Thromboembolisms related to postoperative electrical cardioversions for atrial fibrillation in patients undergoing surgical aortic valve replacement

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Short Title: Cardioversion for postoperative AF

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Abstract

Aims: Postoperative atrial fibrillation (POAF) is a frequent complication after cardiac surgery, and cardioversions (CV) are commonly performed to restore sinus rhythm. However, little data exists on thromboembolic risk related to early postoperative CV and on the recurrence of POAF after CV. CAREAVR study sought to assess the rate of strokes, transient ischemic attacks (TIA) and mortality shortly after POAF-triggered CV in patients who underwent isolated surgical aortic valve replacement (SAVR) with a bioprosthesis.

Methods and Results: Altogether 721 patients underwent isolated SAVR with a bioprosthesis at four Finnish university hospitals. During postoperative hospitalization, after patients with prior chronic AF were excluded, 309/634 (48.7%) of patients had at least one episode of POAF (median time [IQR] 3 [3] days), and an electrical CV was performed in 113/309 (36.6%) of them. The length of hospital stay was not affected by CV. At 30 days follow-up, the rate of stroke, TIA or mortality was higher in those AF patients who underwent CV vs. those who did not (9.7% vs. 3.6%, p=0.04, respectively; adjusted HR 2.63, 95%-CI 1.00-6.92, p=0.05). Similar proportion of patients in both groups were in AF rhythm at discharge (32.7% vs. 35.7%, p=0.18); and at 3 months (25.0% vs 23.6%, p=0.40), respectively.

Conclusion: In this real-world population of patients undergoing isolated SAVR, the rate of POAF was nearly 50%. One third of these patients underwent an electrical CV, and they exhibited over two-fold risk for thromboembolisms and mortality. CV did not affect the short-term prevalence of AF.

Keywords: Aortic valve replacement, atrial fibrillation, cardioversion, postoperative, stroke

Introduction

New-onset postoperative atrial fibrillation (POAF) is a complication after cardiac cardiac surgery that affects 20 to 50% of patients (1,2). POAF is associated with a variety of adverse consequences, including prolonged hospitalization, increased rates of complications and mortality, and increased costs (1,2). POAF is often considered a temporary, surgery-associated phenomenon and, therefore, rhythm control– using antiarrhythmic agents and/or on-demand electrical cardioversion (CV) – is a frequently used strategy. Early postoperative CV for POAF is performed to achieve better hemodynamic status, to maintain sinus rhythm in the long term, and to reduce the risk of thromboembolic complications. A recent study of cardiac surgery patients showed that, after 60-day follow-up, postoperative rhythm control therapy combining amiodarone and on-demand cardioversions (CV) was non-inferior when compared to rate-control therapy in terms of hospitalization length and recurrence rate of AF (3). Nevertheless, CV is known to be associated with a temporary increase in stroke risk. Although the risk is less than 1% in patients with adequate anticoagulation in an elective setting or after CV for acute AF (4-8), the thromboembolic risk associated with CV performed for POAF after cardiac surgery remains unknown. Moreover, little is known about the usefulness of the CV strategy in maintaining sinus rhythm after cardiac surgery in real-life practice.

The CAREAVR study sought to assess the rate of POAF and thromboembolisms in patients undergoing an isolated surgical aortic valve bioprosthesis (SAVR) operation. In this pre-specified analysis, short-term thromboembolic risk and the recurrence of AF were assessed via follow-up among POAF patients who underwent early CV vs. those who did not.

Methods

The CAREAVR is a Finnish multicenter retrospective registry (ClinicalTrials.gov Identifier: NCT02626871) assessing the incidence of AF, thromboembolic complications, and bleeding events

in patients who have undergone isolated SAVR with a bioprosthesis. This study is part of a broader ongoing protocol in Finland to evaluate the thromboembolic and bleeding complications of AF (7-9).

Patient data was reviewed at four Finnish university hospitals (Helsinki, Turku, Oulu, and Kuopio) that performed cardiac surgery over the period 2002-2014 (in Helsinki 2006-2014). Hospital records were reviewed for patients who had undergone cardiac surgery for isolated SAVR with a biological prosthesis. Patients with concomitant coronary bypass, maze procedure, surgery of the ascending aorta or other valve surgery were excluded. In order to obtain reliable and accurate follow-up data, only patients from the hospitals' catchment areas were included in this study. Patient records were individually reviewed with a standardized structured data-collection protocol for preoperative and perioperative data, discharge data, and long-term follow-up events, including POAF, stroke, bleeding, and mortality.

During the period under study, the routine anticoagulation practice in SAVR patients at the study hospitals was enoxaparin 40mg once-a-day subcutaneously started on the evening of the day of surgery and continued until vitamin K antagonist (VKA) treatment (started on the first postoperative day) reached the therapeutic level (INR≥2.0) irrespective of whether patient had POAF or not. Low dose of enoxaparin was used due to presumed high bleeding risk shortly after operation.

The endpoints of the study included the first occurrence of any of 1) a composite of stroke, transient ischemic attack (TIA) or mortality at 30 days; 2) stroke, TIA, or peripheral arterial embolism; 3) mortality, either in-hospital after the index operation or during follow-up after hospital discharge. Strokes were classified using TOAST criteria. For CV-related stroke/TIA event following additional criteria were used: 1) strokes/TIAs diagnosed on the operation date were excluded; and 2) AF diagnosis was objectively documented prior to stroke/TIA.

The diagnosis of POAF was always confirmed by a 12-lead ECG recording, or telemonitoring indicating AF episode of 10 min or longer. An ischemic stroke was defined as a permanent focal neurological deficit adjudicated by a neurologist and confirmed via computed tomography or magnetic resonance imaging. TIA was defined as a transient (<24 hours) focal neurological deficit adjudicated by a neurologist. If stroke was clinically diagnosed during index hospitalization by the treating physician and confirmed by computed tomography or magnetic resonance imaging, a separate adjudication by a neurologist was not required. Thus, only ischemic strokes and TIAs considered definite by the treating neurologist or physician were included in the present study.

An independent, certified third-party data monitor checked the integrity of the data for each study site.

The study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. Because of the retrospective, registry-based nature of the study, informed consent was not required. The study conforms to the Declaration of Helsinki.

Statistical analyses were conducted with SPSS software (version 21.0, SPSS, Inc., Chicago, Illinois). Continuous variables were reported as mean ± standard deviation if normally distributed, and as median [inter-quartile range (IQR)] if they were skewed unless stated otherwise. The data were tested for normal distribution using Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the two study groups were performed using an unpaired t-test or Mann-Whitney test for continuous variables, and a Pearson χ^2 or Fisher's exact test for categorical variables, as appropriate. Logistic regression analysis was used to identify the independent predictors of strokes at 14 days postoperative follow-up and AF recurrence during long-term

follow-up. Two-sided differences were considered significant if the null hypothesis could be rejected at a probability level of 0.05.

Results

A total of 721 patients underwent isolated SAVR with a bioprosthesis at the four hospitals. Of these patients, 87/721 (12.1%) presented with chronic AF, while 96/721 (13.3%) had a history of paroxysmal AF prior to the index operation. During postoperative hospitalization, when patients with prior chronic AF were excluded, a total of 309/634 (48.7%) of patients had at least one POAF episode. The median time to in-hospital POAF was 3 [3] days.

Early postoperative electrical CV was performed in 113/309 (36.6%) of patients with in-hospital POAF. The baseline characteristics of patients who underwent early electrical CV for POAF vs. those who did not are presented in Table 1. There were no significant baseline differences between the groups, except that patients undergoing early electrical CV more frequently had a history of congestive heart failure and slightly higher estimated risk of stroke according to their CHA_2DS_2-VASc score, whereas the rate of chronic pulmonary disease was lower. Importantly, a history of prior paroxysmal AF and echocardiography-derived diameter of the left atrium were comparable between the groups. In a multivariate logistic regression model including age, diabetes, hypertension, prior congestive heart failure, coronary artery disease, prior AF and female gender only prior congestive heart failure remained an independent predictor of POAF triggered CV.

For the assessment of CV-related thromboembolisms at two weeks, stroke/TIA diagnosed on the day of operation and those diagnosed prior to POAF episode were excluded. At two-week follow-up in patients with POAF, the incidence of stroke/TIAs was (3.5% vs. 0.5%, p=0.06) in patients who underwent early CV vs. those who did not, respectively. For comparison, the incidence of two-week stroke was 1.5% and TIA 0.3% in patients without POAF.

Kaplan-Meier estimates for a freedom of a composite of stroke, TIA or mortality at 30 days are presented in Figure 1. Peri- and postoperative outcomes are depicted in Table 2. A composite of stroke, TIA or mortality at 30 days was more frequent in patients with CV compared to those without CV (9.7% vs. 3.6%, p=0.04, respectively). In age- and sex-adjusted Cox regression model, CV was associated with an increased risk of a composite of stroke, TIA or mortality rate at 30 days (HR 2.63, 95%-CI 1.00-6.92, p=0.05). Only one site routinely used CV to treat POAF in patients who were in AF on morning rounds. It appeared that the site had the highest incidence of events. For comparison, incidence of a composite of stroke, TIA and mortality was 14/300 (4.6%) in patients without post-operative AF.

No difference was observed in the length of hospital stay for CV patients compared to those who did not undergo CV. Similarly, the prevalence of patients in AF rhythm was comparable at discharge (32.7% vs. 35.7%, p=0.18); and at 3 months (25.0% vs 23.6%, p=0.40), respectively.

Discussion

The main novel finding of this study was the high incidence of postoperative thromboembolic complications and mortality in patients undergoing electrical CV for POAF after SAVR with a bioprosthesis. Patients with an electrical CV had more than two-fold risk for stroke/TIA/mortality within 30 days from the operation compared to those who did not undergo CV. AF recurrence rates at discharge and at 3 months follow-up were independent of whether in-hospital electrical CV was performed.

These findings have important clinical implications. First, if an electrical CV is performed early after cardiac surgery, an adequate anticoagulation therapy – as recommended for the management of acute and elective CV of AF (10) – is needed. Enoxaparin in prophylactic doses in combination with VKA initiation did not appear to be effective enough to prevent thromboembolic complications in our study, despite the fact that the duration of the AF episode was

considered short (always <48h, in most cases <12h). In fact, more than half of the early strokes/TIAs after electrical CVs occurred when patients were on prophylactic low molecular weight heparin (LMWH) and VKA therapy. In the early postoperative period, patients are in a prothrombotic state related to major surgery, immobilization, and swelling caused by fluid retention (1,2). In addition, the initiation of VKA therapy is also known to suppress proteins C and S levels, and thus, temporarily increase the risk of thromboembolic complications. Therefore, it seems clear that more efficacious means of preventing thromboembolic complications are needed in this clinical setting. Whether more efficacious prevention can be achieved through more effective anticoagulation such as higher-dose LMWH or non-vitamin K oral anticoagulants, or additional antiplatelet therapy, or surgical exclusion of the left atrial appendage remains to be studied in prospective randomized trials.

Second, the decision on whether or not to perform CV in the early postoperative period needs to be thoroughly weighed between the potential benefits of resuming sinus rhythm vs. the risk of adverse thromboembolic complications related to the CV procedure. Rhythm control and on-demand CV for in-hospital POAF are often performed because of the presumed higher thromboembolic risk of a prolonged AF episode. Based on findings of this study, however, this presumption would not appear to be valid in patients undergoing SAVR operation with a bioprosthesis. A randomized trial of rhythm control achieved through amiodarone combined with on-demand CV vs. rate control for new-onset AF after cardiac surgery showed no benefit over to the rhythm control strategy: days of hospitalization, rates of persistent AF 60 days after the onset, and complication rates were equal between both groups (3). As compared with our study, the low incidence and absence of differences in cerebrovascular events between the groups in the trial by Gillinov et al. (3) may be explained by differences in the baseline characteristics such as inclusion of patients undergoing isolated coronary artery bypass grafting, lower estimated stroke risk as well as in the method of cardioversion and some differences in the analysis of the follow-up data.

Another indication for CV in these patients is to achieve better hemodynamic status and earlier discharge. Nevertheless, in our study, hospitalization length was similar in patients who underwent CV compared to those who did not.

Third, thrombus formation in the left atrial appendage is usually responsible for the thromboembolic complications of AF. The local changes promoting thrombus formation start early after the onset of an AF episode. Platelet activation and increased thrombin generation in the left atrium are measurable as early as 15 minutes following induction of AF (11), and profound activation of platelets and coagulation factors has been observed within 12 hours of AF (12). CV of AF is associated with an increased risk of stroke and systemic embolism (4-8,13). Thus, most embolic events in patients with AF occur after successful CV of AF, and within one week from the procedure. In earlier studies, when CV was performed without anticoagulation, the periprocedural risk ranged from 3% to 7% (4,6). Later, thanks to effective anticoagulation therapy, the risk of thromboembolic complications after elective CV of AF reduced below 0.5% (14-17). As a comparison, the long-term thromboembolic risk of AF is approximately 0.3% per month, depending on stroke risk factors, and long-term use of oral anticoagulation decreases this risk to 0.1% to 0.2% per month (18). Moreover, it is possible that cardioembolism originates from another source than left atrial appendage such as from the valve sewing ring before complete endothelialisation occurs. Theoretically, electrical CV could dislodge a thrombus attached to the valve sewing ring. Irrespective of the exact source of cardioembolism, however, the 3.5% thromboembolic risk within a 2 weeks period after electrical CV of POAF in the present data exceeds the “acceptable” risk five- to ten-fold.

Although the baseline characteristics of patients who underwent CV vs. those who did not were generally comparable, some differences merit consideration. The CHA_2DS_2-VASc score was slightly higher in patients who underwent CV, and these patients more often had a history of congestive heart failure compared to those who did not undergo CV. Nevertheless, this small

difference in estimated thromboembolic risk is highly unlikely to explain the large difference in the two-week stroke/TIA rates. Patients who underwent CV had also more frequent and sooner recurrences of AF than patients who did not undergo CV. It is possible that this is due to a more advanced disease burden that cannot be gauged using clinical measures.

We chose to include mortality in the composite endpoint of stroke, TIA and mortality because thromboembolic events may result in sudden death. Moreover, the additional two-week period for CV-associated thromboembolism detection was chosen for two reasons. First, based on our previous findings, > 80% thromboembolisms after CV occur within one week and > 90% within two weeks of CV (7,13). Second, patients undergoing a SAVR with a bioprosthesis are prone to postoperative stroke, and using the two-week criteria made it possible to reduce confounding related to competitive causes of thromboembolisms in this patient group, such as thromboembolisms from the valve bioprosthesis or from the aorta. To secure recognition of all major adverse events, such as strokes, TIAs, and major bleeds, only patients living in the hospitals' catchment areas were included in the registry.

Methodologically, this study has several strengths. A validated, structured case report form was used at all study sites. As a quality control, a professional third party monitored the integrity of the data. Moreover, to the authors' knowledge, this is the largest existing study assessing the safety of early postoperative electrical CV after open-heart surgery. Patients with adjunct surgical procedures such as coronary bypass, left atrial appendage occlusion, mace and pulmonary vein isolation were excluded, and therefore, study population represent relatively homogenous sample of patients undergoing isolated SAVR with a bioprosthesis from four out of five Finnish hospitals performing these operations over ten years enrollment period.

The main limitation of this study is the retrospective nature of data. The decision of rhythm control strategy was at the treating physicians' discretion, and clinical factors not assessed in the case report form may partly account for these decisions. It is also possible that patients who

have fluctuating rhythm between sinus rhythm and AF are more likely to be candidates for CV compared to those with only short episodes of AF or those who remain hemodynamically stable in AF. Patients treated with CV may, therefore, have a higher AF burden. Moreover, enoxaparin was used in prophylactic doses instead of full doses because of the presumed high bleeding risk early after surgery and concomitant VKA initiation. Finally, the number of adverse events was relatively low, but it has been low also in prospective trials such as ENSURE-AF and X-VERT assessing the efficacy of non-vitamin K antagonist vs. warfarin in patients undergoing elective CV of AF (19,20).

Conclusions

In this real-world population of patients without chronic AF undergoing aortic valve replacement with a bioprosthesis, the incidence of in-hospital POAF was nearly 50%. One third of these POAF patients underwent CV, and those who did had more than two-fold risk for thromboembolism or mortality shortly after surgery. The short-term prevalence of AF was not affected by CV.

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Table 1. Baseline characteristics and operative data of patients with new-onset postoperative AF who underwent cardioversion vs. those who did not.

	CV ***(n=113)***	***No CV*** ***(n=196)***	***p-value***
Age, years			**0.70**
mean (SD)	77 (5.6)	76 (7.0)	
median [range]	77 [55-88]	77 [33-91]	
Logistic Euroscore II	2.5 (2.5)	2.4 (2.6)	**0.78**
CHA_2DS_2-VASc score			**0.03**
mean (SD)	4.5 (1.5)	4.1 (1.4)	
median (range)	4.0 [1-8]	4.0 [0-8]	
Females	73 (65)	121 (62)	**0.63**
Body mass index, $kg*m^2$	28 (4.6)^	28 (4.8)	**0.88**
Preoperative eGFR, mL/min	74 (21)	74 (22)	**0.82**
Treatment for diabetes	19 (17)	38 (20)	**0.65**
Treatment for dyslipidemia	70 (62)	105 (54)	**0.19**
Treatment for hypertension	91 (81)	150 (77)	**0.48**
Congestive heart failure	67 (60)	70 (36)	**<0.001**
Concomitant coronary artery disease	30 (27)	49 (25)	**0.79**
History of paroxysmal atrial fibrillation	17 (15.0)	31 (15.8)	**1.0**
Prior myocardial infarction	8 (7.1)	16 (8.2)	**0.83**
Prior percutaneous coronary intervention	4 (3.5)	7 (3.6)	**0.05**
Prior coronary bypass	3 (2.6)	11 (4.6)	**1.0**
Prior aortic valve operation	1 (0.9)	3 (1.5)	**1.0**

Prior stroke	10 (9.1)	15 (8.0)	**0.83**
Prior transient ischemic attack	10 (9.1)	14 (7.5)	**0.66**
Prior systemic arterial embolism	0	1 (0.5)	**1.0**
Prior pulmonary embolism	2 (1.8)	5 (2.6)	**1.0**
Prior venous thromboembolism	2 (1.8)	9 (4.6)	**0.34**
Extracardiac arteriopathy	6 (5.3)	8 (4.1)	**0.77**
Recent acute myocardial infarction	1 (0.9)	2 (1.0)	**1.0**
Pulmonary artery hypertension	31 (34)	46 (27)	**0.26**
Chronic lung disease	13 (12)	45 (23)	**0.02**
Self-reported alcohol consumption*			**0.35**
Abstinent	43 (84)	57 (79)	
Moderate	6 (12)	7 (10)	
Heavy	2 (3.9)	8 (11)	
Hepatic cirrhosis	0	2 (1.0)	**0.53**
Active smoker ’	4 (4.4)	13 (7.5)	**0.43**
Ex-smoker	15 (18)	35 (21)	**0.62**
Previous intracranial bleed	0	3 (1.5)	**0.30**
Previous gastrointestinal tract bleed	5 (4.4)	11 (5.6)	**0.79**
Previous genitourinary tract bleed	3 (2.7)	1 (0.5)	**0.14**
Preoperative echocardiography			
Left ventricular ejection fraction, %	59 (13)	61 (12)	**0.29**
Left atrial diameter, mm	43 (7.1)´`	42 (6.8)	**0.48**

Aortic valve max gradient, mmHg	85 (23)	80 (22)	**0.06**
Aortic valve mean gradient, mmHg	50 (15)	48 (14)	**0.20**
Severe aortic regurgitation, grade >2/4	13 (12)	15 (7.7)	**0.30**
Preoperative antithrombotic medication			
Warfarin	11 (10)	23 (12)	**0.71**
Low molecular weight heparin	4 (3.6)	11 (5.6)	**0.59**
Non-vitamin K antagonist	0	0	**1.0**
Aspirin	73 (65)	108 (55)	**0.12**
ADP receptor inhibitor	1 (0.9)	5 (2.6)	**0.42**

Continuous variables are reported as median [range] or mean (SD) where appropriate; Categorical variables as count (%); BMI: body mass index; eGFR: estimated glomerular filtration rate using CKD-EPI formula

´ valid n=46%

^ valid n=49%

´` valid n=73%

*moderate consumption=< 21(males) / <14 (females) doses/week; heavy consumption= ≥21(males) / ≥14 (females) doses/week

CHA_2DS_2-VASc score = Congestive heart failure, Hypertension, Age≥65 years, Diabetes, Vascular disease, Female sex 1 point each; Age≥75 years, prior stroke 2 points each.

Table 2. Peri- and postoperative outcomes of patients with new-onset postoperative atrial fibrillation who underwent cardioversion vs. those who did not.

	CV (n=113)	**no CV (n=196)**	**p-value**
Time to AF diagnosis (days)			**0.07**
Mean (SD)	2.7 (2.1)	3.2 (2.4)	
Median [range]	2 [0-13]	3 [0-12]	
In-hospital stay (days)			**0.72**
Mean (SD)	9.9 (4.6)	11 (6.4)	
Median [range]	9 [4-39]	9 [4-42]	
Delayed ventilation	13 (12)	19 (9.8)	**0.70**
Deep wound infection	1 (0.9)	1 (0.5)	**1.0**
Mediastinitis	1 (0.9)	1 (0.5)	**1.0**
Pneumonia	8 (7.1)	10 (5.1)	**0.46**
Acute de novo dialysis	1 (0.9)	4 (2.1)	**0.66**
Re-operation for bleeding	14 (12)	15 (7.7)	**0.22**
AF rhythm at discharge	37 (33)	70 (36)	**0.18**
AF rhythm at 3 months follow up	26 (25)	41 (24)	**0.40**
CV-related stroke or TIA 2 weeks*	4 (3.5)	1 (0.5)	**0.06**
30 days follow up			
Stroke	4 (3.5)	3 (1.5)	**0.26**
TIA	2 (1.8)	0	**0.13**
Stroke or transient ischemic attack	6 (5.3)	3 (1.5)	**0.09**
Mortality	5 (4.4)	4 (2.0)	**0.30**
Mortality, stroke or TIA	11 (9.7)	7 (3.6)	**0.04**

Continuous variables are reported as median [range] or mean (SD) where appropriate; categorical variables as count (%). CV, Cardioversion; TIA, Transient ischemic attack; *Events at day 0 and those occurring prior to AF excluded.

Table 3. Detailed patient characteristics of patients with new-onset postoperative AF and stroke/TIA postoperatively at two-week follow-up. Patients with stroke/TIA diagnosed prior to new-onset AF are excluded.

No.	Age	Sex	CHA_2DS_2-VASc	LVEF (%) prior to operation	Left atrial diameter (mm)	Day of CV after operation	Stroke/TIA after operation	Event	INR at the time of event
CARDIOVERSION									
1	71	F	4	43	52	1	2	TIA	N/A
2	75	F	5	66	40	2	8	TIA	1.6
3	80	F	5	70	47	1	1	Stroke	1.3
4	77	M	7	60	N/A	2	7	Stroke	3.3
NO CARDIOVERSION									
1	84	F	6	65	41	N/A	5	Stroke	3.3

CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes mellitus, and prior Stroke, transient ischemic attack or thromboembolism (doubled), Vascular disease, Age 65 to 74, Sex category (female, unless < 65 years and no other risk factors); LVEF=left ventricular ejection fraction; TIA = transient ischemic attack; CV = cardioversion; F = female; M = male; INR=international normalized ratio.

Figure legend.

Figure 1. Kaplan-Meier estimates for freedom from a composite of stroke, TIA or mortality at 30 days.