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The prognostic impact of successful cardioversion of atrial fibrillation in patients with organic heart disease

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Summary The aim of the study was to evaluate the prognostic impact of successful cardioversion (CV) compared to failed CV in patients with atrial fibrillation (AF) and organic heart disease. A total of 471 consecutive patients with organic heart disease from the prospective single center anticoagulation registry ANTIK who underwent CV of AF or atrial flutter were analyzed. 417 patients (89%) could be successfully cardioverted. In 54 patients (11%) CV failed, these patients remained in AF. After 5 years there were 92 (24%) deaths among patients with restored sinus rhythm at index admission and 20 (38%) deaths among those who remained in AF after CV (unadjusted OR 1.9, 95% CI 1.1–3.6). After adjustment for age, gender and ejection fraction, successful CV was not associated with a beneficial effect on mortality (OR 0.72, 95% CI 0.43–1.21). Thus, successful CV is not an independent predictor of mortality on multivariate analysis. However, it remains a marker for a better prognosis in patients with organic heart disease as these patients have a lower unadjusted long-term mortality.

Key words
Atrial fibrillation – cardioversion – prognosis

Introduction

The AFFIRM and RACE trials evaluated strategies of rate control or rhythm control in atrial fibrillation (AF) [21, 23]. Each trial showed that a strategy of rate control was noninferior to a strategy of rhythm control in terms of mortality in a population of older patients, most of whom had persistent, recurrent AF. Indeed, in both studies analysis of the primary end point showed a trend in favor of rate control. At first glance, it may seem that the results render an attempt at cardioversion (CV) obsolete, since the quality of life, the risk of stroke, and mortality were not affected by an attempt to maintain sinus rhythm [3]. However, both studies investigated a heterogeneous group of patients with different underlying cardiac diseases. There was even a subset with pre-existing congestive heart failure (23% of the population), where the mortality trend actually favored rhythm control [20–22]. Hence, the aim of the study was to evaluate the prognostic impact of successful CV compared to failed CV in patients with AF and organic heart disease.

Methods

Patient selection

Patients who were candidates for CV of AF or atrial flutter were eligible for enrollment in the anticoagulation registry ANTIK. Candidates for CV comprised

patients with symptomatic AF or atrial flutter who were admitted to hospital for CV or were referred to an ambulatory arrhythmic clinic. This prospective, single center observational study was designed on an intention to cardiovert basis, consisting of three subpopulations: patients with pure AF, patients with atrial flutter plus a history of AF and patients with pure atrial flutter. Patients with pure atrial flutter (respectively pure AF) had no previous documentation of AF (respectively atrial flutter) either during hospitalization or outpatient visits in the last two years before admission. The ANTIK registry started in 1994 and ended in 2004. Written informed consent was obtained from all patients before participation in the study. Overall 1053 patients were included in the registry. For the present study only patients (n = 471) with organic heart disease who underwent a CV and where a complete follow-up was available (93%) were enrolled. The median follow-up was 62 months (upper and lower quartile: 48 and 82 months). A CV could be performed by electrical CV, antiarrhythmic drugs or ablation. 76% of the patients underwent an electrical CV, 4% received a CV with antiarrhythmic drugs and 20% an ablation therapy of atrial flutter or AF. Electrical CV was performed with a monophasic shock of 100–360 J or a biphasic shock of 120–200 J. Patients who did not respond to the maximum shock received an intravenous bolus of 150 to 300 mg amiodarone. If the electrical CV preceded by amiodarone could not restore sinus rhythm, the arrhythmia was considered permanent, and rate control became the goal of therapy. Patients with successful CV (CV+) had a successful restoration of sinus rhythm by CV and were discharged on sinus rhythm. Patients with failed CV (CV–) remained in AF or atrial flutter after CV or relapsed to AF or atrial flutter until discharge after primarily being successfully cardioverted. Anticoagulation was performed as recommended by the guidelines. Patients with AF or atrial flutter of prolonged duration (> 48 h) had three weeks of effective anticoagulation (INR 2–3) treatment before cardioversion, followed by at least four weeks of phenprocoumon therapy after cardioversion. In patients with AF or atrial flutter lasting less than 48 h, oral anticoagulation therapy was not recommended before cardioversion. However, after cardioversion an overlap of phenprocoumon therapy and intravenous heparin therapy was given to maintain adequate anticoagulation after cardioversion in patients without contraindications for anticoagulation. Patients with atrial flutter were managed with oral anticoagulation at the time of cardioversion in a manner similar to that used for AF. Anticoagulation was defined as being effective if all INR values measured during the last year of follow-up were between 2 and 3.

Statistical analysis

Absolute numbers, percentages, means and standard deviation, median and upper/lower quartile were computed as appropriate. Categorical variables were compared by using the chi-square or Fisher's exact test, as appropriate, and calculating the odds ratio (OR) and the 95% confidence intervals (CI). A logistic regression was performed to find determinants for successful CV. Kaplan-Meier curves were used to analyze differences in the survival rates between the groups. Unadjusted hazard ratios for death from any cause with successful CV as compared with failed CV were given in a subgroup analysis. Cox regression analysis was used to compare the clinical outcome in the different therapy groups. Adjustment was performed for the following variables: age, gender, ejection fraction < 40%. A p-value < 0.05 was considered to be statistically significant.

Results

Characteristics of the patients

Overall 471 consecutive patients with an organic heart disease, who underwent CV, were included in the present study. Baseline clinical data of the enrolled 471 patients are summarized in Table 1. 417 (89%) patients could be successfully cardioverted (CV+). In 54 patients (11%) sinus rhythm could not be achieved or maintained after CV; these patients were discharged with atrial arrhythmias (CV–) (Table 1). Patients with failed cardioversion were 3 years older (66 vs 69 years, OR 1.7, 95% CI 0.9–3.0), had a longer duration of the index arrhythmia before CV, more often a history of stroke and a larger left atrial diameter. Diabetes and a reduced left ventricular dysfunction were more often present in patients with successful CV. The only determinant which was significantly associated with a higher rate of successful CV was atrial flutter (Fig. 1). Only a few patients (2.3%) received class I agents, and it was only given in patients with successful cardioversion (Table 2). At discharge and after 5 years a high number of patients in both groups received oral anticoagulant therapy. The quality of oral anticoagulation was high during the last year of follow-up, an effective INR was present in about 80% of patients (Table 2).

Clinical outcome and subgroups

Unadjusted long-term mortality was lower in patients with successful CV compared to patients with failed CV (24% vs 38%, OR 1.9, 95% CI 1.1–3.6,

Table 1 Baseline characteristics

	Successful CV (n = 417)	Failed CV (n = 54)	Univariate Odds ratios (95% CI)
Age (years)	66 (59/71) [a]	69 (62/73)	1.7 (0.9–3.0)
Male sex	327/417 (78%) [b]	39/54 (72%)	0.7 (0.4–1.4)
Underlying cardiac disease			
Coronary artery disease	225/417 (54%)	23/54 (43%)	0.6 (0.4–1.1)
Hypertensive heart disease	137/417 (33%)	21/54 (39%) [c]	1.3 (0.7–2.3)
Valve disease	82/417 (20%)	11/54 (20%)	1.0 (0.5–2.1)
Dilated cardiomyopathy	68/417 (16%)	7/54 (13%)	0.8 (0.3–1.8)
Left ventricular function			
Normal	225/410 (55%)	37/53 (70%)	1.9 (1.0–3.5)
Mild dysfunction	72/410 (18%)	7/53 (13%)	0.7 (0.3–1.6)
Moderate dysfunction	66/410 (16%)	8/53 (15%)	0.9 (0.4–2.1)
Severe dysfunction	48/410 (12%)	1/53 (2%)	0.1 (0.0–1.1)
Left atrial diameter > 50 mm	68/405 (17%)	14/53 (26%)	1.8 (0.9–3.5)
Duration of index AF < 48 h	184/417 (44%)	7/54 (13%)	0.2 (0.1–0.4)
Recurrent episode of AF	188/417 (45%)	27/54 (50%)	1.2 (0.7–2.1)
Diabetes	84/417 (20%)	4/54 (7%)	0.3 (0.1–0.9)
Hypertension	255/417 (61%)	34/54 (63%)	1.1 (0.6–1.9)
Prior stroke	38/417 (9%)	10/54 (19%)	2.3 (1.1–4.9)

[a] Median values are given with interquartile ranges (the 25th and 75th percentiles); [b] Number of patients and percentage of group specific total number; [c] Patients could have hypertensive heart disease alone or in addition with another underlying heart disease
AF atrial fibrillation; *CI* confidence interval; *COPD* chronic obstructive pulmonary disease; *CV* cardioversion

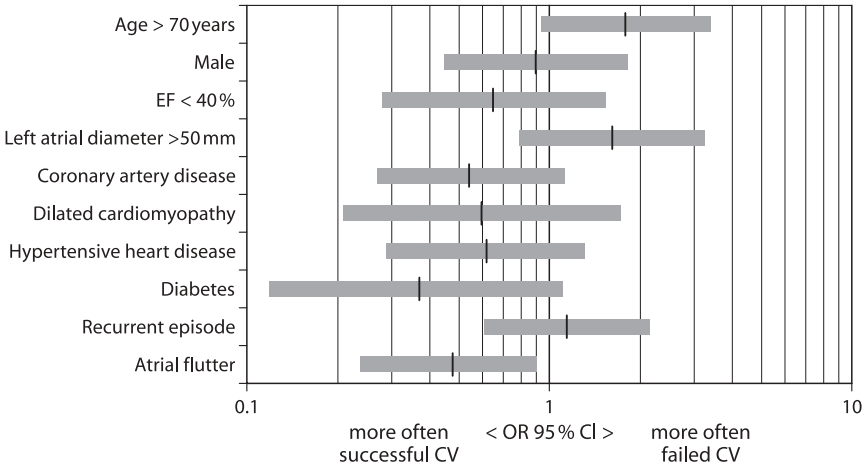

Fig. 1 Determinants for successful cardioversion (multivariable analysis with adjusted odds ratios). *CV* cardioversion

Table 3, Fig. 2). Nonfatal strokes (3.0%), nonfatal systemic thromboembolic complications (0.6%) and severe bleeding (1.4%) occurred only in patients with successful cardioversion (Table 3). In a subgroup analysis successful CV was associated with a lower mortality rate in female patients, patients with preserved EF, first episode of AF and hypertensive heart disease (Fig. 3). In a multivariate analysis adjusting for age, gender and ejection fraction, successful CV showed no significant effect on long-term mortality (HR 0.72, 95% CI 0.43–1.21).

Discussion

Major findings

The present study analyzes unselected consecutive patients with organic heart disease who underwent CV therapy for AF. Patients with successful CV had a lower long-term unadjusted mortality compared to those with failed CV. This was especially true in female patients, patients with preserved left ventricular function, first episode of AF or hypertensive heart disease. However, successful CV was not an independent predictor of mortality.

Table 2 Antiarrhythmic drugs and oral anticoagulation

	Successful CV (n = 417)	Failed CV (n = 54)	Odds ratios (95% CI)
Antiarrhythmic drugs			
Class I	11/417 (2.6%)	0/54 (0%)	Na
Beta-blocker	140/417 (34%)	15/54 (28%)	0.8 (0.4–1.4)
Class III	192/417 (46%)	13/54 (24%)	0.4 (0.2–0.7)
Class IV	16/417 (3.8%)	15/54 (28%)	9.6 (4.4–21)
Digoxin	142/417 (34%)	32/54 (59%)	2.8 (1.6–5.0)
Phenprocoumon at discharge	394/417 (94%)	54/54 (100%)	
Phenprocoumon after 5 years	192/272 (71%)	25/31 (81%)	1.8 (0.7–4.6)
Median INR (95% CI) at follow-up [a]	2.4 (2.0–2.8)	2.6 (2.4–3.1)	

CI confidence interval; *CV* cardioversion; *INR* international normalized ratio
[a] Median INR was calculated out of the last 5 INR results measured during the last year of follow-up

Table 3 Clinical events during the median follow-up time of five years

	Successful CV (n = 417)	Failed CV (n = 54)	Odds ratios (95% CI)
Total deaths	92/387 (24%)	20/53 (38%)	1.9 (1.1–3.6)
Nonfatal myocardial infarction	6/295 (2%)	1/33 (3%)	1.5 (0.2–12.9)
Nonfatal stroke	10/295 (3%)	0/33 (0%)	–
Other nonfatal thromboembolic complications	6/295 (0.6%)	0/33 (0%)	–
Severe bleeding	4/295 (1.4%)	0/33 (0%)	–
Rehospitalization	216/295 (73%)	23/33 (70%)	0.8 (0.4–1.8)

CI confidence interval; *CV* cardioversion

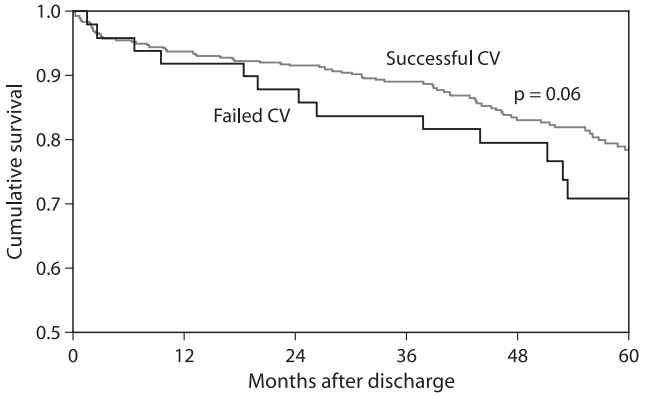

Fig. 2 Survival of patients with organic heart disease: successful versus failed cardioversion (Kaplan-Meier survival curves). *CV* cardioversion

Cardioversion of AF: prognostic impact or prognostic marker?

Large population – based studies demonstrated AF to be associated with an increased risk of cardiovascular mortality [1, 5, 7, 8, 12]. However, it is unclear, if restoration of sinus rhythm in these patients with organic heart disease had improved the prognosis. The present data showed a lower unadjusted long-term mortality in patients with organic heart disease who underwent successful CV of AF. It is questionable if the better prognosis of the patients with successful CV at index admission was caused by the restoration of sinus rhythm or if restoration of sinus rhythm itself was a marker for a better stage of the underlying cardiac disease. It was not documented how many patients remained in sinus rhythm during the follow-up and how large the achieved difference in cardiac rhythm between the study groups was. It might be in the similar range of 30% as previously reported [17, 21, 23]. In addition, after adjusting for age, gender and EF, successful CV was not an independent predictor on mortality in a multivariate analysis. Therefore, one can conlude that not the restoration of sinus rhythm by CV was responsible for the better prognosis, but that failed CV which indicated permanent AF was a marker for the progression of the underlying organic heart disease. It is known that the progression of organic heart disease leads to hemodynamic changes with atrial pressure elevation [18]. Chronic atrial stretch and various neurohormonal abnormalities associated with congestive heart failure lead to atrial structural remodeling including atrial dilatation and atrial fibrosis which promotes AF development and facilitates sustained AF [13, 18]. Hemodynamic changes in organic heart disease may be caused by deterioration of systolic or diastolic dysfunction as well as AF itself [7, 8, 15, 19]. In the present study the better prognosis with successful CV was especially observed in hypertensive heart disease and preserved left ventricular function and not in coronary artery disease or dilated cardiomyopathy. This might be because the prognosis in coronary artery disease and dilated cardiomyopathy is mainly driven by the reduced ejection fraction, whereas in hypertensive heart disease and preserved left ventricular function the extent of diastolic dysfunction may play an additional prognostic role [15]. Failed CV in patients with hypertensive heart disease might be the consequence of chronic hemodynamic changes due to advanced diastolic dysfunction which is associated with a poorer prognosis.

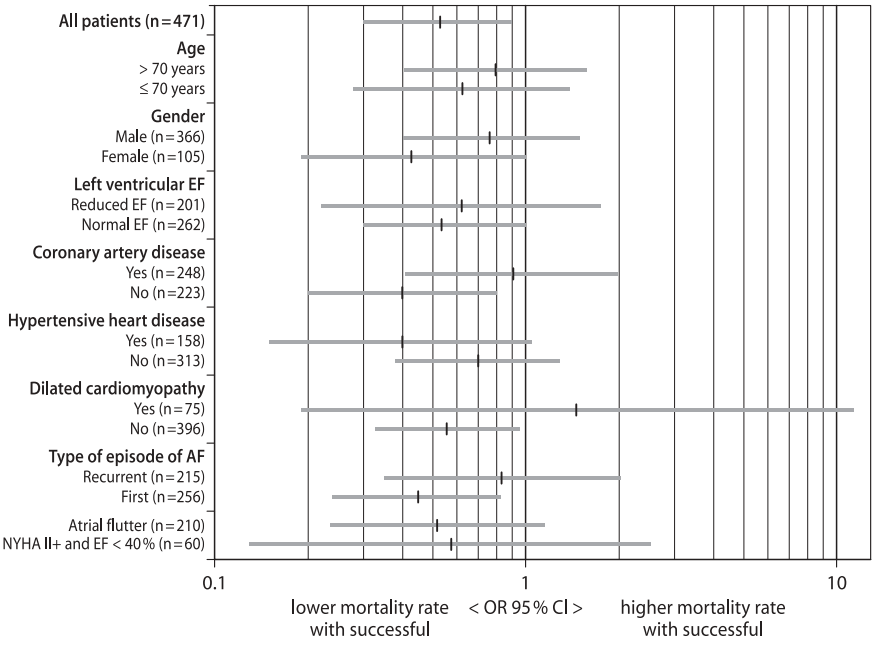

Fig. 3 Hazard ratios for death in prespecified subgroups. *CV* cardioversion; *EF* ejection fraction

The role of antiarrhythmic and anticoagulation therapy

The use of class I and class III agents in AFFIRM and RACE was very high compared to the present study where only a few patients (2.3%) received class I antiarrhythmic drugs [20, 22]. Interestingly, unlike to the present study, female gender and hypertension were markers of worse outcome in the rhythm control groups of AFFIRM and RACE. A possible explanation might be that left ventricular hypertrophy and female gender were associated with an increased risk of drugrelated arrhythmic events [10, 14, 16, 24], and the survival benefit provided by the maintenance of sinus rhythm was negated by the potential proarrhythmic effects and noncardiac toxicities of the antiarrhythmic agents [4, 6]. The rates of nonfatal stroke and other thromboembolic complication in the present study were low at approximately 0.7% per year when comparing with previous studies [2, 9, 25]. The low incidence of strokes might be due to the high rate of anticoagulant therapy and high quality of anticoagulation in both groups. Embolic events occurred only in the group with successful CV during the follow-up. This is in accordance with other studies like RACE where increased embolic events were also observed in the rhythm control group [23]. A possible explanation might be the anticoagulation therapy after CV. In the present study, anticoagulation could be discontinued four weeks after CV in the presence of stable sinus rhythm. AFFIRM and RACE, however, showed that most ischemic strokes occurred in patients in whom anticoagulation had been stopped or in whom the INR was subtherapeutic [21, 23].

Predictors for successful CV

Patients with successful CV more often had reduced ejection fractions and diabetes. This finding might be due to a selection bias as patients were referred to CV by physicians. The only determinant which was significantly associated with a higher rate of successful CV was atrial flutter.

Study limitations

Cardiac rhythm was only evaluated at index admission and not analyzed during the follow-up period. Especially in patients of the CV+ group where sinus rhyhtm could be successfully restored during index admission, cardiac rhythm could have relapsed to AF at any time during the follow-up. Antiarrhythmic and anticoagulation therapy was registered at the index hospital stay and at the 5-year follow-up visit. During the course of the study, this therapy could have changed.

Conclusion

Patients with successful CV have a lower long-term unadjusted mortality compared to those with failed CV. Successful CV is not an independent predictor of mortality. Thus, successful CV is not associated with a prognostic impact on mortality but it remains a marker for a better prognosis in patients with organic heart disease.

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