reduces all-cause mortality. Although, AF is independently associated with increased risk of stroke and death,[1], SR maintenance using different rhythm control strategies, hereunder CMIV, has not shown prognostic benefit,[1,8,13,21,24,26]. This is in line with this study, where the annual incidence of stroke and death corresponded with the average rates for AF patients on anticoagulants,[1]. Whether stroke prevention in CMIV-patients is related to ongoing anticoagulation or LA appendage exclusion remains uncertain, and we neither investigated this.

4.2. Predictors of late AF recurrence

The extent of atrial remodelling facilitating AF triggering ectopic activity and re-entry circuits may be clinically reflected by the SAF subtype as being a strong predictor of recurrence in our cohort. Even though we were unable to group SAF in persistent or permanent, previous studies have underlined the critical distinction between PAF and non-PAF, [1,18,19,24,29]. The lower risk of recurrence in PAF patients could also be a result of insufficient detection, which might partly explain the delay in time to recurrence in our subgroup. On the other hand, a tendency toward greater need of biatrial lesions in SAF patients is frequently stated,[9,10,23,28] reflecting a more extensive remodelling, and, thus, a higher risk of recurrence.

We also found a longer AF duration strongly associated with late recurrence, but to a minor degree than for SAF subtype. This may be explained by our definition of duration, which might not correspond to the real time in AF. Our study was neither powered to investigate duration categorically, where previous studies mainly including SAF patients found a higher risk of recurrence when doing so,[20,23]. This may indicate a tendency toward irreversible remodelling limiting CMIV efficacy in these patients.

Contrary to our clinical hypothesis, patients undergoing valve surgery did not have a higher risk of recurrence, even though severe cardiac valve disease should be highly proarrhythmic. Our study was not yet powered to show a predictive effect of LA dilatation as expected from previous results,[9,15,17,18,21–24]. While the association appeared continuous in these studies, a review including 12 observational studies demonstrated a higher predictive power of LAd/LAvI >6.0 cm/135 mL/m^2,[30]. In our study, the proportion of patients with this LA size was limited. Our insignificant findings may also be related to the limited preoperative TTE data varying in quality, especially regarding atrial dimensions and function.

Comparable with previous findings,[10,15,24], we found the presence of postoperative ATA additionally predictive. Some studies have explained the high incidence of ATAs after cardiac surgery by propagated atrial remodelling together with an ablation-mediated increase in myocardial inflammatory response,[15,31]. The high 8-year success rate demonstrated in the multicenter study,[9] using a 6 months blanking period, possibly suggests that an aggressive rhythm control strategy during short-term follow-up can improve long-term success, why a strict protocol of post-CMIV management seems mandatory.

4.3. Study limitations

The present study has several limitations. Firstly, the observational and retrospective single-centre design together with the limited number of patients allow no definite conclusion regarding procedure efficacy. However, the extended data collection through combination of data sources might facilitate more precise results. We cannot preclude selection bias due to the exclusion of patients, who postoperatively died during the first 3 months. However, in-hospital mortality was not related to the maze procedure, and the consecutive study enrollment may have ensured a homogeneous cardiac risk group with comparable baseline characteristics. We excluded these patients to counterbalance bias elimination in statistical models, because they were not at risk of recurrence. Secondly, success rates may be affected by procedural factors, as CMIV was performed by six expert surgeons, not all lesions were tested for transmurality, and cryoablation was used for enclosing lines. Thirdly, even though the ECG-/Holter monitoring-based follow-up may have improved hospital attendance, optimal rhythm evaluation would rather be continuous monitoring, as we might have missed asymptomatic and paroxysmal ATA episodes. Though, this might not have been critical because of the high recurrence rate.

4.4. Conclusions

The present study shows, that CMIV with complete transmurality of the box lesion set appears to provide limited long-term success in terms of obtaining SR, especially in patients with a longer history of sustained AF, suggesting an association between the extent of atrial remodelling and procedure efficacy. Presence of postoperative ATA is also independently associated with late AF recurrence. Consequently, a careful evaluation of preoperative AF characteristics and a strict protocol of post-CMIV management may be substantial for increasing the applicability of CMIV. High-quality RCTs are necessary to confirm our findings and elucidate the evidence of the procedure potential in modern AF treatment.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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