New-onset postoperative atrial fibrillation after aortic valve replacement: Effect on long-term survival

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ABSTRACT

Objective: There is a paucity of data on long-term survival of new-onset postoperative atrial fibrillation (POAF) after cardiac surgery. Also, mean follow-up in previous studies is confined to a maximum of one decade. This retrospective, longitudinal cohort study was performed to determine the effect on long-term survival of new-onset POAF after aortic valve replacement (AVR) over a mean follow-up of almost 2 decades.

Methods: Kaplan-Meier survival analysis was used to determine long-term survival after AVR, performed between January 1, 1990, and January 1, 1994, in 569 consecutive patients without a history of atrial fibrillation, divided into 241 patients (42.4%) with and 328 patients (57.6%) without new-onset POAF. New-onset POAF was considered in multivariable analysis for decreased long-term survival. After AVR, patients with new-onset POAF were treated with the aim to restore sinus rhythm within 24 to 48 hours from onset by medication and when medication failed by direct-current cardioversion before discharge home.

Results: Mean follow-up after AVR was 17.8 ± 1.9 years. Incidence of new-onset POAF was 42.4%. Kaplan-Meier overall cumulative survival rates at 15 years of follow-up were similar in the patients with new-onset POAF versus those without: 41.5% (95% confidence interval [CI], 35.2-47.7) versus 41.3% (95% CI, 36.0-46.7), respectively. New-onset POAF was not an independent risk factor for decreased long-term survival (hazard ratio 0.815; 95% CI, 0.663-1.001; $P = .052$).

Conclusions: New-onset POAF after AVR does not affect long-term survival when treatment is aimed to restore sinus rhythm before discharge home. (J Thorac Cardiovasc Surg 2017;154:492-8)

New-onset postoperative atrial fibrillation does not affect long-term survival.

Central Message

New-onset postoperative atrial fibrillation does not affect long-term survival when treatment is aimed to restore sinus rhythm before discharge home.

Perspective

New-onset postoperative atrial fibrillation after aortic valve replacement does not affect long-term survival when treatment is aimed to restore sinus rhythm before discharge home. Future studies with a prospective randomized design should be done to confirm this finding in patients undergoing different kinds of cardiac surgery.

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Postoperative atrial fibrillation (POAF) after cardiac surgery is common and affects 10% to 40% of patients undergoing coronary artery bypass grafting (CABG) and more than 50% of patients undergoing valve surgery.¹ Although its

effect on long-term survival remains unclear, POAF is associated with decreased 30-day survival.^{2,3} Regarding new-onset POAF, that is, POAF in patients without a history of atrial fibrillation (AF), the literature is sparse. Recently, incidence rates of new-onset POAF after isolated aortic valve replacement (AVR) or CABG with concomitant AVR were 28% and 39%, respectively.⁴ New-onset POAF appeared

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Scanning this QR code will take you to a supplemental video for the article.

Abbreviations and Acronyms

AF	= atrial fibrillation
AVR	= aortic valve replacement
CABG	= coronary artery bypass grafting
POAF	= postoperative atrial fibrillation

to affect both mental and physical health 6 months after CABG.⁵ In some studies, new-onset POAF was associated with decreased 30-day survival after cardiac surgery.^{6,7} However, in other studies it was not.^{8,9} In most studies, new-onset POAF affected long-term survival after cardiac surgery.¹⁰⁻¹³ However, in these studies, mostly patients undergoing CABG, not valve surgery, were included. Also, mean follow-up was confined to one decade. In one study, new-onset POAF affected long-term survival after CABG, but not after isolated valve or combined valve-CABG procedures.¹⁴ However, mean follow-up was confined to almost 8 years. Recently, new-onset POAF did not affect long-term survival after cardiac surgery.¹⁵ However, mean follow-up was confined to almost one decade. We aimed to determine the effect on long-term survival of new-onset POAF after AVR over a mean follow-up of almost 2 decades.

MATERIALS AND METHODS

In this retrospective longitudinal cohort study, 569 consecutive patients without a history of AF were followed for a mean of 17.8 ± 1.9 years after AVR with or without concomitant CABG, performed between January 1, 1990, and January 1, 1994 (Video 1). Thirty-day and long-term survival rates were determined in 2 subgroups: 241 patients (42.4%) with and 328 patients (57.6%) without new-onset POAF. New-onset POAF was defined as electrocardiographically documented AF lasting for at least several hours, occurring after AVR when the patient was still admitted,

and affecting only patients without a history of AF. Standard therapy to prevent new-onset POAF was prescribing sotalol in patients who were not on beta-blocker therapy before AVR or calcium-antagonists in patients with chronic obstructive pulmonary disease the day after AVR. Patients who were on beta-blocker therapy before AVR were maintained on beta-blocker therapy, which was continued after they were discharged home. Treatment of new-onset POAF was aimed to restore sinus rhythm within 24 to 48 hours from onset by the use of medication, mostly by temporarily prescribing a greater dose of sotalol or a beta-blocker or by temporarily adding digoxin to beta-blocker or calcium-antagonist therapy. When medication failed to restore sinus rhythm within 24 to 48 hours from onset, direct-current cardioversion before discharge was performed. Patients still in AF at discharge underwent direct-current cardioversion within 6 weeks from discharge. Irrespective of the occurrence of new-onset POAF, oral anticoagulants were prescribed in all patients from the day after AVR, for life in case of mechanical AVR and for 3 months in case of biologic AVR. Follow-up data were obtained from our own or referring cardiology departments, general practitioners, and telephone calls to patients and relatives. The study object was agreed on by the Committee on Ethics and Medical Experiments of the St Antonius Hospital, Nieuwegein, The Netherlands. Funding agencies did not play a role in data interpretation.

Definitions of Baseline Characteristics

Baseline characteristics were defined as follows. Recent or old myocardial infarction was defined as myocardial infarction occurring ≤ 6 weeks or > 6 weeks before operation, respectively. Peripheral arterial disease was defined as claudication or surgical or percutaneous intervention on the peripheral arteries, excluding carotid disease. Hypertension was defined as blood pressure $> 140/90$ mm Hg or the use of antihypertensive medication. Severe pulmonary hypertension was defined as mean invasive pulmonary artery pressure > 40 mm Hg. Chronic lung disease was defined as chronic obstructive pulmonary disease, asthma, or pulmonary fibrosis. Normal, moderate, or poor left ventricular function was defined as left ventricular ejection fraction ≥ 50 , ≥ 30 – < 50 %, or < 30 %, respectively (on echocardiography). No, mild/moderate, or severe left ventricular hypertrophy was defined as interventricular septal thickness of < 11 mm, 11 to 15 mm, or > 15 mm, respectively (on echocardiography).

Definitions of Adverse Events

Adverse events were defined as follows. Transient ischemic attack was defined as focal neurologic deficit of sudden onset as diagnosed by a neurologist, lasting < 24 hours with fully reversible symptoms. Ischemic stroke was defined as focal neurologic deficit of sudden onset as diagnosed by a neurologist, lasting > 24 hours and caused by cerebral ischemia. Hemorrhagic stroke was defined as focal neurologic deficit of sudden onset as diagnosed by a neurologist, lasting > 24 hours and caused by cerebral bleeding. Peripheral thromboembolism was defined as arterial thromboembolism to the viscera or extremities, excluding septic embolism. Minor bleeding was defined as bleeding not requiring admission or blood transfusion. Major bleeding was defined as fatal or nonfatal bleeding requiring admission or blood transfusion, excluding hemorrhagic stroke.

Statistics

Calculation of long-term survival was performed by Kaplan-Meier analysis. Identification of independent risk factors for decreased long-term survival was performed by Cox multiple regression analysis (forward stepwise technique). Death was not formally considered a competing risk but was treated as end of follow-up (ie, censor). Binary variables were labeled as yes versus no or missing. Missing data on categorical variables were categorized automatically into the lowest risk category. Continuous and dichotomous variables were analyzed with the Student *t* or Mann-Whitney *U* tests and χ^2 tests, respectively. Two-sided tests of significance are reported, and *P* values $< .05$ were considered statistically significant. Data were analyzed by SPSS version 20 for Windows (IBM Corp, Armonk, NY).

VIDEO 1. Aortic valve replacement procedure, shown from cannulation until chest closure. Because of permanent atrial fibrillation (unlike the study patients), an atrial clip also was placed. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)30414-2/addons](http://www.jtcvsonline.org/article/S0022-5223(17)30414-2/addons).

Variables Considered in Multivariable Analysis

Variables considered in multivariable analysis for decreased long-term survival were a priori based on previous research and included age (continuous variable), sex, previous CABG, hypertension, moderate or severe left ventricular hypertrophy, chronic lung disease, previous ischemic stroke, peripheral arterial disease, insulin- or noninsulin-dependent diabetes, body mass index <20 or ≥ 30 , predominant aortic stenosis or regurgitation, biologic or mechanical AVR, moderate or poor left ventricular function, concomitant CABG, recent or old myocardial infarction, serum creatinine (continuous variable), severe pulmonary hypertension, and new-onset POAF.¹⁶⁻¹⁸

RESULTS

Baseline Characteristics

Table 1 shows baseline characteristics of the patients with new-onset POAF versus those without. There were no significant differences between the 2 subgroups, except the incidence of severe left ventricular hypertrophy, which was lower in the patients with new-onset POAF versus those without (23.7% vs 32.0%, $P = .031$).

Operative Characteristics, Postoperative In-Hospital Adverse Events, and Postoperative Hospital Lengths of Stay

Table 2 shows operative characteristics, postoperative in-hospital adverse events, and postoperative hospital lengths of stay until discharge home in the patients with new-onset POAF versus those without. There were no significant differences between the 2 subgroups, except mechanical ventilation time, which was longer in the patients with new-onset POAF.

Incidence of New-Onset POAF

Incidence rates of new-onset POAF after isolated AVR and after AVR with concomitant CABG were 40.6% (165 of 406 patients) and 46.6% (76 of 163 patients), respectively. The incidence of new-onset POAF in the total study population was 42.4% (241 of 569 patients).

Follow-up

Mean follow-up was 17.8 ± 1.9 years. Follow-up was complete in all patients, except in one patient, who was lost to follow-up 18 months after AVR because of emigration. All other patients, including the 7 patients (2.9%) with new-onset POAF who were still in AF at discharge, were followed for at least 15 years after AVR or until death.

Thirty-Day Survival

Thirty-day mortality in the patients with new-onset POAF was 1.2% (3 of 241 patients), versus 2.7% (9 of 328 patients) in those without ($P = .25$).

Long-Term Survival

During a mean follow-up of 17.8 ± 1.9 years, a total of 169 of 241 patients (70.1%) with new-onset POAF and 231 of 328 patients (70.4%) without new-onset POAF

died. Causes of death were cardiac related in 37.3% of patients with new-onset POAF versus 32.5% in those without ($P = .339$). Kaplan-Meier overall cumulative survival curves of the patients with new-onset POAF versus those without are shown in Figure 1. There was no statistically significant difference between the 2 survival curves (log-rank: $P = .6$). Kaplan-Meier overall cumulative survival rates at 15 years of follow-up in the patients with new-onset POAF versus those without were similar: 41.5% (95% CI, 35.2-47.7) versus 41.3% (95% CI, 36.0-46.7), respectively.

Because the Kaplan-Meier survival graph indicated an early high hazard phase merging into a phase of lower risk, we segmented the follow-up time for each patient in slices of 1 year and did a Cox proportional hazards analysis with new-onset POAF as risk factor together with the interaction term “new-onset POAF” and start time of the interval (relative to the day of surgery). The P value for the interaction term was .19, indicating that the effect of new-onset POAF on long-term survival was not statistically significant and remained stable over time.

Independent risk factors for decreased long-term survival are depicted in Table 3. These were, in order of decreasing significance: previous CABG, poor or moderate left ventricular function, peripheral arterial disease, insulin- or noninsulin-dependent diabetes, greater age, and a greater serum creatinine. New-onset POAF was not an independent risk factor for decreased long-term survival (hazard ratio 0.815; 95% CI, 0.663-1.001; $P = .052$).

In the subgroups of male versus female patients, patients older than versus younger than 65 years of age, and patients with isolated AVR versus AVR with concomitant CABG, new-onset POAF was not an independent risk factor for decreased long-term survival because the P values for effect modification of new-onset POAF and these variables were .73, .78, and .09, respectively.

Long-Term First Adverse Events

Table 4 shows cumulative 18-year probability figures of long-term first adverse events in the patients with new-onset POAF versus those without. Cumulative probability of a first event of (recurrent) AF, transient ischemic attack, ischemic or hemorrhagic stroke, peripheral thromboembolism, or minor or major bleeding at 18 years of follow-up was not significantly different between the 2 subgroups.

DISCUSSION

This study demonstrated that new-onset POAF after AVR did not affect long-term survival when treatment was aimed to restore sinus rhythm within 24 to 48 hours from onset by medication and when medication failed by direct-current cardioversion before discharge home (Figure 2). The mean follow-up of 17.8 ± 1.9 years is, as far as we know, the longest follow-up of new-onset POAF after cardiac

TABLE 1. Baseline characteristics

	New-onset postoperative atrial fibrillation (n = 241)	No new-onset postoperative atrial fibrillation (n = 328)	P value
Age, y	65.4 ± 10.7	64.1 ± 10.9	.158
Male	134 (55.6)	185 (56.4)	.865
Logistic EuroSCORE	4.7 ± 3.8	4.9 ± 5.9	.747
EuroSCORE II	2.2 ± 2.1	2.2 ± 3.0	.995
Society of Thoracic Surgeons Score	1.8 ± 1.3	1.7 ± 1.6	.635
New York Heart Association Class			
I	28 (11.6)	36 (11.0)	.893
II	95 (39.4)	129 (39.3)	1.000
III	96 (39.8)	138 (42.1)	.606
IV	22 (9.1)	25 (7.6)	.540
Concomitant CABG	76 (31.5)	87 (26.5)	.222
Mechanical AVR	149 (61.8)	226 (68.9)	.089
Previous CABG	11 (4.6)	11 (3.4)	.513
Recent myocardial infarction*	5 (2.1)	5 (1.5)	.750
Old myocardial infarction*	28 (11.6)	39 (11.9)	1.000
Previous ischemic stroke	9 (3.7)	11 (3.4)	.821
Peripheral arterial disease*	15 (6.2)	25 (7.6)	.619
Serum creatinine, μmol/L/mg/dL	98.2 ± 59.3/1.1 ± 0.7	94.7 ± 22.9/1.1 ± 0.3	.328
Dialysis	2 (0.8)	0	.179
Hypertension*	126 (52.3)	159 (48.5)	.397
Severe pulmonary hypertension*	9 (3.7)	12 (3.7)	1.000
Unknown	47 (19.5)	87 (26.5)	
Insulin-dependent diabetes	6 (2.5)	10 (3.0)	.801
Noninsulin-dependent diabetes	17 (7.1)	29 (8.8)	.534
Chronic lung disease*	31 (12.9)	35 (10.7)	.430
Predominant aortic stenosis	204 (84.6)	276 (84.1)	.907
Aortic insufficiency†			
No	59 (24.5)	92 (28.0)	.379
Mild	53 (22.0)	84 (26.5)	.231
Moderate	55 (22.8)	63 (19.2)	.291
Severe	53 (22.0)	58 (17.7)	.196
Unknown	21 (8.7)	28 (8.5)	
Peak gradient, mm Hg†	80 ± 31	81 ± 29	.634
Unknown	30 (12.4)	50 (15.2)	
Aortic valve area, cm ² †	0.76 ± 0.30	0.79 ± 0.64	.637
Unknown	129 (53.5)	169 (51.5)	
Left ventricular function*			
Normal	209 (86.7)	277 (84.5)	.473
Moderate	22 (9.1)	36 (11.0)	.488
Poor	10 (4.1)	15 (4.6)	.840
Left ventricular hypertrophy*			
No	104 (43.2)	129 (39.3)	.389
Mild/moderate	80 (33.2)	94 (28.7)	.269
Severe	57 (23.7)	105 (32.0)	.031
Body mass index, kg/m ²	25.7 ± 3.1	25.6 ± 3.4	.579
<20	2 (0.8)	3 (0.9)	1.000
≥20<30	211 (87.6)	290 (88.4)	.794
≥30	28 (11.6)	35 (10.7)	.787

Values are presented as mean ± standard deviation or n (%). EuroSCORE, European System for Cardiac Operative Risk Evaluation; CABG, coronary artery bypass grafting; AVR, aortic valve replacement. *See text for definition. †On echocardiography.

surgery ever, almost twice as long as in the literature. In the present study, new-onset POAF after AVR was not associated with decreased 30-day survival.

Known risk factors for the occurrence of POAF after cardiac surgery include older age, hypertension, a history of AF, congestive heart failure, significant left ventricular

TABLE 2. Operative characteristics, postoperative in-hospital adverse events, and postoperative hospital lengths of stay

	New-onset postoperative atrial fibrillation (n = 241)	No new-onset postoperative atrial fibrillation (n = 328)	P value
Operative characteristics			
Aortic crossclamp time, min, mean $\pm$ SD	74.7 $\pm$ 27.3	74.1 $\pm$ 28.4	.810
Cardiopulmonary bypass time, min, mean $\pm$ SD	109.6 $\pm$ 61.9	107.3 $\pm$ 52.3	.633
Mechanical ventilation time, h, median (IQR)*	18 (13, 22)	16 (11, 20)	.011
Postoperative in-hospital adverse events†			
Inotropic therapy	16 (6.6)	20 (6.1)	.862
Mediastinitis	2 (0.8)	0	.179
Cardiac tamponade	16 (6.6)	17 (5.2)	.473
Myocardial infarction	0	1 (0.3)	1.000
Permanent pacemaker implantation	8 (3.3)	4 (1.2)	.137
Transient ischemic attack	2 (0.8)	1 (0.3)	.577
Ischemic stroke	4 (1.7)	4 (1.2)	.727
Hemorrhagic stroke	0	0	
Major bleeding	2 (0.8)	3 (0.9)	1.000
Postoperative hospital length of stay until discharge			
home, d, median (IQR)*‡			
Range	8-91	8-96	.210

SD, Standard deviation; IQR, interquartile range. *Mann-Whitney *U* test. †Values are presented as *n* (%). ‡Including stay in referring hospital or rehabilitation center, when necessary.

hypertrophy, and possibly prolonged aortic crossclamp and mechanical ventilation times.¹⁹⁻²³ In the present study, these risk factors were not more prevalent in the patients with new-onset POAF versus those without, except mechanical ventilation times, which were longer in the patients with new-onset POAF. The reason for this discrepancy with the literature is possibly the homogeneous group of study patients regarding cardiac history (no history of AF) and kind of cardiac surgery (all AVR, mostly without

concomitant CABG). This finding is in contrast to patients with POAF in the literature, who were mostly patients with or without a history of AF and who mostly underwent CABG, with or without concomitant valve surgery. Possibly, new-onset POAF is in part related to the thoracotomy or cardiopulmonary bypass procedures, because catheter-based AVR recently was associated with a lower incidence of new-onset POAF.²⁴

Based on the similar first adverse event rates in the present study of (recurrent) AF, transient ischemic attack, ischemic or hemorrhagic stroke, peripheral thromboembolism, and minor or major bleeding during long-term

FIGURE 1. Kaplan-Meier overall cumulative survival curves of the patients with new-onset POAF after aortic valve replacement (red line) versus those without (black line), with a mean follow-up of 17.8 $\pm$ 1.9 years. POAF, Postoperative atrial fibrillation.

TABLE 3. Independent risk factors for decreased long-term survival

Risk factor	Hazard ratio	95% Confidence interval	P value
Previous CABG	2.680	1.692-4.244	<.001
Left ventricular function*			.001†
Poor	1.702	1.053-2.750	.030
Moderate	1.651	1.202-2.268	.002
Normal	1.000	Reference	Reference
Peripheral arterial disease	1.572	1.108-2.230	.013
Diabetes			.014‡
Insulin dependent	1.689	0.984-2.899	.057
Noninsulin dependent	1.484	1.050-2.097	.025
No diabetes	1.000	Reference	Reference
Age	1.077‡	1.063-1.091	<.001
Serum creatinine	1.003§	1.001-1.004	.002

CABG, Coronary artery bypass grafting. *See text for definition. †*P* value for more than 2 categorical variables, representing the overall statistical contribution to the model for the variable (the separate *P* values for the variables are to be considered more as measures of precision). ‡Per year. §Per 1.0 μ mol/L/0.011 mg/dL.

TABLE 4. Cumulative probability of long-term first adverse events at 18 years of follow-up

Cumulative probability of long-term first adverse event at 18 y of follow-up (%; 95% confidence interval)	New-onset postoperative atrial fibrillation (n = 241)	No new-onset postoperative atrial fibrillation (n = 328)	P value
(Recurrent) atrial fibrillation	36.7 (27.4-44.9)	35.9 (28.0-43.0)	1.000
Transient ischemic attack	17.8 (10.0-25.0)	15.3 (8.7-21.3)	.843
Ischemic stroke	13.8 (7.9-19.4)	14.7 (8.6-20.4)	.945
Hemorrhagic stroke	10.2 (4.9-15.2)	10.9 (6.3-15.2)	.713
Peripheral thromboembolism	0.0 (0.0-0.0)	1.2 (0.0-2.5)	.311
Minor bleeding	49.2 (39.0-57.7)	48.2 (39.7-55.5)	.994
Major bleeding	39.6 (29.8-48.0)	39.3 (30.8-46.7)	.795

follow-up in the patients with new-onset POAF versus those without, combined with our finding that new-onset POAF did not affect long-term survival, we think that new-onset POAF after AVR can be considered to be a temporary disorder without adverse consequences on the long term. However, this does not imply that new-onset POAF after AVR can be left untreated, because the findings of the present study are based on patients treated with the aim to restore sinus rhythm within 24 to 48 hours from onset by medication and when medication failed by direct-current cardioversion before discharge home. This policy also conforms to the current 2014 American Association for Thoracic Surgery and 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines on new-onset POAF.^{25,26} Striving for sinus rhythm as soon as possible when new-onset POAF occurs also is supported by a recent study that demonstrated that in a porcine model the left atrium underwent significant structural remodeling and decreased contractility after 6 weeks of AF.²⁷

Limitations

A limitation of the present study is that we, because of its retrospective design, did not study patients with different treatment strategies on new-onset POAF. Therefore, we

do not know whether the findings of the present study would still be valid in the event that new-onset POAF was treated in another way than in the present study. Another limitation is that we studied the effect of new-onset POAF only in patients undergoing AVR with or without concomitant CABG, not in patients undergoing isolated CABG or valve surgery other than AVR. A third limitation is the restricted inclusion period (because of limited financing) of 1990 to 1994. However, although more contemporary data would have been very useful to confirm the conclusions of the present study, the restricted inclusion period may have made the study population more homogeneous regarding surgical techniques than it would have been with inclusion right up to date. Also, because of the restricted inclusion period, all study patients were followed for at least 15 years after AVR.

CONCLUSIONS

New-onset POAF after AVR does not affect long-term survival when treatment is aimed to restore sinus rhythm before the patient is discharged home. Future studies with a prospective randomized design should be done to confirm this finding in patients undergoing different kinds of cardiac surgery.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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FIGURE 2. New-onset postoperative atrial fibrillation does not affect long-term survival.

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