Massachusetts-wide study of the incidence of ATrial fibRIllation and stroke occurring after discharge from Cardiac Surgery (MATRICeS)

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1 INTRODUCTION

This Statistical Analysis Plan codifies the analysis of a retrospective research study that has been previously reviewed and approved (2017P002261) by the Partners HealthCare Institutional Review Board (IRB) and will be conducted in accordance with all applicable human subjects' research requirements and applicable federal regulations.

1.1 Study Introduction

Briefly, this study examines the occurrence and neurological consequences of atrial fibrillation, occurring after discharge to home or rehab after cardiac surgery. The study examines patients who underwent cardiac surgery at Cardiac Surgical Programs in Massachusetts between 1/1/2012 and 12/31/2016, with a follow-up period that extends to 12/31/2017.

Detailed data will be obtained from individual Programs that encompasses preoperative medical history, the operative period including details about the operation and also the post-operative period until discharge from hospital. Information about the post-hospital discharge course for individual patients will be obtained from the Massachusetts Center for Health Information and Analysis (CHIA) (https://www.mass.gov/orgs/center-for-health-information-and-analysis). CHIA collects detailed financial and patient-level data from Massachusetts payers and providers, and makes it available to researchers.

1.2 Background Literature

Atrial fibrillation (AF) is the most common cardiac arrhythmia and frequently presents in association with mitral, other valvular and coronary artery disease, notably in the presence of poorer left ventricular function (1,2). Preoperative AF is reported commonly in patients undergoing cardiac surgery, with an incidence of 10-20% (2-8). Even if treated, preoperative AF is associated with a higher incidence of in-hospital postoperative AF, stroke, other cardiac morbidity and mortality (2,6,9-11).

Conventional management of postoperative AF assumes that it results from self-limited causes, such as postoperative pericarditis, surgical stress, and sympathetic stimulation in patients underlying heart disease that can be treated with short-term antiarrhythmics, heart rate reduction, anti-coagulants and anti-platelet agents. However, it is well-known that AF in the immediate postoperative period is associated with increased risk of post-discharge AF and stroke. Observed incidences range widely (3-25%) depending principally on the duration of follow-up and the mode of monitoring (12-14). These studies did not use continuous ECG monitoring to detect AF recurrence, and therefore may have underestimated the incidence of AF by missing asymptomatic AF. Using continuous ECG monitoring the incidence of at least one electrocardiographic episode of AF lasting longer than six minutes is much higher; 60% over the entire follow-up period and 39% occurring more than 3-months after surgery (15).

Thromboembolic stroke is a major preventable cause of morbidity and mortality in patients with post-operative AF (16-18). Studies have demonstrated a risk-unadjusted two to ten-fold increase in embolic events and a threefold increased risk of cardiac death in patients with postoperative AF (12,19,20).

The efficacy of concomitant AF ablation in patients undergoing cardiac surgery, measured as freedom from AF and quality of life, and safety measured as freedom from morbidity and mortality, has been well demonstrated (21-29), especially after mitral valve surgery. Observational studies with large sample sizes and longer follow-up have demonstrated improved survival after surgical ablation in normal sinus rhythm (30-33). Yet the implementation of AF ablation and stroke reduction procedures, while increasing (34,35), remains relatively low in the US (33). This is despite guidelines from National and International Societies (36-39) that support use of these procedures. Concerns voiced about concomitant AF ablation or stroke reduction surgery include increased operative time and complexity, perceived operative risk of the procedures (40), and increased risk of atrio-ventricular block requiring pacemaker insertion (21,34,35,41,42).

2 STUDY SUMMARY AND AIMS

The purpose of this study is to determine the incidence, risk factors and adverse events consequent upon atrial fibrillation after cardiac surgery, as well as the association between prior atrial fibrillation and postoperative atrial fibrillation. The study uses information from local Cardiac Surgical Programs to describe the preoperative medical state and immediate post-operative state. Additionally, information from the post-discharge period will be provided by CHIA, by matching the two sources of information using HIPAA-waived data such as medical record number, date of birth, gender and last name. Once matched, the data are stripped of identifiers.

2.1 Study Design:

We will employ a retrospective cohort design, examining patients who underwent cardiac surgery at Cardiac Surgical Programs in Massachusetts between 1/1/2012 and 12/31/2016, with a follow-up period that extends to 12/31/2017. The study examines the risk factors and incidence of post-operative atrial fibrillation, stroke and other focal neurological events after discharge from hospital.

2.2 Study Population and Sites

The study will examine the medical records of patients who underwent cardiac surgery in Massachusetts between 1/1/2012 to 12/31/2016. It is estimated that ~50,000 patients are eligible for inclusion in this study. The evaluable sample size is derived from a sample of convenience from the following Institutions.

Baystate Medical Center, Springfield, MA
Beth Israel Deaconess Medical Center, Boston, MA
Brigham and Women's Hospital, Boston, MA
Cape Cod Hospital, Hyannis, MA
SouthCoast Health, Fall River, MA
Massachusetts General Hospital, Boston, MA
Mount Auburn Hospital, Cambridge, MA
UMass Memorial Medical Center-University, Worcester, MA

Tufts Medical Center, Boston, MA

2.3 Primary Aims

The Primary Aims of this study are to determine:

1. The risk factors, which includes the main risk factor preoperative atrial fibrillation, for postoperative atrial fibrillation occurring after discharge from hospital in patients who underwent cardiac surgery during admission.
2. The risk factors, which includes the main risk factor preoperative atrial fibrillation, for stroke or other focal neurologic event occurring after discharge from hospital in patients who underwent cardiac surgery during admission.

2.4 Secondary Aims

The Secondary Aims of this study are to determine:

1. The frequency of, and treatments for, atrial fibrillation occurring after discharge from hospital in patients who underwent cardiac surgery during admission.
2. The frequency of stroke or other focal neurologic event occurring after discharge from hospital in patients who underwent cardiac surgery during admission
3. The incidence of all-cause and stroke-related mortality after cardiac surgery.

3 STUDY ENDPOINTS AND COVARIATES

3.1 Definitions of Study Endpoints

1. Postoperative atrial fibrillation occurring after discharge from hospital
2. Stroke or other focal neurologic event occurring after discharge from hospital
3. All-cause mortality
4. Stroke-related mortality

3.2 Definitions of Covariates

Data derived from individual sites will use definitions from the Society of Thoracic Surgeons Adult Cardiac Surgery Database versions 2.7.3 and 2.8.2 (43,44).

3.3 Modifications or derivations of standard variables

Hospital admissions will be defined using continuous in-patient stays (CIS) which combine data from each event within hospital, which includes within hospital transfers. Diagnostic subgroups will be defined using the code recorded for the main diagnosis for the first event within a CIS. The ninth

International Classification of Disease codes (ICD-9) codes will be used to define the specific conditions of interest.

3.4 Unrelated outcomes

Un-related events such as upper or lower limb fracture and xxx will be used as negative controls.

Unrelated adverse events (such as upper or lower limb fracture), which are known not to be caused by prior AF will be used as the composite negative control outcome to examine whether there is unmeasured confounders of the prior AF-postoperative AF association. An observed association between prior-AF and the negative control outcome will reflect the existence of unmeasured confounders. In such cases, these unmeasured confounders will also affect the true prior AF-postoperative AF association (45). When such unmeasured confounding effect is detected, we will provide an adjusted estimate for the hazard ratio of first postoperative AF using an indirect approach (46)

4 ESTIMATION OF ACCESSIBLE EFFECT SIZE

This will be a retrospective cohort study. Patients will be included in the study based on the inclusion and exclusion criteria. All statistical tests will be two-sided and the statistical significance level will be set at 0.05 unless otherwise stated. Assuming 50,000 patients will be included in the analysis, among which 4000 (8%) have prior AF, we will have 80% power to detect a Cohen's effect size of 0.046 at the 0.05 significance level. If 25% of the patients who do not have prior AF have postoperative AF, a Cohen's effect size of 0.046 is corresponding to a 2% difference in the incidence of postoperative AF.

5 DATA SOURCES

6 STUDY POPULATIONS

6.1 Inclusion Criteria

Inclusion criteria for this study are patients who undergo surgical procedures that include coronary artery bypass graft surgery, aortic valve surgery or mitral valve surgery and other valvular surgical procedures.

6.2 Exclusion Criteria

Exclusion criteria for this study are:

Preoperative status

- Prior AF ablation or pulmonary vein isolation procedure of any type
- Prior LA occlusion or ablation procedure of any type

Surgical procedure

- MAZE or other procedure for the treatment or prevention of AF

Ventricular assist device
Heart transplantation
Bacterial endocarditis
Cardiac trauma
Cardiac tumor
Ventricular septal defect repair
Left ventricular aneurysm repair
Pulmonary thromboendarterectomy
Surgical ventricular restoration

6.3 Subgroups

Subgroups may be used in secondary analyses.

6.4 Description of participants

The study participants will be presented as per the CONSORT recommendations (Figure 1). The baseline characteristics will be presented (Table 1). Including:

Demographic characteristics (e.g., age, sex, socioeconomic status)

Baseline exposure characteristics (e.g., smoke exposure)

Baseline disease characteristics

Table 2 (Appendix) will describe the baseline characteristics of the study group comparing patients with post-discharge AF, compared to those without.

Baseline values of primary and/or secondary outcome variables

7 STATISTICAL ANALYSES

7.1 General

Baseline and demographic characteristics will be summarized using descriptive statistics (means, standard deviations or median, interquartile ranges for continuous variables such as age and percentages for categorical variables such as race and ethnicity. When deemed appropriate, they will be compared using Chi-square test, Fisher's exact test, two-sample t test, and Wilcoxon rank-sum test between groups. For each binary outcome we will report odds ratios with 95% confidence intervals and give a two-sided p-value for statistical significance. For analysis of the pre-specified subgroups (primary outcome only) we will report relative risks with 99% confidence intervals with two-sided p-value.

7.1.1 Primary Aims

The standard Cox proportional hazards model will be used to model time to first atrial fibrillation occurrence and time to first stroke or other focal neurologic event, after discharge from hospital,

respectively. The potential risk factors included will be selected based on their univariate association with first event status, as well as clinical significance. Hazard ratios with 95% confidence intervals will be reported with a two-sided p-value for statistical significance. The proportional hazard assumption will be evaluated using graphical tool, and by including time dependent covariate terms.

Since there might be repeated occurrences of atrial fibrillation and stroke or other focal neurologic event for each patient, we will use the Andersen-Gill (AG) model and the Prentice, Williams and Peterson (PWP) models to analyze recurrent events data. The AG model is suitable when the interest is in the overall effect on the intensity of the occurrence of a recurrent event. The PWP models allow us to evaluate the effects of risk factors for the kth event after discharge from hospital, as well as the effects of risk factors for the kth event since the time from the previous event (47). Hazard ratios with 95% confidence intervals will be reported with a two-sided p-value for statistical significance. For time-to-event data analyses, death will be considered a censoring event.

7.1.2 Secondary Aims

Means and standard deviations will be estimated for count outcomes. We will report the two-sided p-value for statistical significance of the difference in means of count outcomes.

The frequencies of atrial fibrillation and stroke or other focal neurologic event will be modeled with Poisson regression with the length of follow-up time as the offset. Potential risk factors included in this model will be selected based on univariate test results, as well as clinical significance. Logistic regression will be used to model the incidence of all-cause and stroke-related mortality after cardiac surgery, respectively.

7.2 Pooling of Sites

The data will be pooled across all participating sites. In logistic and Cox proportional hazards models, site will be treated as a random effect.

7.3 Methods for Handling Missing Data

The frequency and percentage of missing values for each variable will be collected, analyzed and reported. If there are missing values for the outcome variable(s), individual patients will be excluded. Highly incomplete covariates (>33% of observations missing) will be excluded from analyses. If missing values are Missing Completely At Random (MCAR), exclusion of patients with missing observations will be considered. If missing values are Missing At Random (MAR) or not at random (MNAR), multiple imputation will be performed. Missing values, selection or exclusion of observations and variables and handling of missing values in the statistical analysis will be describes carefully and sensitivity analysis will be provided (48-51)

7.4 Statistical Analytical Issues

7.4.1 Adjustments for covariates

There will be covariate adjustment in the primary analysis.

7.4.2 Multiple Comparisons

There will be no adjustment for multiple comparisons. We will report 99% confidence intervals for subgroup analyses of the primary outcome.

7.4.3 Examination of Subgroups

To determine if all subgroups experience similar treatment effects or if there are subgroups that behaved differently. We will report odds ratios with 99% confidence intervals for the primary outcome by the following subgroups, with/without prior atrial fibrillation before surgery, and with/without atrial fibrillation when discharged. We will conduct a test of homogeneity of effects across the subgroups and report a P value. Unless there is strong evidence against the null hypothesis of homogeneity of effects (i.e. $p<0.001$) the overall odds ratios will be considered as the most reliable guide to the approximate relative risks in all subgroups.

7.4.4 Correlated data, bias, confounding and interactions.

Collinearity between risk factors will be evaluated with Variance Inflation Factors (VIF) or generalized VIF. Risk factors with high VIF (>2.5) will be excluded in the models.

7.4.5 Subgroup analyses

Subgroup analyses will be performed as post-hoc analyses to determine if all subgroups experience similar treatment effects or if there are subgroups that behaved differently. The methods will be determined based on:

- Pre-specify subgroups that will be analyzed. Consider subgroups defined by:
    - Baseline values of outcome variables
    - Different types of baseline disease status (e.g., prior atrial fibrillation history)
    - Different levels of key prior exposures (e.g., smoking status/exposure, atrial fibrillation status at discharge)
- Pre-specify how the results will be interpreted:
    - We expect to see that the effects of risk factors will be in the same direction with different intensities. If we are able to identify certain subgroups that are significantly different from others, we will report the results with suggestions for future studies.

7.5 Post-hoc (data driven) analyses:

Post-hoc data driven analyses are allowed after the following are undertaken.

(a) Document which analyses were conducted after the results for the Primary and Secondary Aims are analyzed.
(b) Document the rationale for these analyses.
(c) Pre-specify their interpretation in the context of the primary and secondary results and their impact on the overall trial conclusions.

7.6 Sensitivity Analyses

The negative control outcome analysis mentioned in section 3.4 will be part of the sensitivity analyses, which evaluates whether there is unmeasured confounding effect in the prior AF-postoperative AF association. A similar analysis will be performed for stroke, and all-cause mortality. Additionally, we will report E-values for the associations from these models. The E-value is defined as the minimum strength of association, that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure-outcome association, conditional on the measured covariates

When patient characteristics are significantly different between the prior AF group and non-prior AF group, stratified proportional hazard models with two sets of coefficients will be fitted, and the effects of risk factors will be evaluated. Consistency of the two sets of coefficients would reflect the imbalance of baseline variables is negligible, and one final model will be reported. For the analysis of recurrent data, consistency of the results from AG and PWP models will be monitored.

8 APPENDIX: STUDY ADMINISTRATION

8.1 Confidentiality

Data will be stored on encrypted hard drives and backed up to secure Partners-maintained storage within the Partners firewall. Secure transfer methods will be used. Final results will be reported in aggregate with no individually identifying data.

Linkage is done on a stand-alone PC which is not used by the analysts. The linkage process uses only temporary data sets that are immediately removed once the program has completed. The final analytic data set does not contain any patient names, addresses, or social security numbers. It also does not contain any CHIA case mix data fields.

8.2 Records Retention

We anticipate follow-on studies in the field that can be performed with this data set. Therefore, records will be retained for up to five years for follow-on studies, provided each site agrees to this plan.

8.3 Informed Consent/Assent and HIPAA Authorization

Waiver of informed consent has been granted for this retrospective chart review study as it meets the following criteria pursuant to 45 CRF 46.116(d):

- The research involves no more than minimal risk to the subjects.
- The waiver or alteration will not adversely affect the rights and welfare of the subjects.
- The research could not practicably be carried out without the waiver or alteration.

Waiver of HIPAA authorization has been granted as it meets the following criteria pursuant to 45 CFR 164.512(i)(1)(i)

- The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
    - an adequate plan to protect the identifiers from improper use and disclosure;
    - an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
    - adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
- The research could not practicably be conducted without the waiver or alteration; and
- The research could not practicably be conducted without access to and use of the protected health information.

9 APPENDIX: DATA TO BE OBTAINED FROM MASSACHUSETTS CARDIAC SURGICAL PROGRAMS

Line number	Section	Variable text	STS variable names	STS 2.81 variable numbers	STS 2.73 variable numbers	STS 2.61 variable numbers	STS 2.52 variable numbers
1		STS database version					
2	**B. Demographics**						
3		Patient Last Name	PatLName	50	90	100	100
4		Patient First Name	PatFName	55	100	110	110
5		Zip Code	PatZip	105	210	180	180
6		Medical Record Number	MedRecN	85	170	170	170
7		Date of Birth	DOB	65	130	130	130
8		Gender	Gender	75	150	150	150
9		Race	Race	-	-	190	190
10		Race	RaceDocumented	150	-	-	-
11		RaceCaucasian	RaceCaucasian	155	290	191	-
12		RaceBlack	RaceBlack	160	300	192	-
13		RaceAsian	RaceAsian	165	310	193	-
14		RaceNativeAm	RaceNativeAm	170	320	194	-
15		RacNativePacific	RacNativePacific	175	330	195	-
16		RaceOther	RaceOther	180	340	196	-
17		Ethnicity	Ethnicity	185	350	199	-
18	**C. Hospitalization**						
19		Hospital Name	HospName	205	380	220	220
20		Date of Surgery	SurgDt	310	610	260	260
21		Date of Discharge	DischDt	315	620	270	270
22		Payor	PayorGov	225	420	247	-
23		Payor	PayorComm	275	510	254	-
24		Payor	PayorHMO	280	520	255	-
25	**D. Risk Factors**						
26		Height	HeightCm	330	640	360	360
27		Weight	WeightKg	335	630	350	350
28		Diabetes	Diabetes	360	780	400	400

29	Diabetes - control	DiabCtrl	365	790	410	410
30	Dyslipidemia	Dyslip	370	800	420	420
31	Dialysis	Dialysis	375	810	450	450
32	Hypertension	Hypertn	380	820	460	460
33	Smoker	TobaccoUse	400	-	-	-
34	Smoker	CigSmoker	-	650	370	370
35	Smoker	SmokCurr	-	660	-	-
36	Chronic Lung Disease	ChrLungD	405	860	510	510
37	Sleep Apnea	SlpApn	460	950	-	-
38	Alcohol Use	Alcohol	480	1131	-	-
39	Peripheral Artery Disease	PVD	505	980	530	530
40	Cerebrovascular disease	CVD	525	1010	540	540
41	Prior CVA	CVA	530	1020	470	470
42	Prior CVA-When	CVAWhen	535	1030	480	480
43	CVD TIA	CVDTIA	540	1050	540	540
44	CVD Carotid stenosis	CVDCarSten	545	1070	550	550
45	Right carotid disease	CVDStenRt	550	1071	-	-
46	Left carotid disease	CVDStenLft	555	1072	-	-
47	Priot carotid surgery	CVDPCarSurg	560	1080	-	-
48	WBC Count	WBC	565	690	-	-
49	Last Creatinine	CreatLst	585	750	430	430
50	Infectious endocarditis	InfEndo	385	830	490	490
51	**E. Previous Cardiac Interventions**					
52	Previous Cardiac Interventions	PrCVInt	665	1200	570	570
53	Previous CABG	PrCAB	670	1215	600	600
54	Previous Valve	PrValve	675	1216	610	610
55	Previous valve surgery type 1	PrValveProc1	695	-	-	-
56	Previous valve surgery type 2	PrValveProc2	700	-	-	-
57	Other Previous Cardiac Interventions	POC	805	-	620	620

58	Other previous cardiac intervention 1	POCInt1	810	-	-	-
59	Other previous cardiac intervention 2	POCInt2	815	-	-	-
60	Other previous cardiac intervention 3	POCInt3	820	-	-	-
61	Previous carotid artery surgery	CVDPCarSurg (1080)	-	1080	557	557
62	Previous ICD	PrOCAICD	-	1460	630	630
63	Previous Pacemaker	PrOCPace	-	1470	640	640
64	Previous arrhythmia surgery	POArr	-	1445	-	-
65	Previous other cardiac	PrOthCar	-	1440	-	-
66	Previous congenital	PrOthCongen	-	1450	621	-
67	Previous Aortic Valve Replacement - Surgical	PrevProcAVReplace	-	1220	-	-
68	Previous Aortic Valve Repair - Surgical	PrevProcAVRepair	-	1230	-	-
69	Previous Mitral Valve Replacement - Surgical	PrevProcMVReplace	-	1240	-	-
70	Previous Mitral Valve Repair - Surgical	PrevProcMVRepair	-	1250	-	-
71	Previous Tricuspid Valve Replacement - Surgical	PrevProcTVReplace	-	1260	-	-
72	Previous Tricuspid Valve Repair - Surgical	PrevProcTVRepair	-	1270	-	-
73	Previous Pulmonic Valve Repair / Replacement - Surgical	PrevProcPV	-	1280	-	-
74	Previous Aortic Valve Balloon Valvuloplasty	PrevProcAVBall	-	1285	-	-
75	Previous Mitral Valve Balloon Valvuloplasty	PrevProcMVBall	-	1290	-	-
76	Previous Transcatheter	PrevProcTCVRep	-	1300	-	-

	Valve Replacement					
	Previous Percutaneous	PrevProcPercVRepai				
77	Valve Repair	r	-	1310	-	-
78	**F. Preoperative Cardiac Status**					
79	Previous MI	PrevMI	885	1540	750	750
80	Previous MI - when	MIWhen	890	1550	760	760
81	Prior Heart Failure	PriorHF	920	1590	770	770
82	History of Arrhythmia	Arrhythmia	945	-	840	840
83	History of Arrhythmia	ArrhythWhen	-	1650	-	-
84	VT/VF	ArrhyVtach	-	1660	851	-
		ArrhyVtachSicSinSyn				
85	Sick sinus syndrome	;	-	1680	-	-
86	Third degree heart block	ArrhyTHB	-	1690	852	-
	Second degree heart					
87	block	ArrhyVtachHrtBlk	-	1670	-	-
88	VT/VF	ArrhythVV	950	-	-	-
89	Sick sinus syndrome	ArrhythSSS	955	-	-	-
90	Atrial Flutter	ArrhythAFlutter	960	-	-	-
	Second degree heart					
91	block	ArrhythSecond	965	-	-	-
92	Third degree heart block	ArrhythThird	970	-	-	-
93	Paced rhythm	ArrhythPPaced	975	-	-	-
94	Afib/Aflutter	ArrhythAFib	980	1700	853	-
95	Type of Atrial Fibrillation	ArrhyTyp	-	-	850	850
	Duration of Atrial					
96	Fibrillation	ArrythAFibDur	985	-	-	-
97	Type of Atrial Fibrillation	ArrythAFibTy	-	1701	-	-
98	**G. Preoperative Medications**					
99	ACE inhibitor Use	MedACEI48	1020	1730	900	900
100	Anticoagulant Use	MedACoag	1040	1750	940	940
101	Amiodarone Use	MedAmiodarone	1035	-	-	-
102	Aspirin Use	MedASA	1055	1820	990	990
103	B-blockers <24 hours	MedBeta	1060	1710	890	890
104	B-blockers >2 weeks	MedBetaTher	1065	-	-	-

	Calcium Channel					
105	Blocker	MedCChanTher	1070	-	-	-
	Preoperative					
106	Antiarrhythmics	MedAArrhy	-	1770	-	-
107	Coumadin	MedCoum	1075	1780	950	950
108	**H. Hemodynamics Cath**					
	Number of Diseased					
109	Vessels	NumDisV	1170	1930	1050	1050
110	LV ejection fraction	HDEF	1545	1960	1080	1080
111	Aortic Insufficiency	VDInsufA	1590	2155	1170	1170
112	Aortic Stenosis	VDStenA	1600	2152	1120	1120
113	Aortic Valve Area	VDAoVA	1610	2153	-	-
	Aortic Valve Mean					
114	Gradient	VDGradA	1615	2154	1130	1130
115	Mitral Insufficiency	VDInsufM	1680	2270	1180	1180
116	Mitral Stenosis	VDStenM	1690	2240	1140	1140
	Mitral Valve Mean					
117	Gradient	VDGradM	1705	2260	1180	1180
118	Tricuspid Insufficiency	VDInsufT	1775	2320	1190	1190
119	Tricuspid Stenosis	VDStenT	1785	2300	1150	1150
120	Pulmonary Insufficiency	VDInsufP	1820	2340	1200	1200
121	Pulmonary Stenosis	VDStenP	1840	2330	1160	1160
122	**I. Operative (with sections J, K, L and M)**					
123	AF procedure	AFibProc	2145	-	2470	2470
124	Afib epicardial lesions	OCarAFibEpLes	4070	-	-	-
125	Afib intracardiac lesions	OCarAFibIntraLes	4105	-	-	-
126	Aortic Arch	AortProcTotArch	4355	-	-	-
127	Aortic Arch	ONCArch	-	-	2530	2530
128	Aortic Arch	ONCArch	-	5480	-	-
129	Aortic Hemi-arch	AortProcHemi	4350	-	-	-
130	Aortic Procedure	AortProc	2150	-	-	-
131	Aortic Procedure	OpAortic	-	-	1630	1630
132	Aortic Procedure Type	OCAoProcType	-	5471	-	-
133	Aortic Root	AortProcRoot	4340	-	-	-

134	Aortic Root	ONCAoRt	-	5473	-	-
135	Aortic Valve Procedure	VSAVPr	-	4280	-	-
136	Aortic Valve Surgery	VSAV	3390	4270	-	-
137	Arrhythmia Correction Surgery	OCarACD	-	5400	-	-
138	Arrhythmia Correction Surgery Lead Extraction	OCarACDLI	-	5410	-	-
139	Arrythmia device	OCarACD	4085	5400	2450	2450
140	Ascending Aorta	AortProcAsc	4345	-	-	-
141	Ascending Aorta	ONCAsc	-	-	2520	2520
142	Ascending Aorta	ONCAsc	-	5474	-	-
143	ASD-PFO repair	OCarASD		5240	-	-
144	ASD-PFO repair	OCarASDPFO	4075	-	-	-
145	Atrial Appendage Procedure	OCarAAProc	4080	-	2480	2480
146	Atrial Fibrillation Ablation Procedure	OCarAFibAProc	-	5465	-	-
147	Atrial Fibrillation Surgical Procedure	OCarAFibSur	-	5450	-	-
148	CABG performed	OpCAB	2120	2437	1280	1280
149	Cardiac trauma	OCarTrma	4153	5380	2430	2430
150	Cardiac Tumor	OCTumor	4150	5530	-	-
151	Congenital heart surgery	OCarCong	4162	5300	2410	2410
152	Congenital procedure 1	OCarCongProc1	4515	5340	-	-
153	Congenital procedure 2	OCarCongProc2	4520	5350	-	-
154	Congenital procedure 3	OCarCongProc3	4525	5360	-	-
155	CPB time	PerfusTm	2400	2770	1380	1380
156	CPB utilization	CPBCmb	-	2470	1360	1360
157	CPB utilization	CPBUtil	2325	2740	1350	1350
158	Emergency Operation	Status	1975	2390	1240	1240
159	Heart transplant	OCarCrTx	4152	5390	2440	2440
160	Lead extraction	OCarACDLE	4120	-	-	-
161	Lead Insertion	OCarLeadInsert	4090	-	-	-
162	Left Atrial Appendage	OCarAFibSurLAA	-	5452	-	-

	Obliterated					
163	LV aneurysm repair	OCarLVA	4125	5220	2360	2360
164	Mitral Procedure	OpMitral	-	-	1640	1640
165	Mitral Valve Procedure	VSMVPr	-	4352	-	-
166	Mitral Valve Surgery	VSMV	3495	4351	-	-
	Number of anastomoses					
167	with arterial conduits	DistArt	2625	3190	1520	1520
	Number of anastomoses					
168	with venous conduits	DistVein	2630	3220	1530	1530
	Other Cardiac					
169	Procedure	OpOCard	2140	2490	1310	1310
170	Previous VAD	PrevVAD	3790	4760	1920	1920
	Pulmonary					
	thromboendarterectom					
171	y	OCPulThromDis	4130	5540	-	-
	Pulmonic Valve					
172	Procedure	OpPulm	-	4560	-	-
173	Pulmonic Valve Surgery	VSPV	3685	-	1660	1660
174	Reop surgery	Incidenc	1970	2380	560	560
	Subaortic stenosis					
175	reseaction	OCarSubaStenRes	4135	-	-	-
	Subaortic stenosis					
176	reseaction	ResectSubA	-	4311	-	-
	Surgical Procedure					
177	Location	OCarAFibSurLoc	-	5451	-	-
	Surgical ventricular					
178	restoration	OCarSVR	4145	5290	2400	2400
179	TMR	OCarLasr	4100	5370	2420	2420
	Tricuspid Valve					
180	Procedure	OpTricus	-	4500	-	-
181	Tricuspid Valve Surgery	VSTV	3640	-	1650	1650
182	VAD implant type	VImpTy	-	4850	-	-
183	VAD implanted	VADImp	3840	-	2030	2030
184	VAD Implanted or	VADProc	2130	2480	-	-

	Removed					
185	Valve Surgery	OpValve	2125	2440	1290	1290
186	VSD repair	OCarVSD	4155	5230	2370	2370
187	**N. Other Non-Cardiac Procedures**					
188	Carotid endarterectomy	ONCCarEn	4530	5560	2570	2570
189	**P. Postoperative Events**					
190	Postop stroke	CNStrokP	4810	6030	2630	2630
191	Postop TIA	CNStrokTTIA	4815	6040	2840	2840
192	Atrial Fibrillation	COAtFib	4930	6330	2990	2990
193	Reop for bleeding	COpReBld	4755	5760	2720	2720
194	Postop pacemaker insertion	CRhythmDis	4900	6270	-	-
195	**Q. Mortality**					
196	Mortality	Mortality	5005	6360	3020	3020
197	Date of Death	MtDate	5030	6400	3060	3060
198	Primary cause of death	MtCause	5040	6420	3080	3080
199	**R. Discharge (with Section S)**					
200	Aspirin	DCASA	5060	6460	3120	3120
201	Warfarin	DCCoum	5085	6510	3180	3180
202	Antiarrythmic	DCAArhy	-	6440	3100	3100
203	Antiarrythmic name	DCAArMN	-	-	3110	3110
204	Readmission	Readm30	-	6550	3220	3220
205	Primary readmission reason	ReadmRsn	-	6560	3230	3230
206	Amiodarone	DCAmiodarone	5110	-	-	-
207	Beta-blocker	DCBeta	5105	6480	3140	3140
208	Discharge location	DisLoctn	5045	6520	3190	3190

10 APPENDIX: CHIA-SOURCED VARIABLE DEFINITIONS AND ABSTRACTION

We will create a subset of cardiac surgery patients using all three CHIA databases to maximize the chance of finding a matching cardiac surgery record in RPDR. UHINs for the cardiac surgery cases are identified in the inpatient database where at least one of 15 procedure codes or principal procedure contains an ICD9-CM code for cardiac surgery (3610-3619). The following lists the minimum set of fields needed to complete the merge.

a. MDPHHospNum: MDPH hospital number determined from all hospital IDs in the case mix data
b. AdmitDt: Admission date to hospital
c. ProcDates: Possible dates for cardiac surgical procedure (15 in inpatient, 3 in OOR data)
d. ProcedureCodes: ICD-9-CM and CPT (OOR only) codes for cardiac surgery records (only 3 ICD-9-CM in OOR data)
e. PrincipalProcDate: Date for principal procedure (OOR only)
f. PrincipalProcedure: ICD9-CM code for PCI and CABG records
g. Diagnosis Codes: Diagnosis and DRG codes for conditions
h. DischDate: Discharge date from hospital
i. RecordType20ID: CHIA Record Id Control Number
j. UHIN Unique patient identifier from CHIA
k. DOB: Patient date of birth submitted by hospital
l. MedicalRecordNum: Hospital patient medical record number
m. Gender: Patient gender

11 APPENDIX: PROPOSED TIMELINE

Activity	Jan-Feb 2018	Feb-Mar 2018	Apr-May 2018	May-Jul 2018	Jul-Sep 2018	Sep-Oct 2018	Oct-Nov 2018
Study design							
IRB and DUA approval							
Data submission and merging at CHIA							
Data cleaning and analysis							
Analysis write-up and first circulation							
Paper preparation and second circulation							
Paper submission							

12 APPENDIX: SHELL TABLES AND FIGURES

12.1 Tables

Table 1: Characteristics of the study participants.

Table 2: Comparison of characteristics of patients with post-discharge atrial fibrillation and those patients who did not have post-discharge atrial fibrillation

Table 3: Time-adjusted risk of post-discharge atrial fibrillation

Table 4: Time-adjusted risk of post-discharge stroke

Table 5: Time-adjusted risk of post-discharge mortality

12.2 Figures

Figure 1: CONSORT diagram

Figure 2: Time course of the occurrence of post-discharge AF

Figure 3: Time course of the occurrence of post-discharge stroke stratified by occurrence of post-discharge AF

Figure 4: Time course of the occurrence of post-discharge mortality stratified by occurrence of post-discharge AF

Table 1: Characteristics of the study participants. Data are reported as number and percentage, or median and 10-90% quantiles, as appropriate

CSP = Cardiac surgical program

CHIA = Center for Health Information and Analysis

	Patient characteristic		Data source	Source variable
0	**Demographics**			
1	Age at surgery (years; N/%)		CSP	Calculated
2		<50		SurgDt - DOB
3		50-59		
4		60-69		
5		70-79		
6		≥80		
7	Gender (Male; N/%)		CSP	Gender
8	Race (Caucasian; N/%)		CSP	RaceCaucasian
9	Ethnicity		CSP	Ethnicity
10	Height (cm; mean/SD)		CSP	HeightCm
11	Weight (kg; mean/SD)		CSP	WeightKg
12	BMI (kg/m2; N/%)		CSP	Calculated
13		<20		
14		20-24.9		
15		25-29.9		
16		30-34.9		
17		≥35		
18	**Payor**			
19		Government	CSP	PayorGov
20		Commercial	CSP	PayorComm
21		HMO	CSP	PayorHMO
22	**Prior Medical History**			
23	Atrial fibrillation		CSP and CHIA	ArrhythAFib, ArrythAFibDur, ArrythAFibTy
24	Atrial flutter		CSP and CHIA	ArrhythAFlutter
25	History of arrhythmia		CSP and CHIA	
26	Heart block or sick sinus syndrome		CSP and CHIA	ArrhyVtachSicSinSyn, ArrhyTHB, ArrhyVtachHrtBlk, ArrhythSSS

27	VT/VF		CSP and CHIA	ArrhyVtach, ArrhythVV
28	Smoker past or current		CSP	TobaccoUse, CigSmoker, SmokCurr
29	COPD		CSP	ChrLungD
30	Diabetes		CSP	Diabetes, DiabCtrl
31		NIDDM		
32		IDDM		
33	Dyslipidemia		CSP	Dyslip
35	Dialysis		CSP	Dialysis
36	Hypertension		CSP	Hypertn
37	Peripheral vascular disease		CSP	PVD
38	Sleep apnea		CSP	SlpApn
39	Alcohol use		CSP	Alcohol
40	Cerebrovascular disease		CSP	CVD
41	Prior CVA		CSP	CVA, CVAWhen
42	TIA		CSP	CVDTIA
43	Carotid Stenosis		CSP	CVDCarSten
44	Prior carotid surgery		CSP	CVDPCarSurg
45				
46	**Medications**			
47	ACEI/ARB		CSP	MedACEI48
48	Anticoagulant or anti-platelet drug		CSP	MedACoag
49	Amiodarone		CSP	MedAmiodarone
50	Aspirin		CSP	MEDASA
51	Beta blocker		CSP	MedBeta
52	Calcium channel blocker		CSP	MedCChanTher
53	Antiarrythmic		CSP	MedAArry
54	Coumadin		CSP	MedCoum
55				
56	**Prior Cardiac Status**			
57	Heart failure			PriorHF
58	Prior MI			PrevMI, MIWhen
59		Past		
60		Recent		
61	Prior CABG surgery		CSP	PrCAB

62	Prior mitral valve surgery		CSP	PrValveProc1, PrValveProc2, PrevProcMVReplace, PreProcMVRepair
63	Prior other valve surgery		CSP	PrValveProc1, PrValveProc2, PrevProcAVReplace , PrevProcAVRepair , PrevProcTVReplace , PrevProcTVRepair , PrevProcPV , PrevProcAVBall , PrevProcMVBall , PrevProcTCVRep , PrevProcPercVRepair
64	Other cardiac surgery		CSP	PrOthCar, PrOthCongen, POC, POCInt1, POCInt2, POCInt3
65	Prior ICD placement		CSP	PrOCAICD
66	Prior pacemaker placement		CSP	PrOCPace
67	Prior arrhythmia surgery		CSP	POArr
69				
70	**Preoperative laboratory testing**			
77	White cell count (10^6/dL)		CSP	WBC
78	Creatinine (mg/dL)		CSP	CreatLst
79				
80	**Preoperative Cardiac Imaging**			
81	Number of diseased coronary vessels		CSP	NumDisV
82		0		
83		1		
82		2		
83		>=3		
84	LV Ejection fraction		CSP	HDEF
85		<30%		
86		30-54%		
87		>=55%		
88	Aortic stenosis		CSP	VDStenA
89	Aortic insufficiency		CSP	VDInsufA
90	Mitral stenosis		CSP	VDStenM
91	Mitral insufficiency		CSP	VDinsufM
92	Tricuspid valve disease		CSP	VDStenT, VDStenP
93	Pulmonary valve disease		CSP	VDStenP, VDinsufP

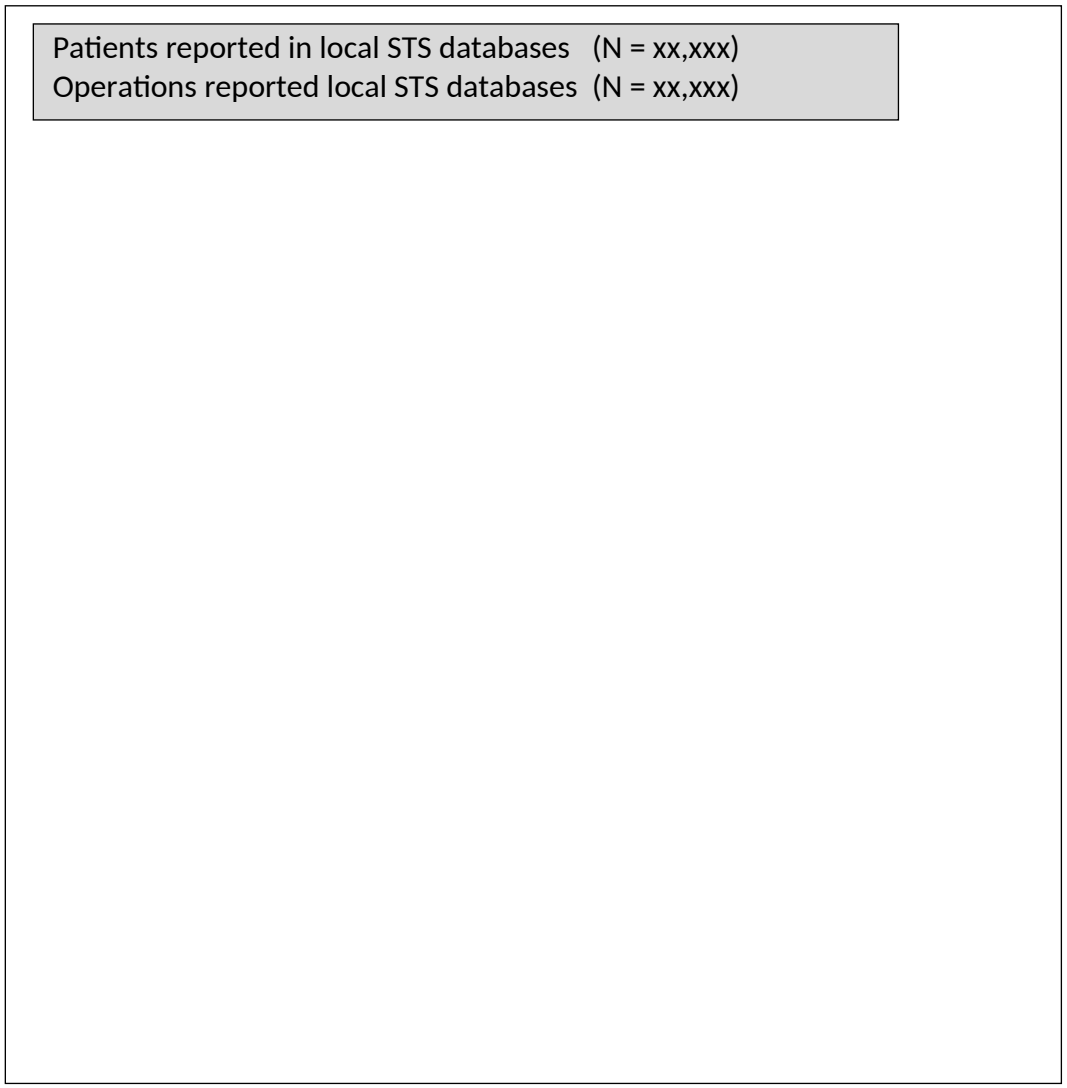
94				
95	**Surgery**			
96	Year of operation		CSP	SurgDt
97		2012		
98		2013		
99		2014		
100		2015		
101		2016		
101	CABG surgery		CSP	OpCAB
102	Number of conduits placed		CSP	DistArt + DistVein
103		1		
104		2		
105		>=3		
106	AVR surgery		CSP	VSAVPr, VSAV
107	MVR surgery		CSP	OpMitral, VSMVPr, VSMV
108	Other valve surgery		CSP	OpPulm, VSPV, OpTricus,VSTV
109	Ascending aortic surgery		CSP	AortProcTotArch, ONCArch, AortProcHemi, AortProc , OpAortic, OCAoProcType, AortProcRoot, ONCAoRt, AortProcAsc, ONCAsc, ONCAsc
110	Other non-CABG, non valvular surgery		CSP	OpOCard
111	Atrial septal surgery		CSP	OCarASD, OCarASDPFO
114	Ventricular outflow tract surgery		CSP	OCarSubaStenRes , ResectSubA
115	Congenital heart surgery			OCarCong , OCarCongProc1 , OCarCongProc2 , OCarCongProc3
116	Carotid endarterectomy		CSP	
117	Reoperation		CSP	Incidenc
118	Surgical urgency		CSP	Status
119		Elective		
120		Urgent		
121		Emergent		
122	Postoperative duration (days)		CSP	DischDt – SurgDt
123				
124	**Post-operative complications**			

125	Stroke	CSP and CHIA	CNStrokP
126	TIA	CSP and CHIA	CNStrokTTIA
127	Atrial fibrillation	CSP and CHIA	COAtFib
128	Reoperation for bleeding	CSP and CHIA	COpReBld
129	Pacemaker inserted	CSP and CHIA	CRythmDis
130	In-hospital atrial fibrillation	CSP	COAtFib
131	In-hospital atrial flutter	CSP	
132			
133	**Discharge medications and devices**		
134	Aspirin	CSP and CHIA	DCASA
135	Warfarin	CSP and CHIA	DCCoum
136	Anti-platelet agent	CHIA	-
137	Beta blocker	CSP and CHIA	DCBeta
138	Amiodarone	CSP and CHIA	DCAmiodarone
139			
140	**Post-discharge atrial fibrillation**		
141	Discharged in AF	CSP	
142	1 - 30 days	CHIA	
143	31 – 90 days	CHIA	
144	91 – 182 days	CHIA	
145	183 – 365 days	CHIA	
146	1 – 2 years	CHIA	
147	2 – 3 years	CHIA	
148	3 – 4 years	CHIA	
149	4 – 5 years	CHIA	
150			
151	**Post-discharge stroke**		
152	1 - 30 days	CHIA	
154	31 – 90 days	CHIA	
155	91 – 182 days	CHIA	
156	183 – 365 days	CHIA	
157	1 – 2 years	CHIA	
158	2 – 3 years	CHIA	
159	3 – 4 years	CHIA	

160		4 – 5 years	CHIA	
161				
162	**Mortality**			
163	30-day mortality		CSP	Mortality and MortalityDate
164	1-year mortality		CSP	Mortality and MortalityDate
165	5-year mortality		CSP	Mortality and MortalityDate

Table 2: Comparison of characteristics of patients with post-discharge atrial fibrillation and those patients who did not have post-discharge atrial fibrillation

Figure 1: CONSORT Diagram.



Excluded after data review (N=x,xxx)

- Inclusion criterion not present
- Exclusion criterion present
- Covariate data not present
- Missing outcome

Eligible patients (N = xx,xxx)

CABG-only surgery (N = xx,xxx)

AVR +/- CABG surgery (N = xx,xxx)

MVR +/- AVR +/- CABG surgery (N = xx,xxx)

13 APPENDIX: STROBE CRITERIA

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

1

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

14 APPENDIX: REFERENCES

1. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. The American journal of cardiology 2013;112:1142-7.
2. Saxena A, Dinh DT, Reid CM, Smith JA, Shardey GC, Newcomb AE. Does preoperative atrial fibrillation portend a poorer prognosis in patients undergoing isolated aortic valve replacement? A multicentre Australian study. The Canadian journal of cardiology 2013;29:697-703.
3. Saxena A, Dinh D, Dimitriou J et al. Preoperative atrial fibrillation is an independent risk factor for mid-term mortality after concomitant aortic valve replacement and coronary artery bypass graft surgery. Interactive cardiovascular and thoracic surgery 2013;16:488-94.
4. Wang TK, Ramanathan T, Choi DH, Gamble G, Ruygrok P. Preoperative atrial fibrillation predicts mortality and morbidity after aortic valve replacement. Interactive cardiovascular and thoracic surgery 2014;19:218-22.
5. Kievisas M, Keturakis V, Vaitiekunas E, Dambrauskas L, Jankauskiene L, Kinduris S. Prognostic factors of atrial fibrillation following coronary artery bypass graft surgery. General thoracic and cardiovascular surgery 2017;65:566-574.
6. Fengsrud E, Englund A, Ahlsson A. Pre- and postoperative atrial fibrillation in CABG patients have similar prognostic impact. Scandinavian cardiovascular journal : SCJ 2017;51:21-27.
7. Levy F, Rusinaru D, Marechaux S, Charles V, Peltier M, Tribouilloy C. Determinants and prognosis of atrial fibrillation in patients with aortic stenosis. The American journal of cardiology 2015;116:1541-6.
8. Quader MA, McCarthy PM, Gillinov AM et al. Does preoperative atrial fibrillation reduce survival after coronary artery bypass grafting? The Annals of thoracic surgery 2004;77:1514-22; discussion 1522-4.
9. Attaran S, Saleh HZ, Shaw M, Ward A, Pullan M, Fabri BM. Does the outcome improve after radiofrequency ablation for atrial fibrillation in patients undergoing cardiac surgery? A propensity-matched comparison. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2012;41:806-10; discussion 810-1.
10. Ngaage DL, Schaff HV, Barnes SA et al. Prognostic implications of preoperative atrial fibrillation in patients undergoing aortic valve replacement: is there an argument for concomitant arrhythmia surgery? The Annals of thoracic surgery 2006;82:1392-9.
11. Saxena A, Virk SA, Bowman S, Bannon PG. Systematic review and meta-analysis on the impact of preoperative atrial fibrillation on short- and long-term outcomes after aortic valve replacement. The Journal of cardiovascular surgery 2017;58:943-950.
12. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2010;37:1353-9.

13. Elahi M, Hadjinikolaou L, Galinanes M. Incidence and clinical consequences of atrial fibrillation within 1 year of first-time isolated coronary bypass surgery. Circulation 2003;108 Suppl 1:II207-12.
14. Pillarisetti J, Patel A, Bommana S et al. Atrial fibrillation following open heart surgery: long-term incidence and prognosis. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing 2014;39:69-75.
15. El-Chami MF, Merchant FM, Smith P et al. Management of New-Onset Postoperative Atrial Fibrillation Utilizing Insertable Cardiac Monitor Technology to Observe Recurrence of AF (MONITOR-AF). Pacing and clinical electrophysiology : PACE 2016;39:1083-1089.
16. Lee R, McCarthy PM, Wang EC et al. Midterm survival in patients treated for atrial fibrillation: a propensity-matched comparison to patients without a history of atrial fibrillation. The Journal of thoracic and cardiovascular surgery 2012;143:1341-51; discussion 1350-1.
17. Lim E, Barlow CW, Hosseinpour AR et al. Influence of atrial fibrillation on outcome following mitral valve repair. Circulation 2001;104:I59-63.
18. Magruder JT, Collica S, Belmustakov S et al. Predictors of Late-Onset Atrial Fibrillation Following Isolated Mitral Valve Repairs in Patients With Preserved Ejection Fraction. Journal of cardiac surgery 2016;31:486-92.
19. Mariscalco G, Klersy C, Zanobini M et al. Atrial fibrillation after isolated coronary surgery affects late survival. Circulation 2008;118:1612-8.
20. Horwich P, Buth KJ, Legare JF. New onset postoperative atrial fibrillation is associated with a long-term risk for stroke and death following cardiac surgery. Journal of cardiac surgery 2013;28:8-13.
21. Al-Atassi T, Kimmaliardjuk DM, Dagenais C, Bourke M, Lam BK, Rubens FD. Should We Ablate Atrial Fibrillation During Coronary Artery Bypass Grafting and Aortic Valve Replacement? The Annals of thoracic surgery 2017;104:515-522.
22. Elbadawi A, Ogunbayo GO, Elgendy IY et al. Impact of Left Atrial Appendage Exclusion on Cardiovascular Outcomes in Patients With Atrial Fibrillation Undergoing Coronary Artery Bypass Grafting (From the National Inpatient Sample Database). The American journal of cardiology 2017;120:953-958.
23. Endo D, Kato TS, Iwamura T et al. The impact of surgical left atrial appendage amputation/ligation on stroke prevention in patients undergoing off-pump coronary artery bypass grafting. Heart and vessels 2017;32:726-734.
24. Gillinov AM, Gelijns AC, Parides MK et al. Surgical ablation of atrial fibrillation during mitral-valve surgery. The New England journal of medicine 2015;372:1399-409.
25. Rankin JS, Lerner DJ, Braid-Forbes MJ, Ferguson MA, Badhwar V. One-year mortality and costs associated with surgical ablation for atrial fibrillation concomitant to coronary artery bypass grafting. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2017;52:471-477.
26. Abreu Filho CA, Lisboa LA, Dallan LA et al. Effectiveness of the maze procedure using cooled-tip radiofrequency ablation in patients with permanent atrial fibrillation and rheumatic mitral valve disease. Circulation 2005;112:I20-5.
27. Blomstrom-Lundqvist C, Johansson B, Berglin E et al. A randomized double-blind study of epicardial left atrial cryoablation for permanent atrial fibrillation in patients undergoing mitral

valve surgery: the SWEDish Multicentre Atrial Fibrillation study (SWEDMAF). European heart journal 2007;28:2902-8.
28. Chevalier P, Leizorovicz A, Maureira P et al. Left atrial radiofrequency ablation during mitral valve surgery: a prospective randomized multicentre study (SAFIR). Archives of cardiovascular diseases 2009;102:769-75.
29. Gillinov AM, Bhavani S, Blackstone EH et al. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. The Annals of thoracic surgery 2006;82:502-13; discussion 513-4.
30. 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. The Journal of thoracic and cardiovascular surgery 2014;148:3027-33.
31. Damiano RJ, Jr., Lawrance CP, Saint LL et al. Detection of Atrial Fibrillation After Surgical Ablation: Conventional Versus Continuous Monitoring. The Annals of thoracic surgery 2016;101:42-7; discussion 47-8.
32. Melo J, Santiago T, Aguiar C et al. Surgery for atrial fibrillation in patients with mitral valve disease: results at five years from the International Registry of Atrial Fibrillation Surgery. The Journal of thoracic and cardiovascular surgery 2008;135:863-9.
33. Badhwar V, Rankin JS, Ad N et al. Surgical Ablation of Atrial Fibrillation in the United States: Trends and Propensity Matched Outcomes. The Annals of thoracic surgery 2017;104:493-500.
34. Ad N, Barnett S, Lefrak EA et al. Impact of follow-up on the success rate of the cryosurgical maze procedure in patients with rheumatic heart disease and enlarged atria. The Journal of thoracic and cardiovascular surgery 2006;131:1073-9.
35. Gammie JS, Haddad M, Milford-Beland S et al. Atrial fibrillation correction surgery: lessons from the Society of Thoracic Surgeons National Cardiac Database. The Annals of thoracic surgery 2008;85:909-14.
36. Calkins H, Kuck KH, Cappato R et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart rhythm 2012;9:632-696 e21.
37. January CT, Wann LS, Alpert JS et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130:2071-104.
38. Ad N, Cheng DC, Martin J et al. Surgical Ablation for Atrial Fibrillation in Cardiac Surgery: A Consensus Statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2009. Innovations (Philadelphia, Pa) 2010;5:74-83.

39. 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. The Annals of thoracic surgery 2017;103:329-341.
40. Ad N, Henry L, Hunt S, Holmes SD. Do we increase the operative risk by adding the Cox Maze III procedure to aortic valve replacement and coronary artery bypass surgery? The Journal of thoracic and cardiovascular surgery 2012;143:936-44.
41. Ad N, Cox JL. The Maze procedure for the treatment of atrial fibrillation: a minimally invasive approach. Journal of cardiac surgery 2004;19:196-200.
42. Worku B, Pak SW, Cheema F et al. Incidence and predictors of pacemaker placement after surgical ablation for atrial fibrillation. The Annals of thoracic surgery 2011;92:2085-9.
43. Shih T, Paone G, Theurer PF, McDonald D, Shahian DM, Prager RL. The Society of Thoracic Surgeons Adult Cardiac Surgery Database Version 2.73: More Is Better. The Annals of thoracic surgery 2015;100:516-21.
44. Jacobs JP, Shahian DM, He X et al. Penetration, Completeness, and Representativeness of The Society of Thoracic Surgeons Adult Cardiac Surgery Database. The Annals of thoracic surgery 2016;101:33-41; discussion 41.
45. Richardson DB, Laurier D, Schubauer-Berigan MK, Tchetgen Tchetgen E, Cole SR. Assessment and indirect adjustment for confounding by smoking in cohort studies using relative hazards models. Am J Epidemiol 2014;180:933-40.
46. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med 2017;167:268-274.
47. Amorim LD, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. Int J Epidemiol 2015;44:324-33.
48. Schafer JL. Multiple imputation: a primer. Statistical methods in medical research 1999;8:3-15.
49. Schafer JL, Graham JW. Missing data: our view of the state of the art. Psychological methods 2002;7:147-77.
50. Vesin A, Azoulay E, Ruckly S et al. Reporting and handling missing values in clinical studies in intensive care units. Intensive care medicine 2013;39:1396-404.
51. Vickers AJ, Altman DG. Statistics notes: missing outcomes in randomised trials. BMJ (Clinical research ed) 2013;346:f3438.