Amiodarone Prophylaxis for Atrial Fibrillation after Coronary Bypass—12 Years Follow-Up

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Abstract

Objectives: Postoperative atrial fibrillation (POAF) is a common complication after cardiac surgery and might be avoided with amiodarone prophylaxis. We investigated the long-term effect of prophylactic amiodarone, in patients undergoing isolated, elective coronary artery bypass grafting (CABG), as well as the long-term prognosis of patients with POAF. **Methods:** We retrospectively analysed patients included in the randomized, control trial RASCABG allocated to either placebo or amiodarone as POAF prophylaxis. Several outcomes were evaluated using national databases. Patients were stratified and compared by prophylactic groups and rhythm. Cox proportional hazard analysis was used for multivariable analysis. Kaplan-Meier survival curves were constructed to assess the probability of survival and cumulative incidence curves. **Results:** Prophylactic amiodarone was not related to long-term side effects in comparison to placebo. Patients who developed POAF, were more likely to develop late AF, and had a worse overall survival. There was no difference in the overall survival between prophylactic groups. In the competing risk analysis, amiodarone and POAF was not associated with an increased risk of readmission, but POAF was associated with an increased risk of late AF HR 2.28 [95% CI 1.15; 4.55]. In the multivariable analysis, amiodarone was not associated with late AF, readmission or long-term mortality. Further, no association was found between POAF and late AF, readmission or long-term mortality. **Conclusion:** Amiodarone is a safe drug for the prevention of POAF in the RASCABG-setting. POAF is related to long-term worse prognosis regarding late AF and mortality.

Keywords

Coronary Artery Bypass Grafting, Atrial Fibrillation, Postoperative Care, Pharmacology

1. Introduction

Postoperative atrial fibrillation (POAF) is a common complication following cardiac surgery with a reported incidence of 15% - 80%, depending on patient characteristics, surgical procedure, surveillance methods and definition of atrial fibrillation (AF) [1] [2] [3] [4]. Usually, POAF develops within the first four days after surgery, with a peak incidence on the second postoperative day [1] [2]. Although the majority of events are uncomplicated and self-limiting, POAF has been associated with a significant increase in hospital stay, morbidity and mortality [2] [4] [5] [6] [7]. The underlying pathophysiology and aetiology of POAF remain unclear, although studies have reported causes of a multifactorial nature, involving inflammation, oxidative stress, electrolyte disturbances, atrial dilation, age-related fibroses, pre-existing structural remodelling and increased sympathetic tone postoperatively [1] [3] [4]. Several possible risk factors for POAF has been found including age, male sex, obesity, combination of coronary artery bypass grafting (CABG) and valve surgery or isolated valve surgery, prior AF or arrhythmia, chronic obstructive pulmonary disease (COPD), congestive heart failure, left atrial enlargement and left ventricular dysfunction [1] [2] [3] [4].

Studies have attempted to determine whether antiarrhythmic drugs already being used in the primary treatment of AF, could prevent the risk of POAF [1] [8] [9] [10] [11]. In 2004-2005, the Danish randomized control trial, RASCABG, was conducted, in which 250 patients undergoing elective, solitary CABG were allocated to receive either amiodarone or placebo, as prophylaxis for POAF with a follow-up of 30-days [12]. As hypothesized, patients in the intervention group experienced a significant reduction in risk of AF at 14%, with a number needed to treat at 6.9 [12]. No severe side effects were found during the 30-days follow-up [12]. To our knowledge, no studies have yet investigated the long-term effect or side-effects of amiodarone on POAF following CABG.

Thus, the objectives of this 12-year follow-up study among patients receiving prophylactic amiodarone or placebo was to: Describe differences in baseline characteristics, the frequency of stroke and heart failure, readmission, late AF, long-term all-cause mortality and long-term side effects, and investigate associations between amiodarone and placebo and the risk of readmission, developing late AF, long-term all-cause mortality and cardiovascular mortality. And, among patients developing POAF to describe differences in baseline characteristics, the frequency of stroke and heart failure, readmission, late AF and long-term all-cause mortality, and to investigate the associations between POAF and the risk of readmission, developing late AF, long-term all-cause mortality and cardiovascular mortality.

2. Materials and Methods

2.1. Study Population and Data Extraction

We retrospectively analysed 12-year follow-up data on 250 patients who were included in the randomized control trial, RASCABG [12]. Inclusion criteria of

the original study were elective CABG, age older than 18 years, willingness to be randomized, and provision of informed consent. Exclusion criteria were other types of heart surgery, previous heart surgery, resting heart rate of less than 40 beats/min, atrial-ventricular blockage of any degree, known AF or atrial flutter, hepatic dysfunction (alanine aminotransferase level more than twice the upper normal limit), hyperthyroidism, pregnancy, breast-feeding, or known adverse reactions to amiodarone [12]. No adverse events were found in the primary study. In the current study, we furthermore excluded patients with protocol violation.

2.2. Variables and Definitions

Baseline data were extracted from the original dataset and the Western Denmark Heart Registry [13]. Data on follow-up were obtained from the Danish Register of Causes of Death, the Western Denmark Heart Registry, and the Danish National Patient Registry [13] [14] [15]. Follow-up data included heart failure, late AF, readmission, stroke, long-term side effects and, long-term all-cause mortality and cardiovascular mortality. Unless specified otherwise, heart failure, late AF, readmission and stroke, will be referred to as HARS (Heart failure, late Atrial fibrillation, Readmission and Stroke). Late AF, stroke, heart failure, long-term side effects, long-term all-cause mortality and cardiovascular mortality were evaluated as binary variables defined by diagnostic codes, classified by the ICD-10 classification. Diagnostic codes were clustered into categories e.g. "cancer", and subcategories e.g. "lung cancer", and converted into variables. Diagnostic codes that only occurred once and could not be categorised with others, were excluded. For the variable of late AF, we included diagnostic codes for atrial flutter, AF and unspecified atrial flutter or fibrillation. Late AF was defined as atrial fibrillation during the follow-up period, occurring after the 30. postoperative day. Long-term mortality was divided into all-cause mortality, defined as death of any cause during the follow-up period, and cardiovascular mortality defined as death due to cardiovascular diseases. Readmission was evaluated as the number of patients readmitted during the follow-up period. Time to readmission and AF, were defined as the time interval from the surgery date, to the first readmission and AF during the follow-up period, respectively.

Data access and processing were approved by Danish Data Protection Agency (2017-41-5275) and the Danish Patient Safety Authority (3-3013-2374/1).

2.3. Statistical Methods

Numerical variables were tested for normality of distribution using the Shapiro-Wilk test, and reported as median and quartiles (interquartile range (IQR) from 25th to 75th quartile) or mean and standard deviation (SD). For categorical variables, the number and percentage of subjects in each category was reported. Baseline differences and differences in stroke, heart failure, readmission, late AF, long-term all-cause mortality and long-term side effects among groups were tested using Students t-test or Mann-Whitney U test, for numerical variables, and Pear-

son's χ^2 test of independence or Fischer's exact test for categorical variables.

We analysed prophylactic groups (intervention vs. placebo) and subgroups (POAF vs. sinus rhythm) separately.

Cox multivariable proportional hazard regression analysis, adjusted for potential confounders, was used to investigate the association between 1) amiodarone and readmission, late AF, long-term all-cause mortality and cardiovascular mortality 2) POAF and readmission, late AF, long-term all-cause mortality and cardiovascular mortality. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI).

Kaplan-Meier survival curves were used to estimate long-term all-cause mortality for prophylactic groups and subgroups respectively, during the follow-up period. Survival time was determined from the date of surgery to date of event or 12 years, having survived the follow-up. Differences in mortality rates between prophylactic groups and subgroups were compared using Log-rank test.

The time-to-event data included time to first AF and time to the first readmission from the date of surgery. Cumulative incidence function (CIF) was used in a Fine and Gray Proportional Hazard Regression Model to investigate the time to event data, in the presence of competing events [16].

All p-values are two-tailed, and a p-value < 0.05 was considered as statistically significant. All the data were analysed using Stata Statistical Software 15.0 (StataCorp LLC, College Station, TX).

3. Results

A total of 196 patients from the RASCABG trial [12] were eligible and included in the follow-up study as two patient were lost to follow-up in Figure 1.

3.1. Baseline Characteristics

In the baseline characteristics, triple vessel disease was overrepresented in the amiodarone group, and the number of grafts used per case, as the use of two grafts was more frequent in the placebo group in Table 1. Patients who developed
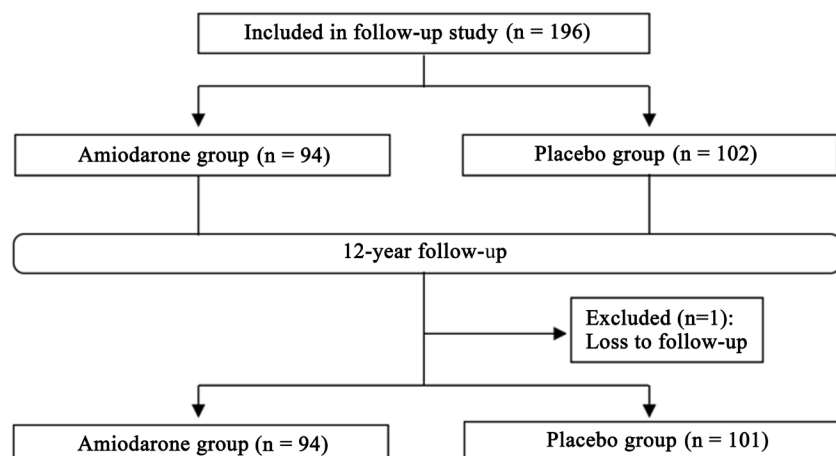

Figure 1. Flowchart of study population.

Table 1. Baseline Characteristics

Characteristics	All	Prophylactic Groups		p-Value*	Subgroups		p-Value*
		Amiodarone	Placebo		POAF	NO POAF	
N (%)	196 (100)	94 (48)	102 (52)	N/A	45 (23)	151 (77)	N/A
Age (median, IQR)	65 (59; 71)	66 (60; 72)	65 (58; 70)	0.605	69 (64; 74)	64 (57; 70)	0.001*
Sex (male, n (%))	166 (85)	83 (88)	83 (81)	0.179	40 (89)	126 (83)	0.373
Current smoker (n (%))	51 (26)	26 (28)	25 (25)	0.616	12 (27)	39 (26)	0.910
Diabetes mellitus (n (%))	48 (25)	23 (25)	25 (25)	0.995	13 (29)	35 (23)	0.434
Hypertension (n (%))	127 (65)	61 (65)	66 (65)	0.978	28 (62)	99 (66)	0.680
Hypercholesterolemia (n (%))	136 (69)	64 (68)	72 (71)	0.704	27 (60)	109 (72)	0.120
Family history of IHD (n (%))	93 (47)	41 (48)	52 (57)	0.238	17 (45)	76 (54)	0.296
History of CNS events (n (%))	46 (24)	21 (23)	25 (28)	0.414	12 (31)	34 (24)	0.413
COPD (n (%))	13 (7)	9 (10)	4 (4)	0.112	6 (13)	7 (5)	0.079
NYHA Class (n (%))							
NYHA Class I	56 (29)	27 (29)	29 (28)	0.964	12 (27)	44 (29)	0.747
NYHA Class II	92 (50)	44 (47)	48 (47)	0.972	17 (38)	75(50)	0.161
NYHA Class III	46 (24)	23 (25)	23 (23)	0.751	15 (33)	31 (21)	0.075
NYHA Class IV	**	**	**	0.498	**	**	0.407
CCS Class (n (%))							
CCS Class I	40 (20)	19 (20)	21 (21)	0.948	13 (29)	27 (18)	0.108
CCS Class II	94 (48)	47 (46)	47 (50)	0.583	17 (38)	77 (51)	0.119
CCS Class III	49 (25)	21 (22)	28 (28)	0.409	12 (27)	37 (25)	0.769
CCS Class IV	13 (7)	7 (7)	6 (6)	0.660	**	10 (7)	1.000
Previous MI (n (%))	93 (47)	45 (48)	48 (47)	0.909	18 (40)	75 (50)	0.254
Previous PCI (n (%))	17 (9)	7 (7)	10 (10)	0.558	**	15 (10)	0.369
Preoperative use of β-blockers (n (%))	170 (87)	81 (86)	89 (87)	0.823	38 (84)	132 (87)	0.606
Preoperative use of statins (n (%))	173 (88)	81 (86)	92 (90)	0.382	38 (84)	135 (89)	0.364
EF (median, IQR)	56 (49; 60)	55 (48; 60)	56 (50; 60)	0.857	56 (45; 60)	57 (50; 60)	0.392
Creatinine (μmol/L) (median, IQR)	88 (75; 99)	89 (75; 99)	87 (76; 99)	0.818	91 (79; 106)	88 (75; 98)	0.106
BMI (mean, SD)	27.52 (4.14)	27.50 (4.06)	27.54 (4.23)	0.943	28.24 (4.37)	27.30 (4.06)	0.184
EuroSCORE I (median, IQR)	2 (1; 4)	3 (1; 4)	2 (1; 4)	0.210	3 (2; 5)	2 (1; 4)	0.009*
Vessels affected (No. (n (%))							
1	**	**	**	0.498	**	**	0.407
2	20 (10)	6 (6)	14 (14)	0.090	6 (13)	14 (9)	0.429
3	174 (89)	88 (94)	86 (84)	0.039*	38 (84)	136 (90)	0.294
Lesion location (n (%))							
Left main stenosis	78 (40)	36 (38)	42 (41)	0.770	26 (58)	52 (34)	0.005*

Continued

LAD	192 (98)	93 (99)	99 (97)	0.622	45 (100)	147 (97)	0.576
RCA	183 (96)	91 (97)	92 (90)	0.063	41 (91)	142 (94)	0.500
CX	188 (96)	91 (97)	97 (95)	0.723	43 (96)	145 (96)	1.000
Peri- and Postoperative Characteristics							
XCL time (minutes) (median, IQR)	46 (35; 59)	47 (37; 59)	46 (32; 57)	0.384	49 (36; 62)	45 (35; 59)	0.279
CPB time (minutes) (median, IQR)	79 (63; 99)	80 (66; 99)	78 (60; 99)	0.611	92 (65; 104)	77 (63; 95)	0.061
Graft per case (No. (n (%)))							
1	**	**	**	1.000	**	**	0.230
2	48 (25)	16 (17)	32 (31)	0.020*	9 (20)	39 (26)	0.425
3	94 (48)	46 (49)	48 (47)	0.793	23 (51)	71 (47)	0.630
4	43 (22)	25 (27)	18 (18)	0.130	11 (24)	32 (21)	0.644
5	10 (5)	7 (7)	**	0.200	**	9 (6)	0.459
Graft usage (n (%))							
LIMA	193 (99)	94 (100)	99 (97)	0.094	45 (100)	148 (98)	1.000
RIMA	7 (4)	4 (4)	**	0.712	**	5 (3)	1.661
Vein graft	184 (94)	89 (95)	95 (93)	0.652	41 (91)	143 (95)	0.476
Radial artery	9 (5)	4 (4)	5 (5)	1.000	**	7 (5)	1.000
Reoperation (n (%))	**	**	**	0.229	**	**	1.000
Postoperative renal dysfunction (n (%))	5 (3)	**	**	1.000	**	**	0.081
Postoperative atrial fibrillation (n (%))	45 (23)	13 (14)	32 (31)	0.004*	45 (23)	N/A	N/A
Postoperative arrhythmia (n (%))	4 (2)	**	**	0.619	**	**	0.552
Postoperative blockage (n (%))	**	**	**	1.000	**	**	1.000
Length of stay in ICU (days) (median, IQR)	1(1; 1)	1 (1; 1)	1 (1; 1)	0.663	1 (1; 1)	1 (1; 1)	0.348
Length of stay in referring department (days) (median, IQR)	6 (5; 8)	6 (5; 8)	6 (5; 7)	0.809	7 (5; 8)	6 (5; 7)	0.004*

POAF = Postoperative atrial fibrillation. IQR = Interquartile range. IHD = Ischemic heart disease. CNS = Central nerve system. COPD = Chronic obstructive pulmonary disease. NYHA = New York Heart Association. CCS = Canadian Cardiovascular Society grading of angina pectoris. MI = Myocardial infarction. PCI = Percutaneous coronary intervention. EF = Ejection fraction (%). BMI = Body Mass Index. LAD = Left anterior descending. CX = Circumflex artery. RCA = Right coronary artery. XCL time = Aortic Cross-clamp time. CPB time = Cardiopulmonary bypass time. LIMA = Left internal mammary artery. RIMA = Right internal mammary artery. ICU = Intensive Care Unit. **Three or fewer cases. * Significant *p*-value < 0.05. N/A = Not applicable.

POAF were older, received placebo, more likely to have higher EuroSCORE, and left main stenosis compared to patients who stayed in sinus rhythm. Further, patients with POAF had a longer stay in referring department.

3.2. Long-Term Side Effects

Potential long-term side effects of amiodarone were evaluated based on registered diagnostic codes as described in the method section. When comparing the subcategories, we found no statistically significant difference between prophylactic groups. Furthermore, no statistically significant difference between prophylactic groups was found, when comparing the uncategorized diagnostic codes.

3.3. HARS and Long-Term Mortality

There were no statistically significant differences between prophylactic groups regarding HARS in Table 2. When comparing subgroups, though, patients who developed POAF, were more likely to develop late AF. None of the other variables of HARS were statistically significant different between subgroups. Among the 195 patients included in the follow-up analysis, 36% died during the 12-year follow-up. Of those, 39% died of cardiovascular diseases and 58% of others causes with no significant differences between the prophylactic groups. Cause of death was not registered in two patients (3%). Patients who developed POAF, had a higher long-term all-cause mortality compared with those who stayed in sinus rhythm in Table 2.

3.4. Factors Associated with Late AF, Readmission and Long-Term Mortality

In both the uni- and multivariable Cox regression analysis, amiodarone was not statistically significant associated with an increased risk of readmission, late AF, long-term all-cause mortality or cardiovascular mortality in Table 3. In the univariable Cox regression analysis POAF was associated with a higher risk of late AF [95% CI 2.28 1.15; 4.56], long-term cardiovascular mortality HR 2.34 [95% CI 1.10; 5.00] and all-cause mortality HR 1.74 [95% CI 1.05; 2.88], although not significant in the adjusted analysis in Table 4. POAF was not associated with a higher risk of readmission in Table 4.

Table 2. Follow-up data on heart failure, late AF, readmission, stroke and long-term all-cause mortality.

	All	Prophylactic Groups		p-Value*	Subgroups		p-Value*
		Amiodarone	Placebo		POAF	NO POAF	
Variables							
Long term all-cause mortality (n (%))	71 (36)	35 (37)	36 (36)	0.818	22 (49)	49 (33)	0.047*
Readmission (n (%))	190 (97)	91 (97)	99 (98)	0.674	44 (98)	146 (97)	1.000
Late AF (n (%))	34 (17)	21 (22)	13 (13)	0.082	13 (29)	21 (14)	0.020*
Stroke (n (%))	25 (13)	12 (12)	13 (14)	0.684	9 (20)	16 (11)	0.100
Heart failure (n (%))	22 (11)	12 (13)	10 (10)	0.527	5 (11)	17 (11)	0.967

POAF = Postoperative atrial fibrillation. AF = Atrial fibrillation. *Significant p-value < 0.05.

Table 3. Unadjusted and adjusted Cox Proportional Hazard Regression Models Association between amiodarone and readmission, late AF, long-term cardiovascular mortality and all-cause mortality.

	Readmission		Late AF		Long-Term Cardiovascular Mortality		Long-Term All-Cause Mortality	
	Univariable HR (95% CI)	Multivariable[a] HR (95% CI)	Univariable HR (95% CI)	Multivariable[b] HR (95% CI)	Univariable HR (95% CI)	Multivariable[c] HR (95% CI)	Univariable HR (95% CI)	Multivariable[a] HR (95% CI)
Amiodarone	0.97 (0.73; 1.29)	0.94 (0.69; 1.26)	1.80 (0.90; 3.59)	2.01 (0.99; 4.11)	1.07 (0.51; 2.43)	1.30 (0.61; 2.78)	1.06 (0.67; 1.69)	0.96 (0.59; 1.55)

HR = Hazard ratio. CI = Confidence interval. POAF = Postoperative atrial fibrillation. AF = Atrial fibrillation. [a]Adjusted for age, POAF and Vessels affected 3; [b]Adjusted for age and POAF; [c] Adjusted for POAF.

3.5. Long-Term Survival

Despite non-violation of proportional hazard assumption, the survival curves for the prophylactic groups crossed more than once in Figure 2(a).

Table 4. Unadjusted and Adjusted Cox Proportional Hazard Regression Models Association between POAF and readmission, late AF, long-term cardiovascular mortality and all-cause mortality

	Readmission		Late AF		Long-Term Cardiovascular Mortality		Long Term All-Cause Mortality	
	Univariable HR (95% CI)	Multivariable[a] HR (95% CI)	Univariable HR (95% CI)	Multivariable[b] HR (95% CI)	Univariable HR (95% CI)	Multivariable[c] HR (95% CI)	Univariable HR (95% CI)	Multivariable[a] HR (95% CI)
POAF	0.81 (0.58; 1.14)	0.78 (0.54; 1.12)	2.28 (1.15; 4.56)	1.60 (0.79; 3.25)	2.34 (1.10; 5.00)	1.62 (0.75; 3.51)	1.74 (1.05; 2.88)	1.17 (0.67; 2.04)

HR = Hazard ratio. CI = Confidence interval. POAF = Postoperative atrial fibrillation. AF = Atrial fibrillation. [a]Adjusted for age, EuroSCORE, Left main stenosis, and Length of stay in referring department; [b]Adjusted for age, EuroSCORE; [c]Adjusted for age.
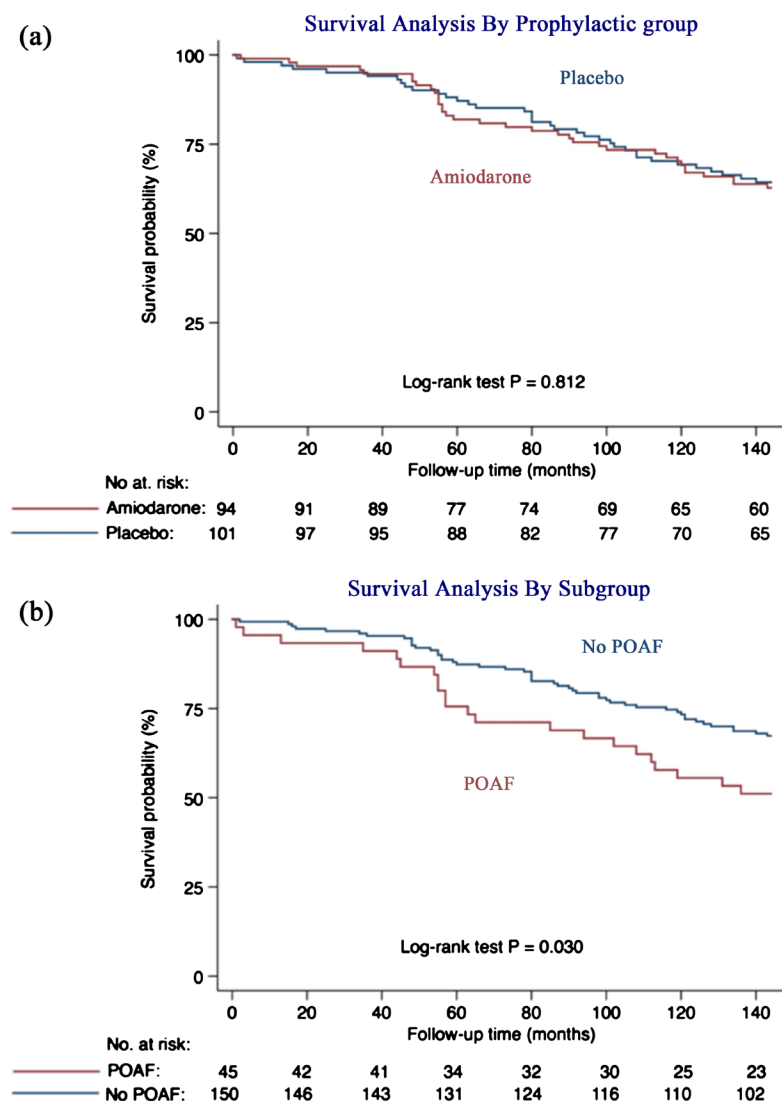

Figure 2. Kaplan Meier survival curves displaying long-term survival of patients undergoing coronary artery bypass grafting, stratified by prophylactic groups (a), and subgroups (b). Risk tables are displayed under the curves. POAF: postoperative atrial fibrillation.

Since the overall survival of our cohort was greater than 50% at the last time point, we were not able to calculate the median survival time. When comparing the survival curves of the prophylactic groups, we found no statistically significant difference in the overall long-term survival in Figure 2(a). However, we did find a decreased overall long-term survival, in patients who developed POAF in Figure 2(b).

3.6. Competing Risk Analysis

We investigated the cumulative incidence function (CIF) of readmission and late AF with death as a possible competing risk within prophylactic groups (a) and subgroups (b), respectively in Figure 3 and Figure 4. No statistically significant differences in the risk of readmission were found. POAF was associated with an increased risk of late AF HR 2.28 [95% CI 1.15; 4.55], when accounting for death as a competing risk. Amiodarone was not associated with late AF.
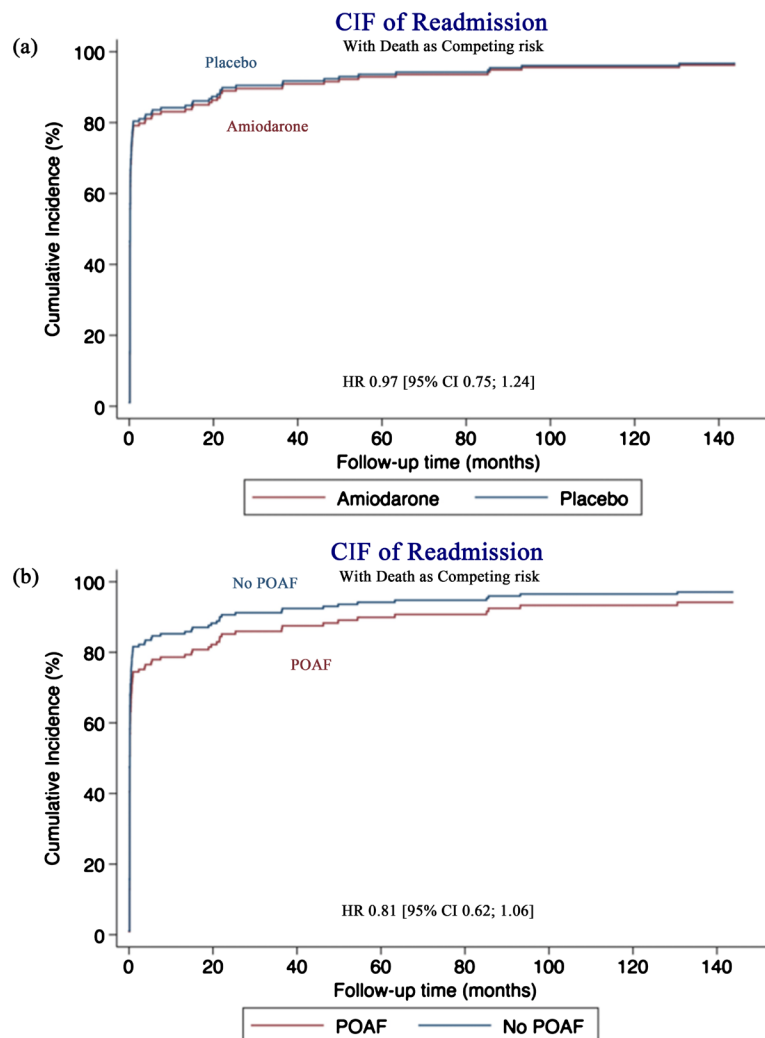

Figure 3. Cumulative incidence function (CIF) of readmission, with death as a competing risk, stratified by prophylactic groups (a), and subgroups (b). Competing risk regression was used to estimate subdistribution HR (SHR). POAF: postoperative atrial fibrillation.
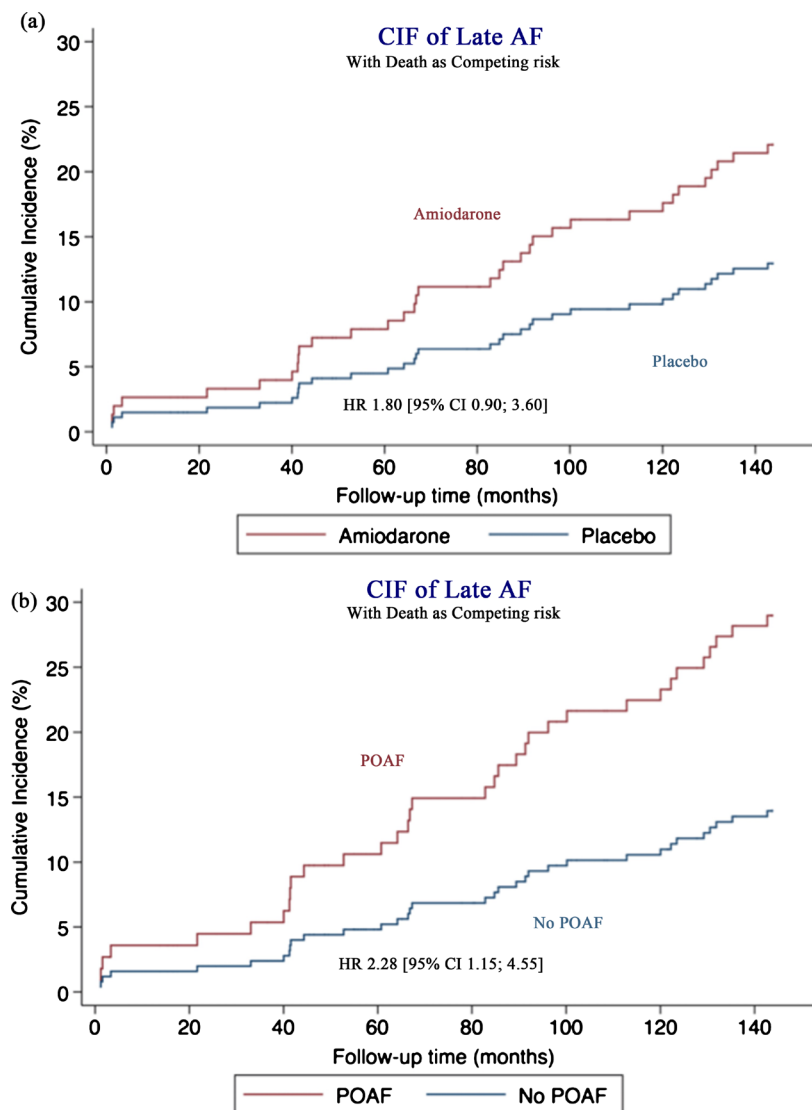
Figure 4. Cumulative incidence function (CIF) of late AF, with death as a competing risk, stratified by prophylactic groups (a), and subgroups (b). Competing risk regression was used to estimate subdistribution HR (SHR). POAF: postoperative atrial fibrillation.

4. Discussion

In this 12-year follow-up study, we found no differences in long-term side effects within the prophylactic groups. Furthermore, the long-term overall survival was not statistically significant different within prophylactic groups, and there was no association found between amiodarone and the risk of late AF, readmission or long-term mortality, in the competing risk analysis or multivariable analysis. While no difference was found in the long-term overall survival between pro-phylactic groups, patients who developed POAF had a worse long-term overall survival, and were more likely to develop late AF, compared to patients who stayed in sinus rhythm. In the competing risk analysis, POAF was not associated with an increased risk of readmission. However, POAF was associated with an increased risk of late AF, when accounting for death as a competing risk. In the

multivariable analysis, no associations were found within subgroups regarding late AF, readmission or long-term mortality.

The use of amiodarone has previously been associated with a number of short-term side effects and more serious adverse effects including skin cancer and toxicity of lung, thyroid and liver [17] [18] [19] [20] [21]. In this current study, we found no statistically significant increased risk for patients who had amiodarone prophylaxis in the RASCABG regime. Furthermore, we found no statistically significant difference in the risk of readmission, late AF or long-term mortality within prophylactic groups, indicating that amiodarone may be less hazardous than previous alleged [17] [18] [19] [20] [21].

When comparing subgroups, patients who developed POAF were more likely to develop late AF and die compared to patients who remained in sinus rhythm. This finding is consistent with studies investigating the association between POAF, late AF and long-term mortality [5] [22] [23] [24].

In current studies, POAF has been associated with an increased risk of late AF, and long-term mortality [5] [22] [23] [24]. Despite corresponding findings of the competing risk regression and survival analysis, POAF was not associated with an increased risk of late AF, and long-term mortality in the adjusted Cox regression analysis of our study. This might be due to inadequate power when adjusting for possible confounders.

Strength and Limitations

The main strengths of our study are the population, which were included from a double-blinded, randomized control trial, and the data source, as follow-up data were obtained from validated national databases. Additionally, the original RASCABG study was powered by the number of patients included, reflecting a verified sample size calculation, minimizing type II error. Naturally, some limitations should be noted. First, the study was based on data from single center study, which may limit the generalizability of the results, though, the surgical procedures were performed by 10 different cardiac surgeons. Second, some of the follow-up data were based on diagnostic codes and the validity of the results, therefore it depends on similar reporting. Third, as many other retrospective studies, our study contained missing data. In total, missing data were present in 20 baseline variables, with missing values ranging from 0.4% to 15.7%.

5. Conclusion

Amiodarone was found to be a safe option in the prophylactic setting of RASCABG within a 12-year follow-up period and should be considered in patients undergoing isolated, elective CABG. POAF was found to be related with long-term worse prognosis regarding late AF and mortality.

Funding Statement

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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