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Amiodarone prophylaxis for atrial fibrillation of high-risk patients after coronary bypass grafting: a prospective, double-blinded, placebo-controlled, randomized study

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Aims Atrial fibrillation (AF) occurs often in patients after coronary artery bypass grafting (CABG) and can result in increased morbidity and mortality. Previous studies using P-wave signal-averaged electrocardiogram (P-SAECG) have shown that patients with a longer filtered P-wave duration (FPD) have a high risk of AF after CABG. We have shown that patients with an FPD $\geq$ 124 ms and a root-mean-square voltage of the last 20 ms of the P-wave 20 $\leq$ 3.7 μV have an increased risk of AF after surgery. Accordingly, the aim of this study was to investigate whether or not prophylactic peri-operative administration of amiodarone could reduce the incidence of AF in this high-risk group undergoing CABG identified by P-SAECG.

Methods and results In this prospective, double-blinded, placebo-controlled, randomized study, 110 patients received either amiodarone ($n = 55$) or placebo ($n = 55$). During CABG, two patients of both groups died. Amiodarone was given as 600 mg oral single dose one day before and from days 2 through 7 after surgery. In addition, amiodarone was also administered intravenously during surgery in a 300-mg bolus for 1 h and as a total maintenance dose of 20 mg/kg weight over 24 h on the first day following surgery. The primary endpoint was the occurrence of AF after CABG. The secondary endpoint was the hospitalization length of stay after CABG. The baseline characteristics were similar in both treatment groups. The incidence of post-operative AF was significantly higher in the placebo group compared with the amiodarone group (85 vs. 34% of patients, $P < 0.0001$). The prophylactic therapy with amiodarone significantly reduced the intensive care (1.8 $\pm$ 1.7 vs. 2.4 $\pm$ 1.5 days, $P = 0.001$) and hospitalization length of stay (11.3 $\pm$ 3.4 vs. 13.0 $\pm$ 4.3 days, $P = 0.03$). In the amiodarone group, concentrations of amiodarone and desethylamiodarone differed significantly between patients with AF and sinus rhythm (amiodarone: 0.96 $\pm$ 0.5 vs. 0.62 $\pm$ 0.4 μg/mL, $P = 0.02$; desethylamiodarone: 0.65 $\pm$ 0.2 vs. 0.48 $\pm$ 0.1 μg/mL, $P = 0.04$).

Conclusion The incidence of post-operative AF among high-risk patients was significantly reduced by a prophylactic amiodarone treatment resulting in a shorter time of intensive care unit and hospital stay. Our data supports the prophylactic use of amiodarone in peri-operative period in patients at high risk for AF after CABG.

Introduction

Atrial fibrillation (AF) has been shown to increase morbidity and mortality after coronary artery bypass grafting (CABG) and results in prolonged stays in the intensive care unit (ICU) and in the hospital.[1–3]

Various clinical risk factors for post-operative AF include older age, the withdrawal of β-blockers, stenosis of the right coronary artery (RCA), reduced left ventricular (LV) function, or LV hypertrophy.[1–6] In addition, previous studies have shown the utility of P-wave signal-averaged electrocardiogram (P-SAECG) in predicting AF after CABG.[3–6] Because of different averaging and filtering methods in P-SAECG, various thresholds have been defined. However, most studies[3–6] identified a prolonged

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filtered P-wave duration (FPD) as a useful feature for predicting a new onset of AF.

In a previous study, we found that an FPD $\geq$ 124 ms and a root-mean-square voltage of the last 20 ms of the P-wave (RMS 20) $\leq$ 3.7 μV were assessed with an increased risk of post-operative AF with a specificity of 75%, a sensitivity of 78%, a negative predictive value of 86%, a positive predictive value of 64%, and an accuracy of 76%.[3] Thus, all patients who met with these P-SAECG criteria were considered as high risk for post-operative AF.[3] In addtion, FPD $\geq$ 124 ms and RMS 20 $\leq$ 3.7 μV was defined as the threshold of P-SAECG and was the only independent pre-operative predictor with an eight-fold risk for a new onset of AF after CABG.[3] Therefore, the threshold of P-SAECG was a suitable and easy measurable value for a pre-operative risk stratification to identify the high-risk patients for post-operative AF.

Meta-analysis of studies including unselected populations showed a superior effect of amiodarone, a class III antiarrhythmic drug, in preventing post-operative AF.[1,2,7,8]

We tested in a prospective, double-blinded, placebo-controlled, randomized study the efficacy of prophylactic amiodarone therapy in high-risk patients identified based on P-SAECG undergoing CABG.

Methods

Between March and November 2002, patients who had undergone cardiac catheterization for coronary heart disease and were being considered for CABG with use of a heart–lung machine (HLM) were screened (*Figure 1*). Patients were included if they were in normal sinus rhythm with heart rate >50 bpm. Patients were excluded if they required concomitant valve surgery, had a heart rate <50 bpm at rest, a second-degree or higher degree AV block, symptomatic sick sinus syndrome, pre-existing class I or III antiarrhythmic therapy, untreated thyroid disease, haemodynamically unstable condition (systolic blood pressure <90 mmHg), recent (<1 week before surgery) myocardial infarction, serum creatinine >2 mg/dL or serum aspartate aminotransferase or alanine aminotransferase concentration four times or more above normal values. One to seven days before surgery, 287 patients who met the inclusion

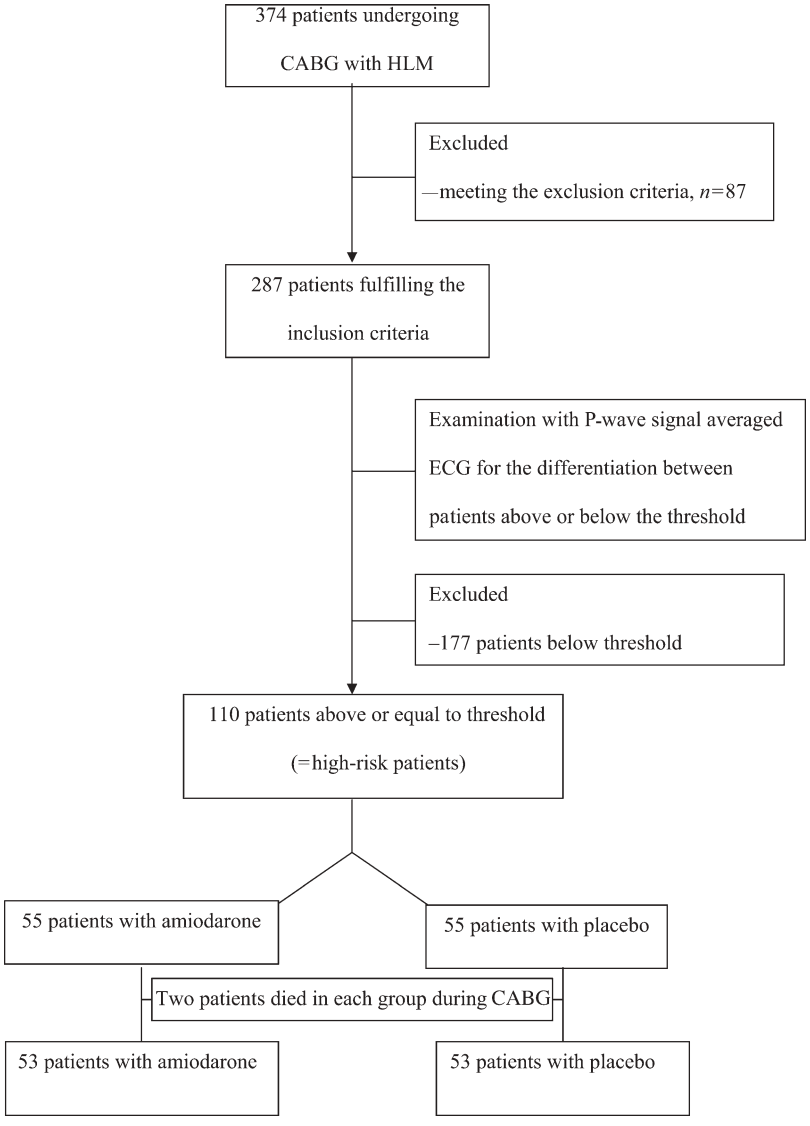

Figure 1 Flow diagram of the study. The threshold was defined as FPD $\geq$ 124 ms and RMS 20 $\leq$ 3.7 μV.[3]

criteria and had no contra-indications were examined with P-SAECG (*Figure 1*). This allowed identification of the high risk group (FPD $\geq$ 124 ms and RMS 20 $\leq$ 3.7 μV). A total of 110 eligible patients who met the P-SAECG criteria for high-risk patients were included in our study and randomly assigned in a double-blinded fashion to either amiodarone (55 patients) or placebo (55 patients). The study complies with the Declaration of Helsinki and the study protocol was approved by the local medical Ethics Committee. All patients gave written, informed consent before entering the study.

Study protocol

Patients received three identically designed tablets/day (amiodarone or placebo) one day before and then from two to seven post-operative day. The daily oral dosage was 600 mg in the amiodarone group (Cordarex, Sanofi-Synthelabo, France). Intravenous amiodarone (Cordarex, Sanofi-Synthelabo, France) was given peri-operatively with a bolus of 300 mg administered over 1 h and a maintenance dose as a continuous infusion of 20 mg/kg weight for 24 h (*Figure 2*). The placebo group was given glucose peri-operatively as a bolus and infusion for 24 h. The hospital pharmacy dispensed the study drug according to a computer-generated, randomized list that remained confidential. Unblinding of patients was performed only in case of emergency or at the end of the study. All clinical and study personnel were blinded to the study group assignment throughout the study. Compliance was monitored by pill count and was 100%. The study was not funded by any pharmaceutical company. Additional medical treatments were left at the discretion of the treating physicians and not mandated by the study protocol. Patients received a 24 h-Holter ECG (Marquette Holter recorder 8500 with five leads, Marquette Electronics, Inc., Milwaukee, Wisconsin, USA) one day before surgery to document sinus rhythm and absence of any pre-operative AF.

After surgery, each patient was admitted to the ICU and subsequently transferred to a monitored unit. A Holter ECG (Marquette Holter recorder 8500 with five leads) was performed continuously for 7 days after surgery. The QTc intervals were measured according to Bazett's formula at the baseline and at day 7 after surgery.[9] Management of peri-operative AF was directed by the cardiac surgery team.

Study endpoints

The primary endpoint of the study was the occurrence of AF in the post-operative period. AF was defined as an electrocardiographically confirmed episode of AF for more than 10 min.[3,10] The secondary endpoints were ventricular tachyarrhythmia after CABG, post-operative length of stay in ICU and in hospital associated with corresponding costs, amiodarone concentration, and incidence of an effective amiodarone concentration. Episodes of ventricular fibrillation or sustained ventricular tachycardia lasting 30 s or longer were defined as ventricular tachyarrhythmia. All endpoints were independently adjudicated after discharge by two cardiologists blinded to treatment assignment, on the basis of clinical records and ECG tracings.

Acquisition and analysis of the P-SAECG

The P-SAECG was recorded from an *X*, *Y*, and *Z* leads system (Predictor, Kaiser Medizintechnik, Germany) as described before.[3] The measurement lasted 15 min. The P-wave was retained as a trigger of the averaging process, and the signals were digitized at a frequency of 1000 samples/s with 16-bit accuracy. A sinus P-wave template was selected manually by the operator. P-waves were recorded until a noise endpoint of 0.5 μV was achieved in the PQ interval. Approximately 500 beats were used to complete the signal averaging. The P-wave complexes of filtered *X*, *Y*, and *Z* leads were combined to a vector magnitude $\sqrt{(X^2 + Y^2 + Z^2)}$. The FPD of the vector magnitude was defined as the interval between the onset and the offset points. The RMS 20 was also determined.

Measurement of amiodarone plasma concentration

Serum amiodarone and desethylamiodarone concentrations were measured by high-performance liquid chromatography as described earlier.[9] An effective therapeutic amiodarone level was defined as a concentration $\geq$0.7 μg/mL and a desethylamiodarone concentration $\geq$0.4 μg/mL.[11] Serum concentration of amiodarone was measured at day 7 after surgery.

Cost data

Hospital charges were obtained from the Heinrich-Heine University Duesseldorf Claims Management Database. The costs for each patient from the time of surgery until hospital discharge were estimated, as were the costs of the hospital stay (1600€ for the first 10 days and 70€ for each additional day) and the ICU (834€/day). Charges for CABG depended on the type of operation, for example, using saphenous vein bypass (11 779€), internal

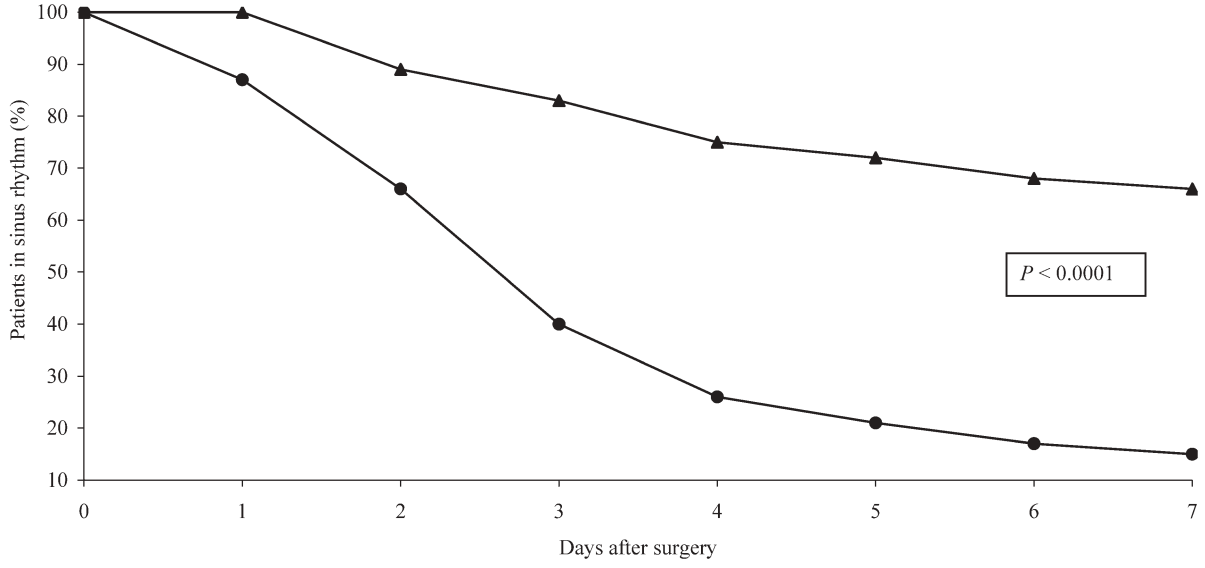

Figure 2 Kaplan–Meier analysis of percentages of patients remaining free from AF after CABG. Triangles, patients with amiodarone; circles, patients with placebo.

mammary artery bypass (11 512€), a combination of both (12 739€), re-operation (12 545€), or additional use of an intra-aortic balloon counterpulsation (1871€). The costs of the amiodarone therapy were estimated at 1.34€ per 200 mg tablet and 9.59€ per 150 mg intravenous drug.

Surgical procedure

After the initiation of cardiopulmonary bypass, myocardial protection was achieved by cooling to 28°C and with cold crystalloid cardioplegia, or with cross-clamp fibrillation and a temperature of 32°C. CABG was performed in all patients with the aid of HLM. Conduits for bypass included whenever possible the internal mammary artery.

Echocardiography

Left atrial size was measured by M-mode and two-dimensional echocardiography in all patients before and after CABG using the Toshiba ultrasonic device (Model SSH-160 A, Toshiba Corp., Japan) equipped with a 2.5-MHz transducer.

Statistics

From retrospective studies,[1,2,7,8] we estimated an efficacy of 50% for amiodarone to maintain sinus rhythm throughout the study period. We estimated an occurrence of AF in the placebo group of 64% because of the result of our previous study.[3] A risk of losing patients in the follow-up was assessed at 10%. With an alpha level of 0.05 and a test power of 0.80, the resulting sample size was estimated to be 55 patients for each treatment group.

We performed a full data set analysis for all outcomes without imputation of missing values. All data are presented as mean values ± standard deviation for continuous variables and as percentages for categorical variables. Discrepancies in proportions were evaluated for statistical significance using the χ^2 or Fisher's exact test. Student's *t*-test was used for comparing continuous variables excepting stay in ICU as its distribution was skew. Here, the Mann–Whitney *U* test was employed. We exploratorily analysed within the amiodarone and the placebo group additional factors for the onset of AF (blocker withdrawal, age ≥65 years, left atrial size ≥41 mm, FPD, RMS 20) using χ^2 test or Fisher's exact test (categorical variables) and Student's *t*-test (continuous variables). A measurement of the linear association between the two variables was evaluated using Pearson's correlation coefficient. All statistical tests were two-tailed. The Kaplan–Meier analysis with a log-rank test was used to compare the probability of AF free survival in the treatment group. A *P*-value ≤0.05 was considered indicative of significance. The statistical package used was SPSS 12.0 for Windows.

Table 1 Pre-operative characteristics

Characteristics	Amiodarone	Placebo	*P*-value
Number (males/females)	55 (48/7)	55 (42/13)	0.14
Age (years)	64.9 ± 10.3	66.7 ± 9.0	0.34
Patients with age ≥65 years, *n* (%)	35 (64%)	36 (65%)	0.84
Mean body mass index (kg/m^2)	28.3 ± 3.6	28.1 ± 3.4	0.8
Resting heart rate (bpm)	68.4 ± 11.4	68.4 ± 11.5	0.97
NYHA classification, *n* (%)			
I	2 (4)	4 (7)	0.41
II	28 (51)	25 (45)	0.57
III	25 (45)	26 (48)	0.85
IV	0	0	1
Angiographic results			
Number of vessels	2.9 ± 0.4	2.9 ± 0.3	0.77
RCA, *n* (%)	54 (98)	55 (100)	0.32
Left anterior descending artery, *n* (%)	54 (98)	52 (95)	0.31
Left circumflex artery, *n* (%)	52 (95)	52 (95)	1
Ejection fraction (%)	61.4 ± 12.6	63.6 ± 11.2	0.35
LVEDP (mmHg)	9.1 ± 3.4	9.1 ± 3.9	1
Echocardiographic results			
Left atrial diameter (mm)	40.9 ± 3.5	40.0 ± 3.1	0.19
Left atrial diameter ≥41 mm, *n* (%)	27 (49)	22 (40)	0.34
Major additional diseases			
Hypertension, *n* (%)	46 (84)	49 (89)	0.41
LV hypertrophy, *n* (%)	16 (35)	15 (31)	0.83
Diabetes mellitus, *n* (%)	17 (31)	18 (33)	0.84
Chronic obstructive pulmonary disease, *n* (%)	10 (18)	8 (15)	0.61
Prior CABG, *n* (%)	7 (13)	5 (9)	0.55
Myocardial infarction, *n* (%)	30 (55)	28 (51)	0.76
Anterior wall infarction, *n* (%)	11 (37)	13 (46)	0.46
Posterior wall infarction, *n* (%)	19 (63)	15 (54)	0.46
Medication			
Ace inhibitor, *n* (%)	40 (73)	35 (64)	0.31
β-blockers, *n* (%)	41 (75)	40 (73)	0.83
Verapamil, *n* (%)	4 (7)	4 (7)	1
Digitalis, *n* (%)	4 (7)	1 (2)	0.17
Statin, *n* (%)	53 (96)	53 (96)	1

LVEDP, LV end-diastolic pressure.

Results

Of 110 patients included in the study, 55 patients received amiodarone, and 55 received placebo and served as controls. No patient had a history of any type of AF before. Two patients from each group died during the operation and were excluded from the analysis of the onset of AF, costs, hospitalization, stay in ICU, and concentration of amiodarone.

Amiodarone vs. placebo

The patients did not differ significantly between the placebo and amiodarone groups in terms of age, sex, medications, cardiac diseases, surgery, angiography, echocardiography, body mass index, or P-SAECG values (*Tables 1–4*). The mean time of onset of AF (3.0 ± 1.4 vs. 3.7 ± 1.6 post-operative day) was similar in both the groups. The incidence of post-operative AF (*Figure 2*) was significantly lower in amiodarone- than in placebo-treated patients (34 vs. 85%, $P < 0.0001$). Even considering the worst case that AF occurred in the two dead patients of the amiodarone group and sinus rhythm in the two patients of the placebo group, the result still showed a significantly higher incidence of AF in the placebo group (36 vs. 82%, $P < 0.0001$). The risk of AF was reduced with amiodarone treatment in high-risk patients absolutely by 51% and relatively by 77% (95% confidence interval 0.91; 0.036–0.235; $P < 0.0001$). The onset of symptomatic AF was similar in both groups [4/18 patients (22%) vs. 14/45 patients (31%), $P = 0.49$]. A recurrence of AF was observed in three patients (17%) of the amiodarone

Table 2 Operative values of patients

	Amiodarone	Placebo	*P*-value
Number (*n*)	55	55	
Number of grafts	3.6 ± 0.8	3.3 ± 0.6	0.19
Internal mammary artery graft, *n* (%)	50 (91)	50 (91)	1
Operation time (min)	219.4 ± 45.3	204.6 ± 45.5	0.32
Clamp time (min)	42.6 ± 19.9	37.4 ± 17.5	0.18
Number of patients with cardioplegia, *n* (%)	19 (35)	16 (29)	0.55
Cardioplegia (mL)	1962.1 ± 484.1	1814.9 ± 508.8	0.41
Antegrade flow of cardioplegia, *n* (%)	19 (100)	16 (100)	1
IABP, *n* (%)	6 (11)	7 (13%)	0.77
AF after surgery, *n* (%)[a]	18 (34)	45 (85)	<0.0001
Symptomatic bradycardia after surgery, *n* (%)[a]	3 (5%)	1 (2%)	0.31

IABP, intra-aortic balloon counterpulsation.
[a]Analysis with 53 patients in each group.

Table 3 Post-operative medical therapy

	Amiodarone	Placebo	*P*-value
ACE-inhibitor withdrawal, *n* (%).	13 (34)	11 (33)	0.94
β-blocker withdrawal, *n* (%)	13 (33)	15 (39)	0.53
Verapamil withdrawal, *n* (%)	3 (100)	1 (25)	0.14
Digitalis withdrawal, *n* (%)	1 (25)	0	0.8

group and in 12 patients (27%) of the placebo group ($P = 0.41$) during the time of hospitalization.

The prophylactic therapy with amiodarone significantly reduced the ICU admission time (1.8 ± 1.7 vs. 2.4 ± 1.5 days, $P = 0.001$), and the length of hospitalization (11.3 ± 3.4 vs. 13.0 ± 4.2 days, $P = 0.03$). This resulted in significantly lower costs for hospitalization including the additional costs for amiodarone (intravenous administration 133.19 ± 19.26€) in the amiodarone cohort (18 428 ± 1575 vs. 19 352 ± 1760€, $P = 0.007$).

The incidence of ventricular tachyarrhythmias (three from placebo and one from treatment) showed no difference ($P = 0.32$) between the amiodarone- and placebo-treated patients during the post-operative follow-up. In addition, two patients of the placebo group died from incessant ventricular fibrillation on the 3rd and on the 7th day after CABG.

The number (3.4 ± 0.9 vs. 3.7 ± 1.1 per hour, $P = 0.17$) or the mean frequency (192.4 ± 34.6 vs. 191.1 ± 39.5 bpm, $P = 0.94$) of short episodes of atrial tachycardias lasting 2–11 s (mean duration 5.7 ± 2.3 s) frequently on the Holter ECG after CABG were not different between placebo- or amiodarone-treated patients. AF showed a higher maximum ventricular rate (166.7 ± 37.5 vs. 139.6 ± 36.5 bpm, $P = 0.02$) and a longer duration (17.7 ± 7.7 vs. 8.1 ± 5.4 h, $P < 0.0001$/range 8.8–43.5 h from placebo, 4.6–23.7 h from amiodarone) in placebo-treated patients.

The withdrawal of medical therapy was similar in the placebo- and the amiodarone-treated patients (*Table 3*). The ACE-Inhibitor was withdrawn because of hypotension in all patients. The β-blocker therapy was withdrawn because of hypotension of eight patients and because of sinus bradycardia of 20 patients. The reasons for the withdrawal of medical therapy did not differ between the placebo and the amiodarone group.

Post-operative pneumonia (one patient in each group) or the development of post-cardiotomy syndrome (four from placebo, five from treatment) was not different between the two groups. The values of creatine kinase, creatine kinase (cardiospecific), glutamate oxalacetate transaminase, lactate dehydrogenase or C-reactive protein measured one day after surgery showed no significant differences. Three transient ischaemic attacks (two from placebo, one from treatment) occurred during the post-operative follow-up.

Side effects

Amiodarone therapy had to be withdrawn in three patients after the onset of AF because of symptomatic bradyarrhythmias (two patients) and development of a third-degree AV block, necessitating implantation of a pacemaker (one patient). Three patients developed nausea during the amiodarone therapy. Symptomatic hypotension or other side effects were not observed.

In addition, one patient in the placebo group needed a pacemaker implantation because of a third-degree AV block. Seven patients in the placebo group were treated for 4 days with amiodarone after the onset of atrial tachyarrhythmias. All patients converted to sinus rhythm within 2 days after the onset of AF. No patient had nausea in the placebo group.

Analysis within the amiodarone and placebo group

Within the amiodarone group, we found no difference in QTc intervals at the baseline or during the post-operative follow-up between the amiodarone subgroup with AF (AF-A) and with sinus rhythm AF (SR-A). The amiodarone (0.62 ± 0.5 vs. 0.95 ± 0.5 μg/mL, $P = 0.05$) and desethylamiodarone (0.48 ± 0.2 vs. 0.64 ± 0.2 μg/mL, $P = 0.04$) concentrations were significantly lower in AF-A than in SR-A. In addition, an effective amiodarone concentration was present more in SR-A than in AF-A (74 vs. 20% of patients, $P < 0.0001$) (*Figure 3*). Patients with or without an effective

Table 4 Comparison of amiodarone and placebo groups and their subgroups

	Amiodarone[a]	SR-amiodarone	AF-amiodarone	Placebo[a]	SR-placebo	AF-placebo
Number (males/females)	55 (48/7)	35 (32/3)	18 (16/2)	55 (42/13)	8 (6/2)	45 (34/11)
Patients with age ≥65 years, *n* (%)	35 (65)	20 (57)	13 (72)	36 (66)	6 (75)	29 (64)
β-blockers withdrawal, *n*(%)	13 (33)	9 (31)	4 (36)	15 (39)	3 (43)	12 (39)
Left atrial diameter						
Left atrial diameter ≥41 mm, *n* (%)	27 (49)	19 (54)	8 (44)	22 (40)	3 (38)	18 (40)
Number of SAT/h (*n*)	3.4 ± 0.9	3.4 ± 1.4	3.4 ± 1.8	3.7 ± 1.1	3.0 ± 0.6	3.8 ± 1.1*
P-SAECG						
FPD (ms) before CABG	140.8 ± 11.7	139.8 ± 10.8	142.8 ± 14.0	140.0 ± 9.6	137.6 ± 7.1	140.4 ± 9.8
RMS 20 (μV) before CABG	3.07 ± 0.65	3.01 ± 0.67	3.16 ± 0.62	3.07 ± 0.56	2.93 ± 0.64	3.14 ± 0.50

SR, subgroup with sinus rhythm; AF, subgroup with AF; SAT, short atrial tachycardias.
[a]Two patients died in each group during the surgery.
*$P = 0.05$ in comparison with placebo subgroup with sinus rhythm.

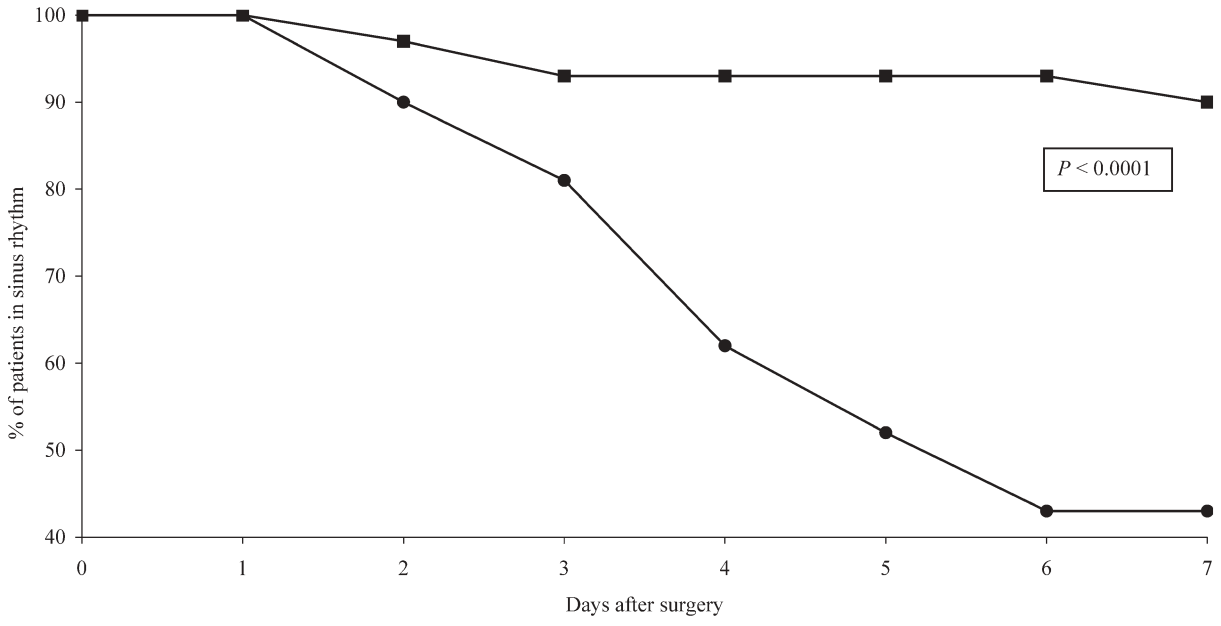

Figure 3 Kaplan–Meier analysis of percentages of patients treated with amiodarone remaining free from AF after CABG depending on amiodarone concentration. An effective amiodarone concentration was defined as an amiodarone concentration ≥0.7 μg/mL and a desethylamiodarone concentration ≥0.4 μg/mL. Squares, patients with an effective concentration; circles, patients with an ineffective concentration.

amiodarone concentration did not differ in any baseline characteristics especially in body mass index (28.3 ± 3.2 vs. 27.6 ± 3.8, $P = 0.36$).

The incidence of patients with β-blocker withdrawal, with age ≥65 years and left atrial size ≥41 mm as well as left atrial size before and after CABG were not significantly different among the four subgroups (*Table 4*).

Discussion

Prophylactic amiodarone therapy reduced significantly the incidence of AF in high-risk patients. Selection of high-risk patients was possible based on the criteria of P-SAECG (FPD ≥ 124 ms and RMS 20 ≤ 3.7 μV). Amiodarone was well tolerated and did not increase the peri-operative complications. The prophylactic amiodarone therapy of high-risk patients was not associated with proarrhythmia or other serious adverse effects and reduced significantly the ventricular rate among patients with AF.

Amiodarone treatment

In our study, the incidence of post-operative AF in the placebo group was very high compared with other studies.[1–8,10,12–20] We were able to identify a subset of patients with very high risk for post-operative AF with the P-SAECG criteria that was shown in our former and the present study.[3] Other clinical assessments like age, reduced LV function, or enlarged left atrial size did not achieve the predictive value of P-SAECG criteria.[3] These high risk patients showed a significant benefit with prophylactic amiodarone treatment and the therapy was well tolerated.

Different therapeutic regimes for prophylactic amiodarone treatment were described. Our high-risk group received

oral amiodarone treatment before and after surgery and peri-operative intravenous amiodarone therapy. Unlike previous studies,[12–17] our study definitively shows that by using the P-SAECG criteria to identify high-risk patients, we treated a homogeneous group with high risk for post-operative AF. But the measurement of P-SAECG was not a routine examination in many centers. Although the applicability of P-SAECG was available in specialized centres, the threshold of P-SAECG was a suitable and easy measurable value for a pre-operative risk stratification to identify the high-risk patients for post-operative AF.

Some studies[18–20] that examined a prophylactic amiodarone therapy as ARCH or AFIST were not comparable to our study because they included unselected patients with different heart operations as valvular or concomitant CABG and valvular surgery. In other placebo-controlled studies that included unselected populations and different schemes,[12–17] attempts to prevent post-operative AF after CABG by using amiodarone were occasionally successful. A solely oral therapy with 1000–1600 mg amiodarone pre-operatively and with 400 mg amiodarone for 7 days after surgery showed no significant effect.[12] The AF incidence was 24.7% in the amiodarone group and 32.8% in the placebo group without a significant amiodarone efficacy. Different results were achieved in studies with an exclusive intravenous treatment.[13–15] Hohnloser *et al.*[13] and Lee *et al.*[15] found a significant reduction in post-operative AF with different intravenous schemes. Hohnloser *et al.*[13] achieved a significantly reduction of AF (5 vs. 21% of patients, $P < 0.05$) with a bolus of 300 mg amiodarone followed by a dosage of 1200 mg for two days (days 2 and 3) and 900 mg for the next two days (days 4 and 5). Lee *et al.*[15] brought about a significant reduction ($P = 0.01$) of AF among the amiodarone group (12%) in comparison with the placebo group (34%) due to a pre- and post-operative intravenous amiodarone therapy (150 mg bolus and a maintenance dose of 0.4 mg/kg/h for 3 days pre- and 5 days post-operative). Dorge *et al.*[14] examined two different amiodarone dosages (group I: 300 mg bolus and a maintenance dose of 20 mg/kg weight for 3 days; group II: 150 mg bolus, maintenance dose of 10 mg/kg weight for 3 days) without a significant influence on AF onset. AF occurred in 24% patients of group I, in 28% patients of group II, and in 34% patients of the placebo group.

A peri-operative intravenous therapy with a subsequent oral therapy of amiodarone also showed different results.[16,17] The AF incidence was not significantly different for amiodarone (17%) and placebo (20%) with an intravenous peri-operative maintenance dose of 15 mg/kg weight and a maximum intravenous dosage of 1500 mg and a daily oral dose of 600 mg for 5 days.[16] The decisive difference between both studies was the longer oral amiodarone treatment in the study of Tokmakoglu *et al.*,[17] who found a significant reduction in AF. The significant reduction ($P < 0.001$) of AF from 8.3% in the amiodarone group to 33.6% in the placebo group was achieved with an intravenous bolus of 300 mg, a maintenance dose of 1200 mg for 24 h, and 450 mg at the next day followed by an oral treatment of 600 mg until discharge.[17]

In all of the studies, the amiodarone therapy was well tolerated and appeared to reduce the occurrence of post-operative AF. Amiodarone treated patients had a low number of side effects without a significant difference compared with the placebo-treated patients. The reason for the low number of side effects might be the short amiodarone treatment for eight days.

Concentration of amiodarone and desethylamiodarone

In our study, we found a lower amiodarone and desethylamiodarone concentrations, and a lower incidence of an effective amiodarone concentration in the amiodarone subgroup with AF. In other studies[1,2,7,8,12–20] the amiodarone concentration was not assessed with a distinction between an effective or ineffective concentration between patients with and without post-operative AF.

The metabolism and bioavailability of amiodarone depends on food intake and on different enzymes.[21–25] These influences might explain the different concentrations of amiodarone and desethylamiodarone in our study. Patients with an ineffective amiodarone concentration had a higher incidence of AF because the effect of amiodarone depends on the dosage.[9,11,13] Thus, a more prophylactically effective amiodarone concentration among all high-risk patients should reduce the onset of AF after CABG.

Costs

AF onset after CABG leads to higher costs as well as longer hospitalization.[1,3,18–20,26,27] In our study, the costs and hospitalization period were reduced by prophylactic amiodarone treatment in high-risk patients. Other studies also showed a reduction of costs and time spent in the hospital among an unselected population.[1,18–20,26,27] The reduction of costs and hospitalization was achieved by a reduction of AF and a reduction of morbidity that are shown in former studies.[1,18–20,27] But a significant reduction of costs was only achieved in the study of Daoud *et al*[18] and Zimmer *et al.*[27] The reason for the unattained reduction of costs might be an inadequate reduction of hospitalization and an inadequate reduction of AF after CABG in the amiodarone treatment of an unselected population.[27] But we treated high-risk patients identified by P-SAECG criteria, who profited more from a prophylactic amiodarone treatment than patients without a pre-operative risk stratification.[1,18–20,26,27] Within the context of reduced financial resources for the public health, our study shows that we can identify a high-risk population for post-operative AF with P-SAECG and that we can reduce the incidence of AF by establishing a well-tolerated and safe prophylactic amiodarone therapy.

In conclusion, our study results suggest that amiodarone administered according to this scheme reduces the onset of post-operative AF in a safe and well-tolerated manner among high-risk patients. We have shown the possibilities of saving costs with prophylactic amiodarone treatment, especially with regard to reduced financial resources for public health. Thus, prophylactic treatment can be considered effective and should be used routinely for high-risk patients undergoing CABG in order to reduce the duration of hospital stays and costs.

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References

1. Mahoney EM, Thompson TD, Veledar E, Williams J, Weintraub WS. Cost-effectiveness of targeting patients undergoing cardiac surgery for therapy with intravenous amiodarone to prevent atrial fibrillation. *J Am Coll Cardiol* 2002;**40**:737–745.
2. Zimmer J, Pezzullp J, Choucair W, Southard J, Kokkinos P, Karasik P, Greenberg MD, Singh SN. Meta-analysis of antiarrhythmic therapy in the prevention of postoperative atrial fibrillation and the effect on hospital length of stay, costs, cerebrovascular accidents and mortality in patients undergoing cardiac surgery. *Am J Cardiol* 2003;**9**:1137–1140.
3. Budeus M, Hennersdorf M, Röhlen S, Schnitzler S, Felix O, Reimer K, Feindt P, Gams E, Wieneke H, Sack S, Erbel R, Perings C. Predicting of atrial fibrillation after coronary bypass grafting: The role of chemoreflex-sensitivity and P wave signal averaged ECG. *Int J Cardiol* 2006; **106**:67–74.
4. Zaman AG, Archbold RA, Helft G, Paul EA, Curzen NP, Mills PG. Atrial fibrillation after coronary artery bypass surgery. A model of preoperative risk stratification. *Circulation* 2000;**101**:1403–1408.
5. Stafford PJ, Kolvekar S, Cooper J, Fothergill J, Schlindwein F, de Bono DP, Spyt TJ, Garratt CJ. Signal averaged P wave compared with electrocardiography or echocardiography for prediction of atrial fibrillation after coronary bypass grafting. *Heart* 1997;**77**:417–422.
6. Aytemir K, Aksoyek S, Ozer N, Sait A, Oto A. Atrial fibrillation after coronary artery bypass surgery: P wave signal averaged ECG, clinical and angiographic variables in risk assessment. *Int J Cardiol* 1999;**69**:49–56.
7. Crystal E, Connolly SJ, SLeik K, Ginger TJ, Yusuf S. Interventions on prevention of postoperative atrial fibrillation in patients undergoing heart surgery: a meta-analysis. *Circulation* 2002;**106**:75–80.
8. Kowey PR, Taylor JE, Rials SJ, Marinchak RA. Meta-analysis of the effectiveness of prophylactic drug therapy in prevention supraventricular arrhythmia early after coronary artery bypass grafting. *Am J Cardiol* 1992;**69**:963–965.
9. Zipes DP, Prystowsky EN, Heger JJ. Amiodarone: electrophysiologic actions, pharmacokinetics and clinical effects. *J Am Coll Cardiol* 1984; **3**:1059–1071.
10. Kalman JM, Munawar M, Howes LG, Louis WJ, Buxton BF, Gutteridge G, Tonkin AM. Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. *Ann Thorac Surg* 1995; **60**:1709–1715.
11. Debbas N, du Cailar C, Sassine A, Derancourt J, Demaille J, Puech P. Determination of cardiac and plasma drug levels during long term amiodarone therapy. *Eur J Clin Pharmacol* 1983;**13**:69–81.
12. Redle JD, Khurana S, Marzan R, Mc Cullough PA, Stewart JR, Westveer DC, O'Neill WW, Bassett JS, Tepe NA, Frumin HI. Prophylactic oral amiodarone compared with placebo for prevention of atrial fibrillation after coronary artery bypass surgery. *Am Heart J* 1999;**138**:144–150.
13. Hohnloser SH, Meinertz T, Dammbacher T, Steiert K, Jähnchen E, Zehender M, Fraedrich G, Just H. Electrocardiographic and antiarrhythmic effects of intravenous amiodarone: Results of a prospective, placebo controlled study. *Am Heart J* 1991;**121**:89–95.
14. Dorge H, Schoendube FA, Schoberer M, Stellbrink C, Voss M, Messmer BJ. Intraoperative amiodarone as prophylaxis against atrial fibrillation after coronary operations. *Ann Thorac Surg* 2000;**69**:1358–1362.
15. Lee SH, Chang CM, Lu MJ, Lee RJ, Cheng JJ, Hung CR, Chen SA. Intravenous amiodarone for prevention of atrial fibrillation after coronary artery bypass grafting. *Ann Thorc Surg* 2000;**70**:157–161.
16. Butler J, Harriss DR, Sinclair M, Westaby S. Amiodaron prophylaxis for tachycardias after coronary artery bypass surgery: a randomised, double blind, placebo controlled trial. *Br Heart J* 1993;**70**:56–60.
17. Tokmakoglu H, Kandemir O, Gunaydin S, Catav Z, Yorgancioglu C, Zorlutuna Y. Amiodarone vs. digoxin and metoprolol combination for prevention of postcoronary bypass atrial fibrillation. *Eur J Cardiothorac Surg* 2002;**21**:401–405.
18. Daoud EG, Strickberger SA, Man KC, Goyal R, Deeb GM, Bolling SF, Pagani FD, Bitar C, Meissnere MD, Morady F. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. *N Eng J Med* 1997; **337**:1785–1791.
19. Guarnieri T, Nolan S, Gottlieb SO, Dudek A, Lowry DR. Intravenous amiodarone for prevention of atrial fibrillation after open heart surgery: The Amiodarone Reduction in Coronary Heart (ARCH) Trial. *J Am Coll Cardiol* 1999;**34**:343–347.
20. Giri S, White MC, Dunn BD, Felton K, Freeman-Bosco L, Reddy P, Tsikouris JP, Wilcox HA, Kluger J. Oral amiodarone for prevention of atrial fibrillation after heart surgery, the Atrial Fibrillation Suppression Trial (AFIST): a randomised placebo-controlled trial. *Lancet* 2001;**357**:830–836.
21. Riva E, Gerna M, Latini R, Giani P, Volpi A, Maggioni A. Pharmacokinetics of amiodarone in man. *J Cardiovasc Pharmacol* 1982;**4**:264–269.
22. Meng X, Mojaverian P, Doedee M, Lin E, Weinryb I, Chiang ST, Kowey PR. Bioavailability of amiodarone tablets administered with and without food in healthy subjects. *Am J Cardiol* 2001;**87**:432–435.
23. Libersa CC, Brique SA, Motte KB, Caron JF, Guedon-Moreau LM, Humbert L, Vincent A, Devos P, Lhermitte MA. Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. *Br J Clin Pharmacol* 2000; **49**:373–378.
24. Ohyama K, Nakajima M, Nakamura S, Shimada N, Yamazaki H, Yokoi T. A significant role of human cytochrome P450 2C8 in amiodarone N-deethylation: an approch to predict the contribution with relative activity factor. *Drug Metab Dispos* 2000;**11**:1303–1310.
25. Soyama A, Hanioka N, Saito Y, Murayama N, Ando M, Ozawa S, Sawada J. Amiodarone N-deethylation by CYP2C8 and its variants, CYP2C8*3 and CYP2C8 P404A. *Pharmacol Toxicol* 2002;**91**:174–178.
26. Haan CK, Geraci SA. Role of amiodarone in reducing atrial fibrillation after cardiac surgery in adults. *Ann Thorac Surg* 2002;**73**:1665–1669.
27. Zimmer J, Pezzullo J, Choucair W, Southard J, Kokkinos P, Karasik P, Greenberg MD, Singh SN. Meta-analysis of antiarrhythmic therapy in the prevention of postoperative atrial fibrillation and the effect on hospital length of stay, costs, cerebrovascular accidents, and mortality in patients undergoing cardiac surgery. *Am J Cardiol* 2003;**91**:1137–1140.