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Mortality, Morbidity, and Quality of Life After Circumferential Pulmonary Vein Ablation for Atrial Fibrillation

Outcomes From a Controlled Nonrandomized Long-Term Study

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OBJECTIVES This study was designed to investigate the potential of circumferential pulmonary vein (PV) ablation for atrial fibrillation (AF) to maintain sinus rhythm (SR) over time, thus reducing mortality and morbidity while enhancing quality of life (QoL).

BACKGROUND Circumferential PV ablation is safe and effective, but the long-term outcomes and its impact on QoL have not been assessed or compared with those for medical therapy.

METHODS We examined the clinical course of 1,171 consecutive patients with symptomatic AF who were referred to us between January 1998 and March 2001. The 589 ablated patients were compared with the 582 who received antiarrhythmic medications for SR control. The QoL of 109 ablated and 102 medically treated patients was measured with the SF-36 survey.

RESULTS Median follow-up was 900 days (range 161 to 1,508 days). Kaplan-Meier analysis showed observed survival for ablated patients was longer than among patients treated medically ($p < 0.001$), and not different from that expected for healthy persons of the same gender and calendar year of birth ($p = 0.55$). Cox proportional-hazards model revealed in the ablation group hazard ratios of 0.46 (95% confidence interval [CI], 0.31 to 0.68; $p < 0.001$) for all-cause mortality, of 0.45 (95% CI, 0.31 to 0.64; $p < 0.001$) for morbidities mainly due to heart failure and ischemic cerebrovascular events, and of 0.30 (95% CI, 0.24 to 0.37; $p < 0.001$) for AF recurrence. Ablated patients' QoL, different from patients treated medically, reached normative levels at six months and remained unchanged at one year.

CONCLUSIONS Pulmonary vein ablation improves mortality, morbidity, and QoL as compared with medical therapy. Our findings pave the way for randomized trials to prospect a wider application of ablation therapy for AF. (J Am Coll Cardiol 2003;42:185–97) © 2003 by the American College of Cardiology Foundation

Atrial fibrillation (AF), the most common of all therapy-demanding cardiac arrhythmias, afflicts about 5% of a general middle-age population and is associated with high risk of stroke and death (1–3). Patients may experience a severely diminished quality of life (QoL) and frequent hospitalization (3,4).

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The desirable therapeutic goal in treating AF is to restore and maintain sinus rhythm (SR)—thus avoiding long-term anticoagulation—reducing thromboembolic risk, enhancing cardiac performance, and improving survival (5,6).

However, arrhythmia recurs within one to two years in at least 50% of patients despite antiarrhythmic drug therapy, which in turn may increase mortality (5–8). This has catalyzed the development of nonpharmacologic approaches to fully restore SR control over the atrium (9,10). The established dominance of the left atrium (LA) in the region of pulmonary veins (PVs) in triggering and/or maintaining AF prompted the development of new strategies for radio-frequency (RF) transcatheter ablation at this critical region (11–14). We devised circumferential PV ablation, a safe and effective therapeutic strategy for AF, which targets the venous-atrial junction (12,13). Its outcomes, however, had not been properly assessed or compared with those for medical therapy in a controlled, long-term study.

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Abbreviations and Acronyms

AF = atrial fibrillation
CAD = coronary artery disease
CI = confidence interval
ECG = electrocardiogram
HR = hazard ratio
LA = left atrial/atrium
MI = myocardial infarction
PV = pulmonary vein
QoL = quality of life
RF = radiofrequency
SR = sinus rhythm

We report on the clinical course of 1,171 patients with AF. The outcomes of the 589 patients who underwent circumferential PV ablation were compared with those of the 582 subjects who received medical treatment for SR control. The purpose of the study was to investigate the potential of ablation to maintain SR over time, thus reducing mortality and morbidity while enhancing QoL.

METHODS

Study population. Between January 1998 and March 2001, a total of 1,171 consecutive patients from all over Italy with symptomatic AF were referred to San Raffaele University Hospital's cardiac electrophysiology unit. We excluded patients because of the following reasons: contraindication to anticoagulation; New York Heart Association functional class IV; myocardial infarction or cardiac surgery within the past three months; sick sinus syndrome or atrioventricular conduction disturbances without an artificial pacemaker; ventricular tachyarrhythmias; thyroid dysfunction; or unsuccessful cardioversion to SR by drugs and/or electroshock.

The decision to undergo catheter ablation or medical treatment was left to the patient's own preferences or to the judgment of the electrophysiologist involved in each case, who decided intervention in cases of ≥2 previous ineffective trials with antiarrhythmic drugs, >2 AF-related hospital admissions during the 2 years before entering the study, or ≥2 years of antiarrhythmic drug treatment.

The study was approved by the hospital's ethics committee, and all patients gave their written informed consent.

Treatment of AF. ABLATED PATIENTS. Circumferential PV ablation was performed in 589 patients. All patients had to be taking effective oral anticoagulation medication for at least four weeks. Oral anticoagulants were replaced on admission by heparin to maintain a partial thromboplastin time of 60 to 90 s (control 30 s). Heparin was stopped 4 to 6 h before ablation, as trans-septal catheterization was required. The ablation technique's details have been published previously (12,13). Briefly, three-dimensional LA maps and PV profiles were reconstructed through a transseptal route using a nonfluoroscopic electrogeometric mapping system (CARTO, Biosense-Webster, Diamond Bar, California) (10,12,13). After characterizing PV ostia, RF energy was delivered by the distal electrode of the navigation catheter to create circular lines of conduction block around each vein ostium. An intravenous dose of 75 U heparin/kg of body weight was administered during ablation, followed by an infusion to maintain a partial thromboplastin time of 60 to 90 s.

This purely anatomic approach yields either an atriovenous electrical disconnection, as demonstrated by elimination of PV ostial potentials and absence of discrete electrical activity inside the lesion during pacing outside the ablation line, or a profound atrial electroanatomic remodeling, as expressed by voltage abatement inside and around the encircled areas, partially involving the LA posterior wall (Fig. 1) (12,13).

Procedures averaged 165 ± 22 min, with an ablation time of 59 ± 15 min for delivering 93 ± 18 RF pulses. Four patients (0.7%) required pericardiocentesis for cardiac tamponade. There were no strokes or other thromboembolic events. After ablation and during follow-up, no patient developed symptoms suggestive of PV stenosis. Transesophageal Doppler-echocardiography, performed within three days and one to six months after ablation, showed no high-velocity turbulence near the ostia suggestive of PV narrowing in any of the patients. Post-RF, all patients were given warfarin, whereas a previously ineffective antiarrhythmic was prescribed to patients (n = 115) who had in-hospital AF episodes and/or needed electrical cardioversion at the end of the procedure. At discharge, all patients were in SR. Both antiarrhythmics and anticoagulation were discontinued at three months in the absence of recurrences, with evidence of LA transport function by Doppler-echocardiography.

MEDICALLY TREATED PATIENTS. This study group comprised 582 subjects who were given antiarrhythmic medications for SR control throughout the follow-up period. In patients with intermittent AF, antiarrhythmic therapy was initiated during SR, whereas patients with nonself-terminating or chronic AF underwent pharmacological and, if necessary, electrical cardioversion followed by prophylactic antiarrhythmic agents to maintain SR. Anticoagulation was used in accordance with published guidelines (1,6) and could be stopped at the physician's discretion if SR had been maintained for at least three months.

At hospital discharge, all patients were in SR, 33% were on amiodarone, 17% on propafenone, 15% on flecainide, 13% on sotalol, 9% on quinidine, 6% on disopyramide, and 7% on >1 antiarrhythmic agent.

Follow-up and outcome measures. At referral, all patients' data were prospectively recorded in a computerized database. Follow-up began when patients were discharged, and we considered information until April 2002.

Follow-up consisted of outpatient visits with serial 12-lead electrocardiograms (ECGs), echocardiograms, and 24-h Holter monitoring performed on symptom recurrence or routinely at 1, 3, 6, 9, and 12 months in the first year, and

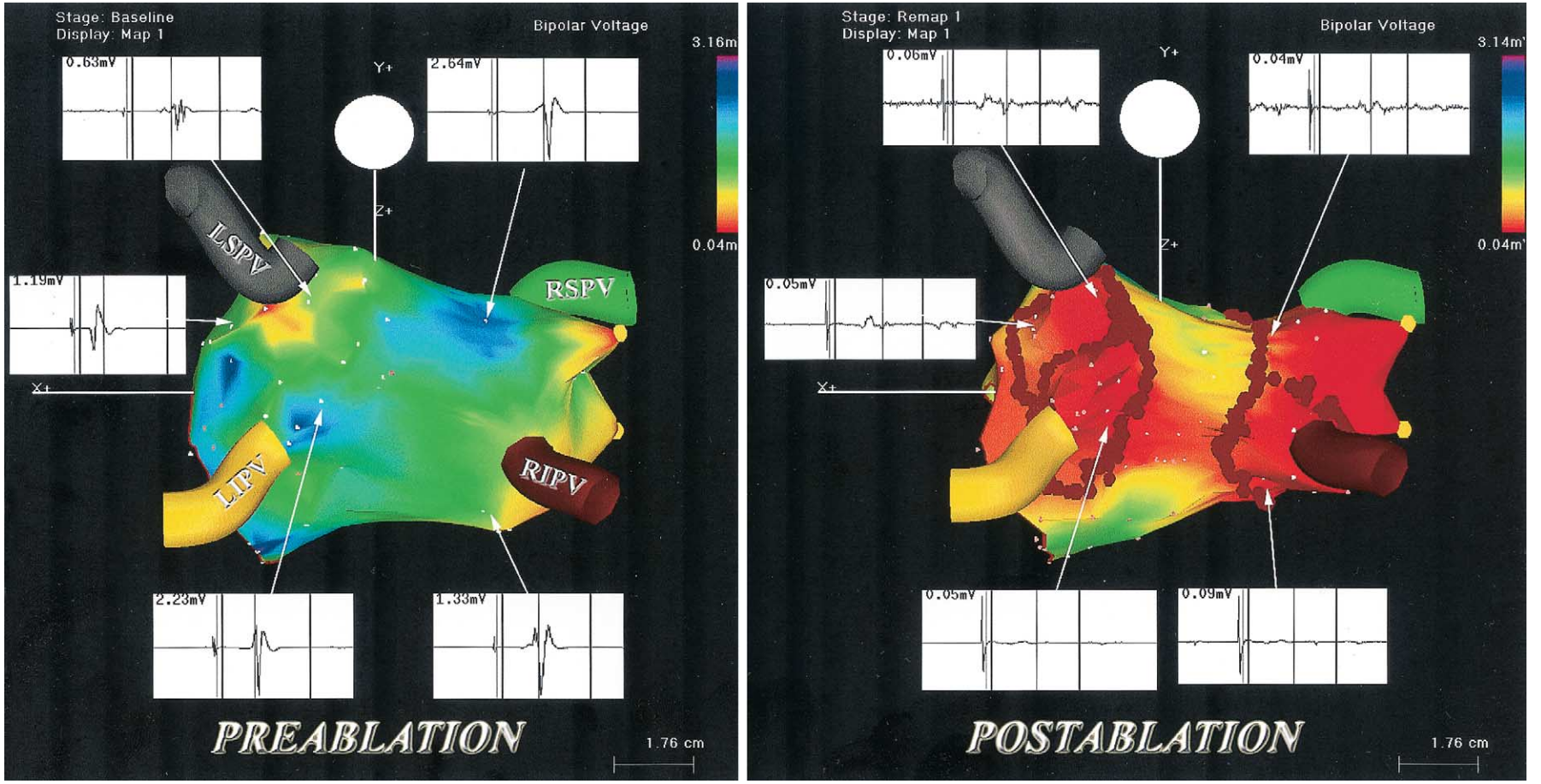


Figure 1. Three-dimensional left atrial (LA) voltage maps (posteroanterior view: **left,** preablation; **right,** postablation), depicting peak-to-peak bipolar electrogram amplitude. Color **red** represents lowest voltage, and **purple,** highest voltage. **Claret red spheres** represent radiofrequency lesions. In postablation, areas within and around the ablation lines, involving to some extent the LA posterior wall, show low-amplitude (<0.1 mV) electrograms. Preablation insets show pulmonary vein (PV) ostial potentials indicating the activation of muscular fibers capable of conducting impulses in or out of the veins. By creation of lesions around each vein ostium, PV potentials are no longer detected **(insets)** at the same ostial points recorded before ablation. LSPV = left superior pulmonary vein; LIPV = left inferior pulmonary vein; RSPV = right superior pulmonary vein; RIPV = right inferior pulmonary vein.

Table 1. Baseline Characteristics of Patients Who Underwent Ablation and of Patients Treated Medically at Time of Hospital Admission

Characteristic	Ablation Group (n = 589)	Medical Group (n = 582)	p Value
Age (yrs)	65± 9*	65 ± 10	0.99‖
Male gender (%)	58	59	0.95¶
Follow-up duration, median (range), (days)	861 (161–1491)	911 (179–1508)	0.22#
Out-patient visits (no./yrs)	3.2 ± 2.1	3.0 ± 2.4	0.13‖
History of AF†			
Duration (yrs)	5.5 ± 2.8	3.6 ± 1.9	<0.001‖
Paroxysmal (% of patients)	69	71	0.45¶
Chronic (% of patients)	31	29	0.45¶
Antiarrhythmic drugs (no. of trials)	3.1 ± 2.1	2.3 ± 1.5	<0.001‖
Medical history and conditions (% of patients)			
No cardiovascular disease	34	35	0.72¶
Hypertension	46	43	0.29¶
Diabetes	11	10	0.60¶
Cigarette smoking	49	46	0.34¶
Cholesterol >5.17 mmol/l	42	37	0.08¶
CAD	23	22	0.81¶
Dilated cardiomyopathy	5	4	0.40¶
Valvular disease	9	8	0.39¶
Prior stroke or TIA	16	15	0.12¶
Chronic lung disease	9	10	0.55¶
Cardiovascular drugs used	42	41	0.73¶
New York Heart Association functional class	1.3 ± 0.9	1.2 ± 0.7	0.09‖
Hospital admission (times/yrs)‡	2.4 ± 1.5	2.2 ± 1.6	0.04‖
Echocardiography			
LV ejection fraction (%)	54 ± 12	55 ± 14	0.22‖
LV fractional shortening (%)	33 ± 10	34 ± 7	0.07‖
LA diameter, long-axis view (mm)	46 ± 9	45 ± 8	0.06‖
LV mass index (g/m^2)	138 ± 56	135 ± 65	0.53‖
Peak mitral A-wave velocity (m/s)§	0.57 ± 0.08	0.56 ± 0.10	0.11‖

*Plus-minus are means ± SD. †Paroxysmal AF was defined as recurrent self-terminating episodes lasting fewer than seven days; chronic AF as AF persistent for at least seven days. ‡Hospital admissions refer to the two years before entering the study. §Data relative to patients evaluated during sinus rhythm. ‖p values by independent-samples *t* test. ¶By chi-squared test. #By independent-samples Wilcoxon-Mann-Whitney *U* test.

AF = atrial fibrillation; CAD = coronary artery disease; LA = left atrial; LV = left ventricular; TIA = transient ischemic attack.

every 6 months thereafter. Patients were also asked to maintain a log of symptoms suggestive of AF, and transtelephonic monitoring was considered to document the cause of symptoms. Moreover, patients, relatives, and primary physicians were also advised to report, by phone or E-mail, adverse events and hospitalizations occurring in-between visits.

Atrial fibrillation recurrence was defined as a symptomatic episode lasting more than 10 min and confirmed by ECG. To estimate the arrhythmia burden after the first recurrence, we measured the frequency of relapses as episodes/patient-year. Adverse events included heart failure requiring IV therapy, myocardial infarction (MI), cerebrovascular accident, transient ischemic attack (TIA), and peripheral embolism. Hospitalizations were measured as times/year. We examined hospital records, death certificates, and autopsy reports, and we classified deaths as either cardiovascular or noncardiovascular. An independent committee classified all events after masked review of the data.

In September 2000 we started measuring QoL with the 36-Item Short-Form General Health Survey (SF-36) (4,15,16). To assess the one-year time course of QoL we reported results of consecutive ablated (n = 109) and medically treated (n = 102) patients discharged by March 2001. Patients were interviewed at the time of admission and at three-month intervals thereafter.

Statistical analysis. Continuous data were previously examined by normality test. Parametric or nonparametric tests for independent or related samples were used as appropriate, and were specifically reported in the Results section. For discrete variables, the chi-squared test was performed, unless the Fisher exact test was required for frequency tables when >20% of the expected values were <5. Observed survival rates for both groups—presented as Kaplan-Meier plots—were compared among them and with the life-expectancy for persons of the same gender and calendar year of birth in the general Italian population by two- and one-sample log-rank tests (17).

A Cox proportional-hazards model was used to estimate the effect of treatment on all-cause mortality and freedom from adverse events or AF recurrence, while adjusting for other prognostic factors. The effect of being in SR on mortality and morbidity was estimated by introducing into the Cox model a time-dependent variable that assumed a

Table 2. Causes of Death and Adverse Events During Follow-Up

	Ablation Group (n = 589)	Medical Group (n = 582)	
	No. of Patients		Total
Death			
Cardiovascular causes	18	59	77
Congestive heart failure	8	23	31
Myocardial infarction	8	10	18
Sudden*	0	12	12
Ischemic stroke†	2	14	16
Noncardiovascular causes	20	24	44
Respiratory failure	5	7	12
Cancer	8	9	17
Infection	3	2	5
Other	4	6	10
Total	38	83	121
	No. of Events		Total
Adverse event‡			
Congestive heart failure	32	57	89
Myocardial infarction	7	8	15
Peripheral embolism	1	3	4
TIA	8	27	35
Ischemic stroke	4	15	19
Hemorrhagic stroke	2	7	9
Total	54	117	171
No. of patients with events	46	98	144

*At the time of death, 6 patients were on amiodarone, 3 on flecainide, 1 on sotalol, and 2 on propafenone and sotalol. †At the time of death all but 7 patients (1 ablated and 6 medically treated, p = 0.70 by the Fisher exact test) were on warfarin with a mean international normalized ratio (INR) of 2.3 ± 1.0 (range, 1.8–3.6). ‡Among the 4 peripheral embolisms, 35 transient ischemic attacks (TIAs) 19 ischemic, and 9 hemorrhagic strokes, 2, 26, 14, and 8 occurred during warfarin therapy, with mean INRs before the event of 2.4 ± 0.3 (range, 2.2–2.6), 2.1 ± 0.9 (range, 1.7–3.6), 2.0 ± 1.2 (range, 1.8–3.2), and 2.5 ± 0.5 (range, 1.9–4.2), respectively.

value of 1 until the first relapse occurred, and 0 thereafter. The AF burden was analyzed under the assumption of a Poisson distribution for the number of observed relapses to calculate the rate ratio, as the ratio of the observed frequencies of recurrence for the two groups, and the 95% confidence interval (CI). Generalized linear models for repeated measures were used to model change in QoL scores over time (18). Separate multivariate models, adjusted for relevant baseline characteristics listed in Figure 3, were used to assess changes in SF-36 physical and mental summary component scores, and the independent relationship of treatment and AF recurrence with QoL. Analyses were performed by S-PLUS-for-Windows (release 6, Basingstoke, Hampshire, UK) and SPSS-for-Windows (release 11.01, SPSS Inc., Chicago, Illinois). A two-sided $p < 0.05$ was regarded as significant.

RESULTS

Patients. The two treatment groups appeared well balanced, except for longer arrhythmia duration, greater number of antiarrhythmics tried, and more frequent hospitalization in the ablation group (Table 1). The overall median follow-up period was 900 days, with no significant difference in duration and intensity between groups. Nineteen patients (2%) were lost to follow-up.

Survival. At the latest assessment, 38 (6%) ablated patients and 83 (14%) in the medical group had died (Table 2). Cardiovascular deaths occurred less frequently in the ablation group with lower number of fatalities due to heart failure and ischemic strokes and no sudden death, although noncardiovascular mortality was comparable between the two groups. Of the total 77 patients who died of cardiovascular reasons, 58 (75%) had concurrent AF at time of death. Of note, 23 (74%) and 11 (61%) of the 31 and 18 deaths due to heart failure and MI occurred in subjects with AF. Observed survival for ablated patients was longer than among medically treated patients and not different from that expected for age- and gender-matched persons of the Italian population (Fig. 2). A reduction of 54% occurred in the risk of death for ablated patients ($p < 0.001$), with history of coronary artery disease (CAD), ejection fraction (EF) <45%, LV mass index >125 g/m^2, and age >65 years independently associated with higher risk of dying (Fig. 3A).

Morbidities. Forty-six (8%) ablated and 98 (19%) medically treated patients were managed for a total of 54 and 117 adverse events, respectively (Table 2). Heart failures and ischemic cerebrovascular events occurred more frequently in the medical group. The majority of patients (n = 104, 72%) with adverse events had AF at the time of the event. All four cases of peripheral embolism occurred in subjects with AF, as well as 89% and 79% of the 35 TIAs and 19 ischemic strokes. Respectively, 54% and 49% of ablated and medically managed patients had thromboembolic complications while receiving inadequate (international normalized ratio <2) or no anticoagulant therapy (p = 0.75, by chi-squared test). Ablated patients were less than half as likely as medically treated patients to have morbid events (hazard ratio [HR], 0.45; 95% CI, 0.31 to 0.64). Risk factors of death predicted adverse events too, as did history of cerebrovascular insults and being male (Fig. 3B). The adverse event-free survival probabilities were significantly higher among ablated patients (Fig. 4).

Effect of SR on mortality and morbidity. Maintenance of SR, as a time-dependent variable, was associated with significantly lower mortality and adverse event rates, either considering all patients (HR, 0.24; 95% CI, 0.16 to 0.37, and HR, 0.22; 95% CI, 0.15 to 0.31, respectively) or the two treatment groups (ablation: HR, 0.21; 95% CI, 0.09 to 0.48, and HR, 0.33; 95% CI, 0.16 to 0.68; medical: HR, 0.19; 95% CI, 0.12 to 0.32, and HR, 0.13; 95% CI, 0.08 to 0.21). We also found a somewhat reduced beneficial prognostic value of ablation, with no substantial changes in other predictive factors of death and adverse events (Figs. 3A and 3B).

Recurrences, LA size and function, and hospitalization. At final analysis, 120 ablated and 340 medically treated patients had their first relapses. Of the 120 recurrent ablated patients, 31 (26%) developed recurrent persistent AF, as

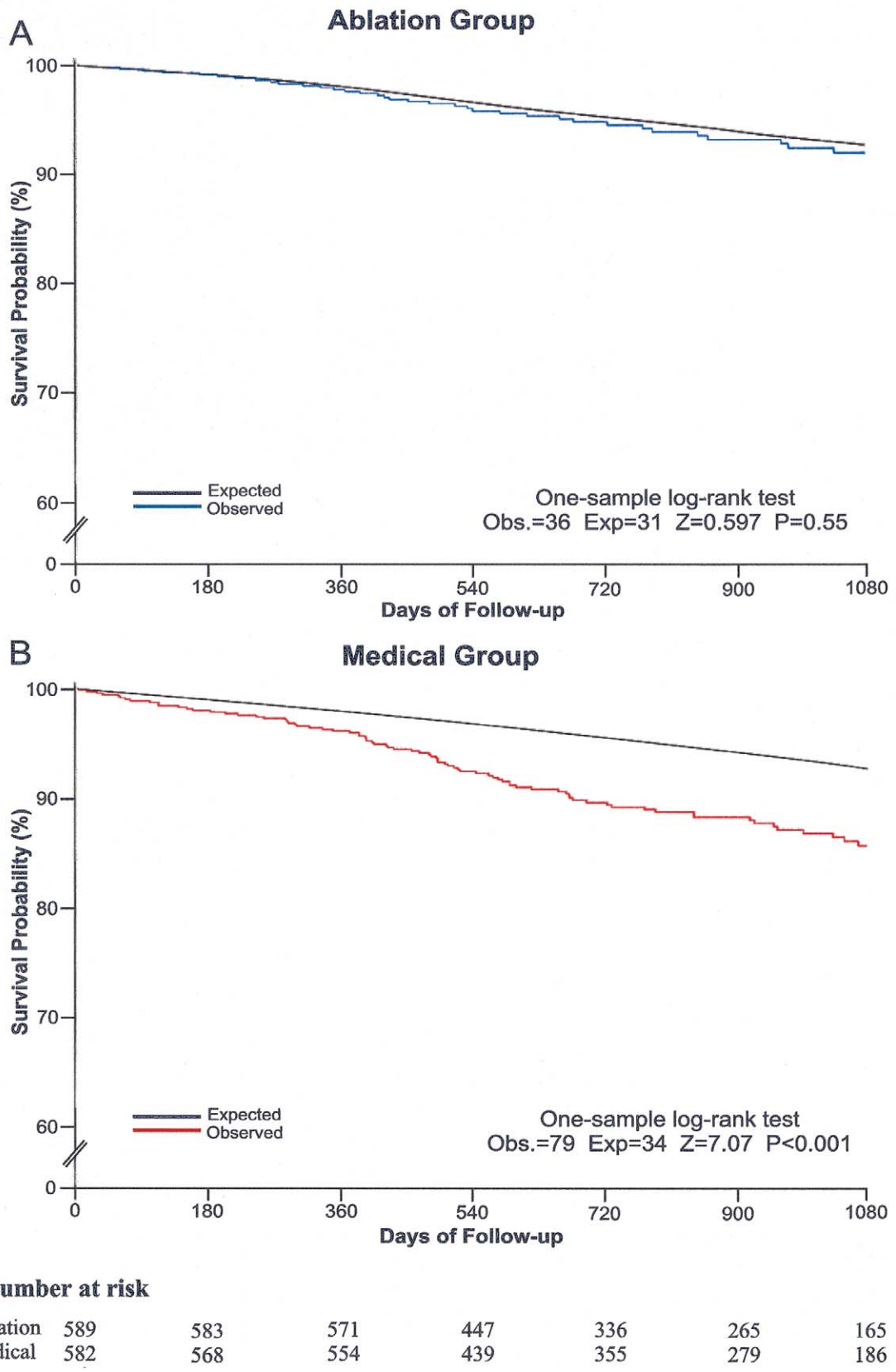


Figure 2. Observed and expected survival in the ablation and medical groups. The observed survival among ablation patients did not differ ($p = 0.55$) from the expected **(A)** and was significantly longer than that observed in the medical group, whose survival proved worse than that expected **(B)**. Observed survival probabilities were 98%, 95%, and 92% at one, two, and three years, respectively, among ablated patients, and 96%, 90%, and 86%, respectively, among those medically treated ($p < 0.001$).

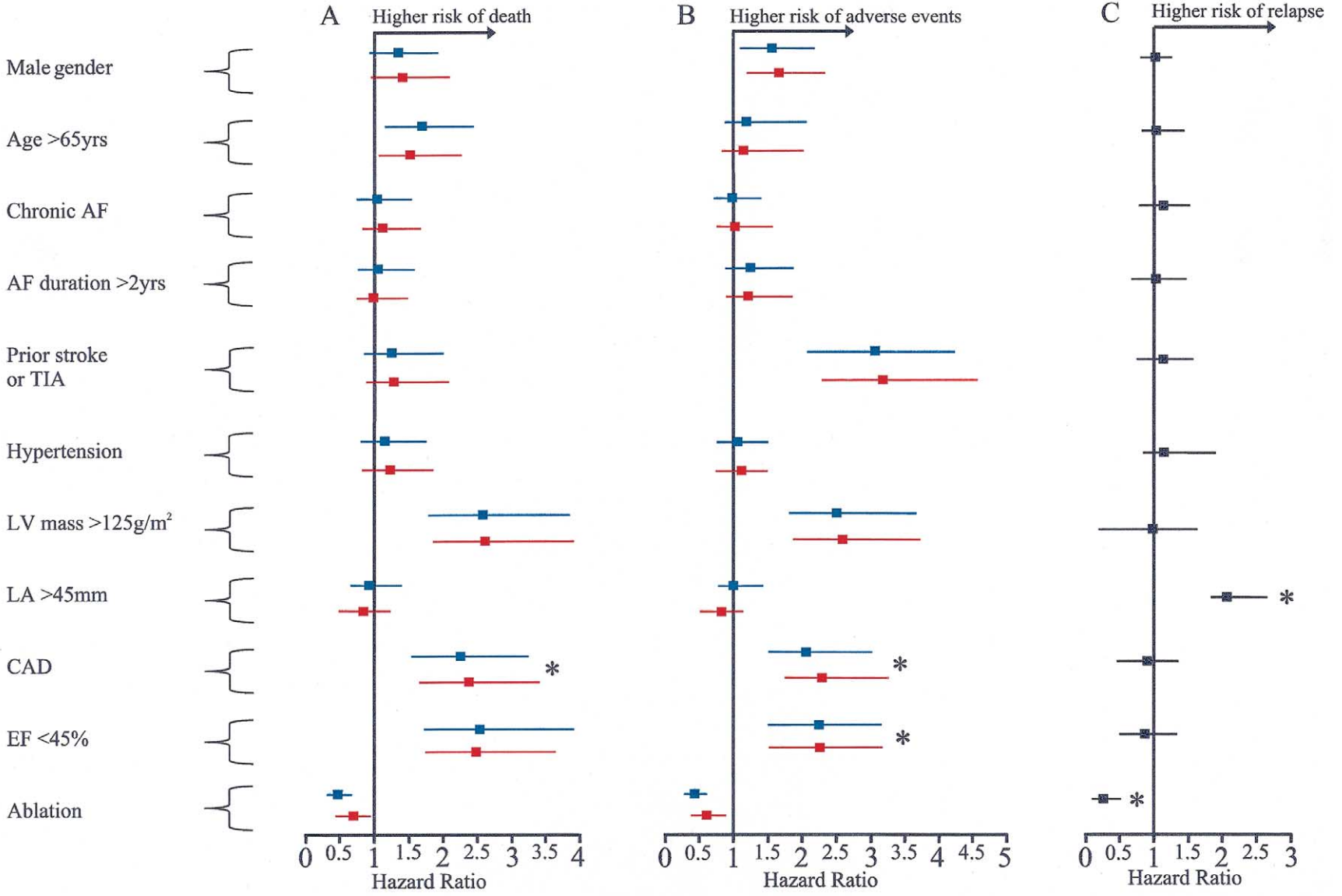


Figure 3. The hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of death, adverse events, and atrial fibrillation (AF) recurrence in the ablation group as compared with the medical group. In **A** and **B,** for each covariate, the corresponding HR and 95% CI are represented before **(blue line)** and after **(red line)** the introduction into the Cox model of maintenance of sinus rhythm (SR) as time-dependent variables. There was evidence of nonproportional hazards between the two treatment groups over time ($p < 0.001$) for recurrent AF, with a significant treatment interaction ($p < 0.001$); the corresponding HR for ablation was 0.30 (95% CI, 0.24 to 0.37) and must be interpreted as an average value during the entire follow-up period **(C)**, as well as the other HRs indicated by asterisks **(*)** in **A** and **B.** By entering maintenance of SR, ablation patients' HRs for the risk of all-cause death and adverse events went from 0.46 (95% CI, 0.31 to 0.68; $p < 0.001$) and 0.45 (95% CI, 0.31 to 0.64; $p < 0.001$) to 0.66 (95% CI, 0.44 to 0.97; $p = 0.04$) and 0.61 (95% CI, 0.42 to 0.86; $p = 0.007$), respectively. CAD = coronary artery disease; EF = ejection fraction; LA = left atrial; LV = left ventricular; TIA = transient ischemic attack.

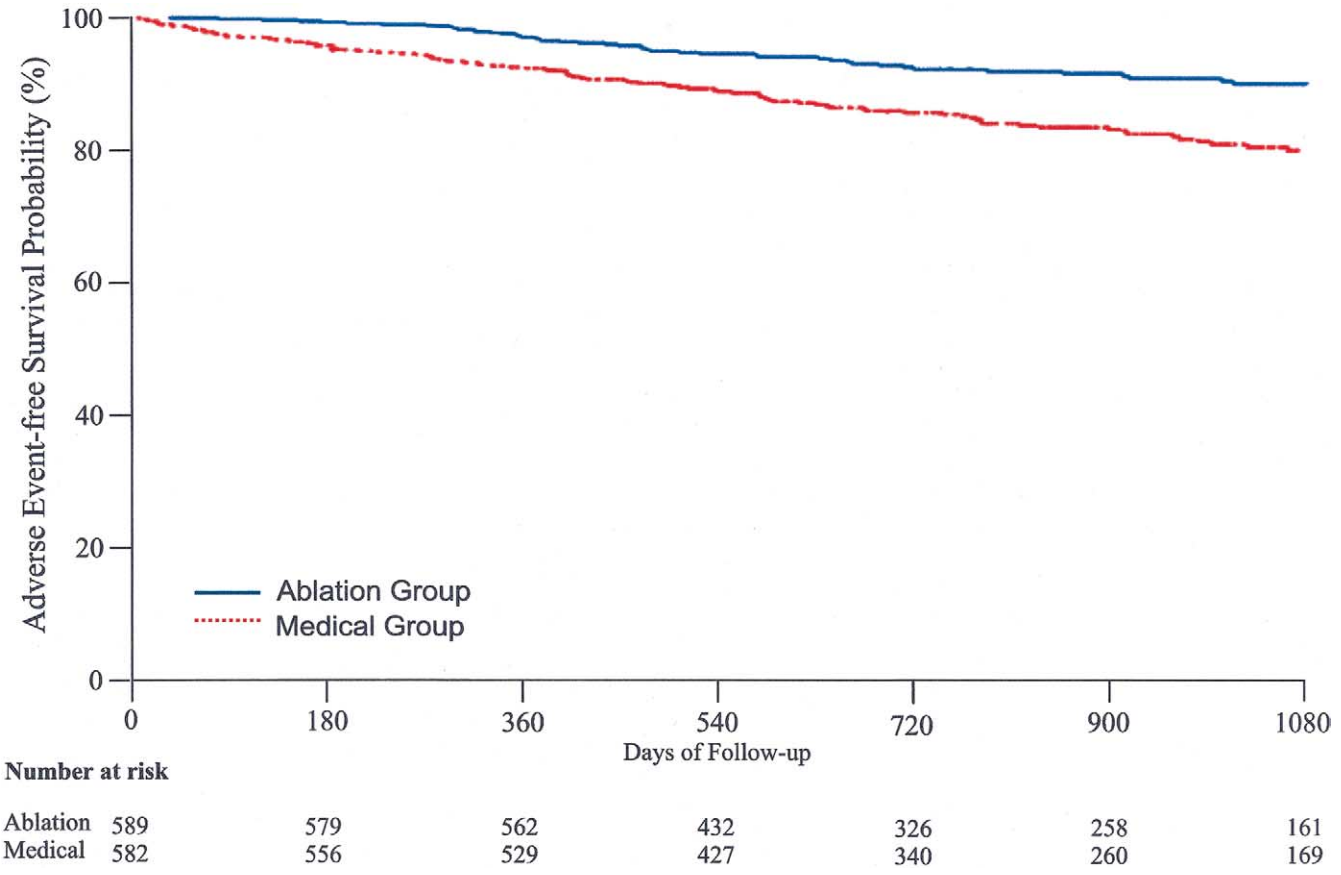


Figure 4. Kaplan-Meier estimates of the percentages of patients remaining free of any adverse events. Percentages of patients event-free were 97%, 94%, and 91% at one, two, and three years, respectively, among ablated patients, and 93%, 87%, and 81%, respectively, among those medically treated ($p < 0.001$).

well as 221 (65%) of the 340 medically managed patients with recurrences. Among the 45 recurrent ablated patients who had history of chronic AF, 28 (62%) developed paroxysmal AF. Of note, 12 (2%) ablated patients developed atypical LA flutters, which were successfully treated with linear lesions from the left inferior PV to the mitral annulus (60%) or connecting the superior (25%) or the inferior (15%) PVs.

Recurrence rates were significantly lower among ablated patients (Fig. 5). The protective effect of ablation increased over time, highlighting that patients had their arrhythmia cured if they did not lapse back to AF within ~10 months. Multivariate regression analysis was performed, including all variables listed in Figure 3, as well as early (within the first two weeks) recurrence of AF, need of cardioversion after completing ablation, and low-voltage encircled PV ostial area <15% of LA surface: only LA diameter >45 mm and reduced encircled area independently predicted long-term recurrences in ablated patients (HR, 3.37; 95% CI, 2.19 to 5.19, and HR, 3.58; 95% CI, 2.41 to 5.32, respectively); arrhythmia type and duration did not.

Arrhythmia burdens of 5.4 and 2.1 relapses/patient-year were observed among medically treated and ablated patients, respectively (rate ratio, 0.38; 95% CI, 0.32 to 0.56).

A nearly fourfold mean reduction in LA size and 1.5-fold mean increase in peak A-wave velocity were observed in nonrecurrent ablated patients compared with not-recurrent patients in the medical group (Table 3).

Hospitalizations were reduced in ablated patients with or without recurrences (Table 4). Not-recurrent medically treated patients were also hospitalized less, although more than not-recurrent ablated patients, with admissions mostly (53%) due to drug-related side effects.

Quality of life. As Figure 6 shows, at baseline both treatment groups, which were clinically comparable (Table 5), rated their health status similarly and lower than persons of the same sex and gender in the general Italian population ($p < 0.001$, by unpaired t test with Bonferroni correction) (16). Both physical and mental functioning scores showed similar changes over time in each group. A significant ($p = 0.007$) time trend over one year was detected only in ablated patients ($p = 0.004$), who reached normative levels at six months, with no further changes at one year. On multivariate analysis, AF recurrence was independently associated with significant reductions in physical and mental functioning in the medical group and impaired psychological well-being among ablated patients (all $p < 0.01$).

DISCUSSION

We found circumferential PV ablation for AF improves mortality, morbidity, and QoL, as compared to medical

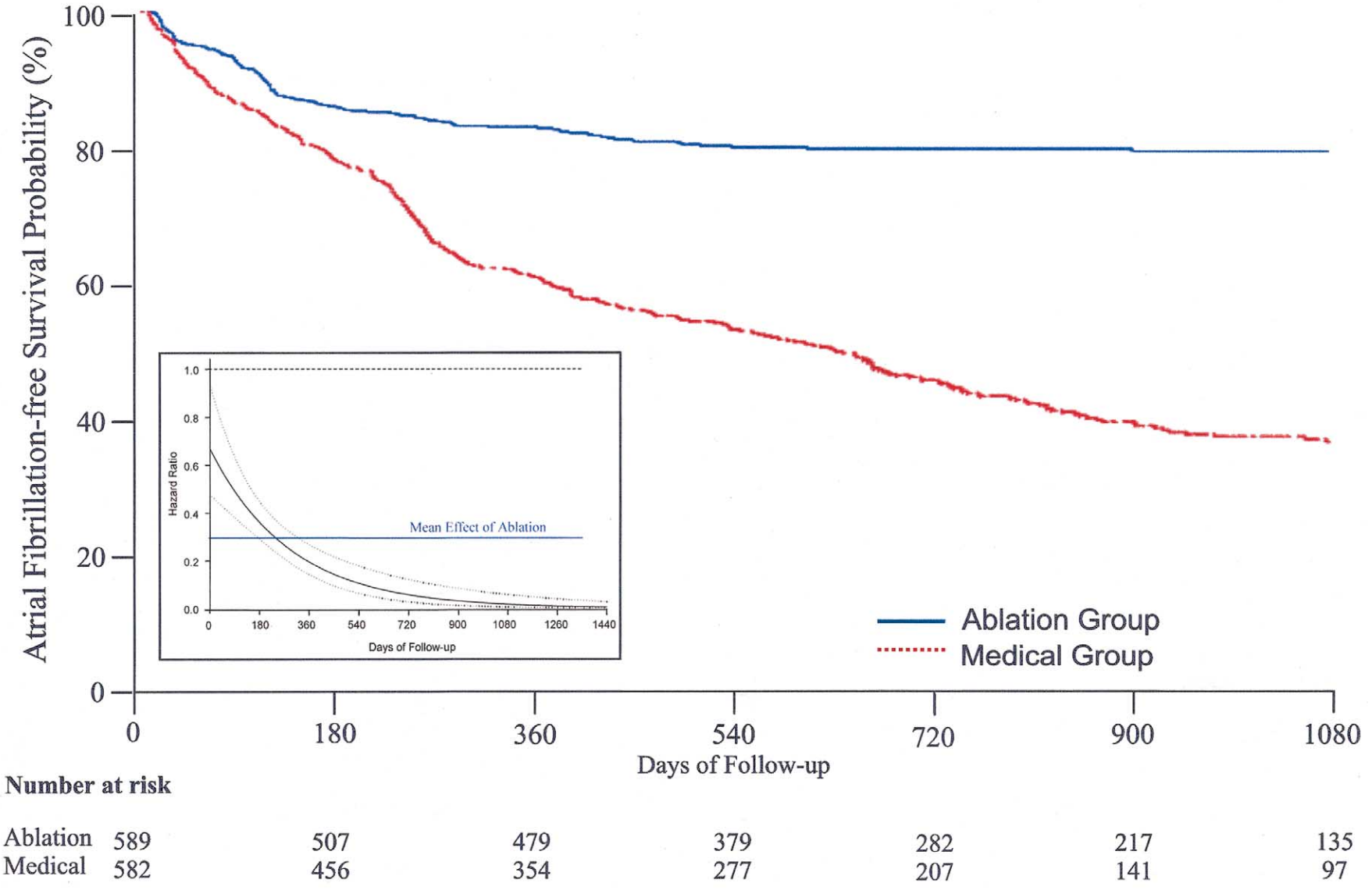


Figure 5. Kaplan-Meier estimates of the percentages of patients remaining free of atrial fibrillation (AF) recurrence. Percentages of AF-free patients were 84%, 79%, and 78%, respectively, at one, two, and three years among ablated patients, and 61%, 47%, and 37%, respectively, among those medically treated ($p < 0.001$). The favorable effect of ablation on AF recurrence increased over time during the entire follow-up period, with an average risk of 0.30 **(inset)**.

Table 3. Impact of Treatment on LA Size and Transport Function in Patients Grouped According to the Occurrence of Recurrent Atrial Fibrillation

	LA Size*		LA Transport Function*	
	Recurrent	Nonrecurrent	Recurrent†	Nonrecurrent
Ablation	−4.6 (−10.0 to 0.8)	−11.51 (−15.41 to 7.61)‡	0.05 (−0.02 to 0.11)	0.12 (0.08 to 0.17)§
Medical therapy	−2.13 (−5.33 to 1.07)	−2.92 (−5.37 to −0.47)‡	−0.12 (−0.24 to 0.21)	0.08 (0.01 to 0.16)§

*Echocardiographic left atrial (LA) size was defined as medial-lateral atrial diameter in mm and LA transport function as peak mitral A-wave velocity in m/s; their changes are presented as mean values with corresponding 95% confidence intervals in parentheses, or medians with 25th to 75th percentiles in parentheses, as appropriate. †Data relative to patients evaluated during sinus rhythm. ‡p values <0.01 by related-samples *t* test. §p values <0.01 by related-samples Wilcoxon signed-rank test, for changes from baseline to the latest follow-up echocardiographic examination.

therapy. Atrial fibrillation has been associated with a doubling of the risk for death and a quintupling of that for stroke compared with subjects in SR, after adjustment for coexisting cardiovascular conditions (2,3). Our ablated patients had a remarkable HR for death of 0.46 and reductions of 70% and 55% in the risk of recurrent AF and major morbidities, respectively, due mainly to heart failure and ischemic cerebrovascular insults. It is significant that ablation lengthened survival to almost that expected for the general population, emphasizing the importance of potentially preventable deaths among AF patients. However, the extent of this benefit must be interpreted in light of the fact that a sizable proportion of our patients had no cardiovascular disease and the median follow-up period was 900 days. Accordingly, data on longer follow-up will be needed.

Maintenance of SR and clinical implications. Another important finding was that maintenance of SR as a time-dependent variable was associated with reductions in the risk of death (76%) and adverse events (78%), with ablation still preserving its beneficial effects, yet with relatively higher HRs of dying (0.66 vs. 0.46) or experiencing morbid events (0.61 vs. 0.45). That ablation still preserved its favorable prognostic effects would suggest the potential advantage of maintaining SR with antifibrillatory agents is outweighed by their proclivity to cause life-threatening proarrhythmia and serious side effects or to exacerbate ischemia or heart failure by their negative inotropic actions (5–8). Indeed, sudden death and heart failure were key contributors in shortening survival in the medical group as were ischemic cerebrovascular events in increasing morbidity. In the latter, the higher incidence of TIAs and strokes was likely secondary to recurrent AF, as no significant difference was noted in the proportions of patients not receiving anticoagulants or with inadequate anticoagulation between the two treatment groups, whereas concurrent AF was observed in the vast majority of cases with thromboembolic events.

Table 4. Impact of Treatment on Hospitalization in Patients Grouped According to the Occurrence of Recurrent Atrial Fibrillation*

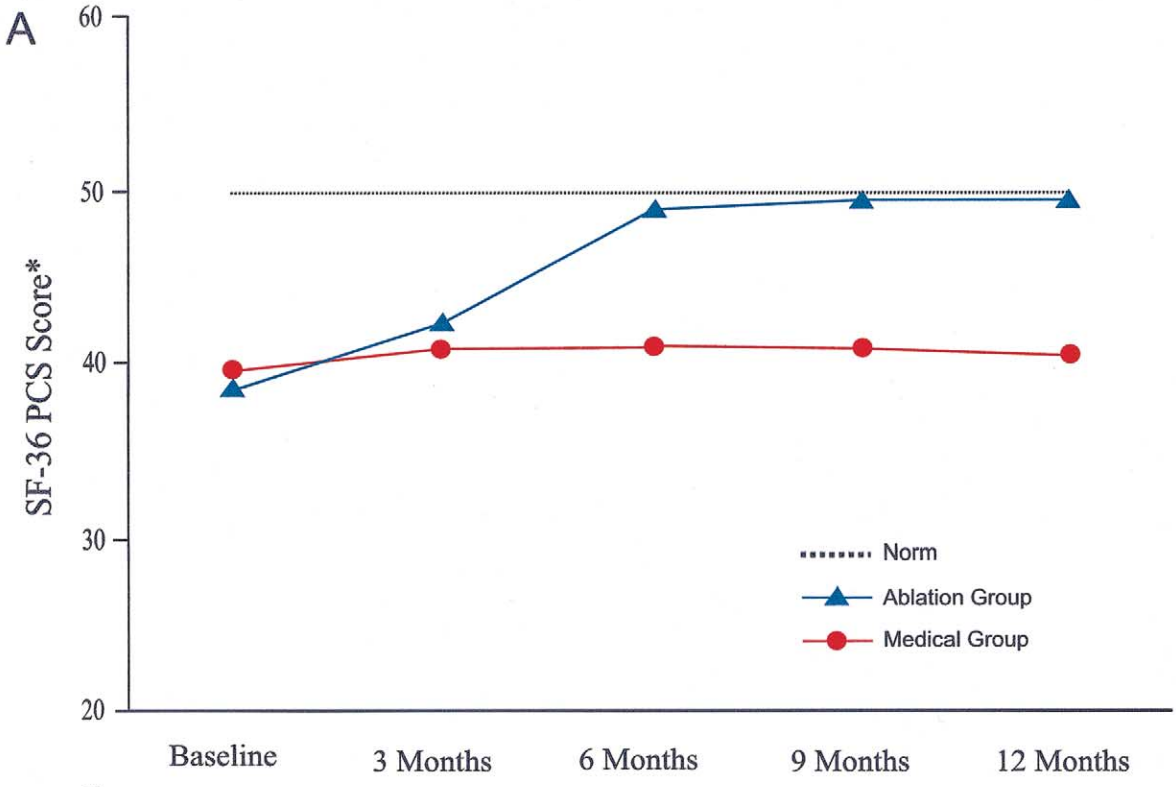
	Recurrent	p Value†	Nonrecurrent	p Value†
Ablation	−0.7 (−1.9 to 0.2)	0.04	−1.8 (−4.7 to −0.7)	<0.001
Medical therapy	0.5 (−0.7 to 2.8)	0.43	−1.2 (−2.9 to −0.8)	0.01

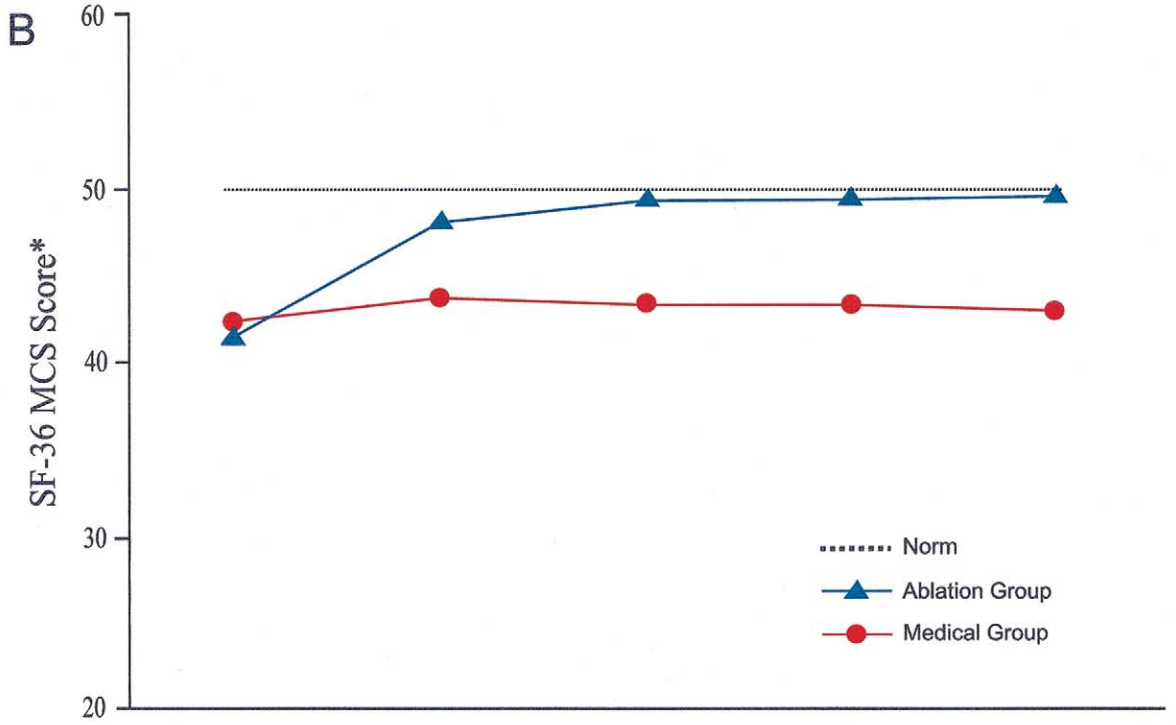
*Changes in hospitalization rates (times/year), from two years before entering the study and during follow-up, are described by medians with 25th to 75th percentiles in parentheses. †p values are by related-samples Wilcoxon signed-rank test.

With regard to this, it is noteworthy to emphasize that in our patient population of ablated and nonablated patients, whose characteristics were remarkable for the absence of structural heart disease other than hypertension, many patients who developed or died from congestive heart failure or MI had recurrent AF. Taken together, all these findings imply maintenance of SR affects prognosis, perhaps because of improved hemodynamics and atrial transport function, with greater benefit for patients with stiff ventricles, such as those with hypertension; other benefits include reduced risks of tachycardia-mediated cardiomyopathy and of cerebral and coronary artery thromboembolism (5,6). That SR resulted as a strong prognostic determinant, with coexisting heart conditions such as CAD, LV hypertrophy, and systolic dysfunction all preserving their predictive power, reinforces the concept that, AF, by itself or as hastening factor, may cause excess mortality and morbidity. Its prevention and treatment should, therefore, always be pursued.

Ablation was three-fold as effective as were drugs in preventing recurrences of AF, despite the fact that the ablation group had more patients with longer arrhythmia duration and more previously failed drug trials, and the recurrence rates among our medically treated patients were very similar to those of previous studies using various antifibrillatory compounds, including the relatively safe amiodarone (5–7). Moreover, the arrhythmia burden among ablated patients was approximately three-fold as low as that in the medical-therapy group. Of note, both recurrent and nonrecurrent ablated patients experienced significantly fewer hospitalizations that patients treated medically, and this has implications for overall cost.

Paroxysmal versus chronic AF. Circumferential PV ablation was efficacious in both paroxysmal and chronic AF. This indicates our anatomic approach produces either the electrical isolation of PV foci triggering the arrhythmia or a profound electroanatomic remodeling involving the atrial tissue adjacent to vein ostia-substrate for AF maintenance (12,13). Indeed, a reduced extent of the encircled PV ostial area was a strong predictor of recurrences. This may explain why the success rates of this ablative technique in both arrhythmia types are higher than in mapping-guided strategies isolating PVs at their ostia, without excluding any atrial myocardium (14). Moreover, circumferential PV ab-





Responders

Ablation	109	108	108	105	107
Medical	102	102	99	96	97

Figure 6. Changes in quality of life over time in the ablation and medical groups. The computation of aggregate scores for the physical (PCS, **A**) and mental (MCS, **B**) components and missing data were handled as suggested by the developers of the SF-36 (15).

Table 5. Baseline Clinical Characteristics at Time of Hospital Admission of Ablated and Medically Treated Patients Included in the Quality of Life Analysis

Characteristic	Ablation Group (n = 109)	Medical Group (n = 102)	p Value
Age (yrs)	66 ± 8*	64 ± 11	0.13†
Male gender (%)	56	57	0.88‡
History of AF			
Duration (yrs)	5.1 ± 2.6	3.8 ± 2.1	<0.001†
Paroxysmal (% of patients)	67	70	0.64‡
Antiarrhythmic drugs (no. of trials)	2.9 ± 2.2	2.2 ± 1.4	0.007†
Medical history and conditions (% of patients)			
No cardiovascular disease	36	37	0.88‡
Hypertension	44	44	0.99‡
Diabetes	10	11	0.81‡
CAD	22	24	0.73‡
Dilated cardiomyopathy	4	4	0.99‖
Valvular disease	8	9	0.79‡
Prior stroke or TIA	14	13	0.83‡
Cardiovascular drugs used	44	42	0.77‡
New York Heart Association functional class	1.4 ± 0.8	1.3 ± 0.6	0.31†
Hospital admission (times/yrs)	2.5 ± 1.6	2.0 ± 1.4	0.02†

*Plus-minus are means ± SD. †P values by independent-samples *t* test. ‡By chi-squared test. ‖By the Fisher exact test.
CAD = coronary artery disease, TIA = transient ischemic attack.

lation appears to significantly alter the atrial anatomy necessary for AF initiation and/or maintenance as demonstrated by the marked LA size reduction with improved transport function in patients with no recurrence.

Health status. To evaluate new therapy thoroughly, its impact on the quality of patients' everyday lives should also be defined. Our ablated patients, differently from patients treated medically, enjoyed better general health, and their physical and psychological well-being scores reached the levels of the general population, suggesting an all-around impact. The possibility of a persistent placebo effect of ablation appears minimal, because QoL at one-year was essentially the same as that at six months; moreover, AF recurrence also negatively impacted health status in ablated patients.

Study limitations. Our findings and conclusions should be interpreted in the light of the limitations imposed by a nonrandomized assignment of patients to the two treatment groups. With such an observational design, selection bias cannot be excluded; however, the inclusion of consecutive patients, the analysis of all data based on multivariate regression models, and the review of all events by an independent committee unaware of the two treatment groups minimized such bias. Moreover, although the considered clinical characteristics of the two groups were not identical, the differences did not substantially indicate a more favorable prognosis for one group over the other.

Recurrences were quantified based on patient symptoms and serial ECGs and Holter monitors, whereas transtelephonic monitors were available for symptomatic patients. Therefore, our criterion to define AF recurrence may have underestimated the true recurrence rates, as many AF episodes may be asymptomatic. Our findings deserve careful consideration, because they were obtained in a very experienced center and need to be confirmed in further studies.

Conclusions. Because in both our ablation and antiarrhythmic groups, SR maintenance was associated with significantly lower mortality and adverse event rates, the present study questions the results of three recent AF trials (Pharmacological Intervention in Atrial Fibrillation, Atrial Fibrillation Follow-up Investigation of Rhythm Management, and Rate Control vs. Electrical Cardioversion for Persistent Atrial Fibrillation [PIAF, AFFIRM, and RACE, respectively]), which demonstrated, contrary to prevailing practice, the lack of benefit of rhythm control over heart rate control by drugs (19–21).

On the one hand, these conflicting results could be explained by the fact that it is difficult to directly compare our study with others because patient populations are inevitably different. Indeed, RACE and AFFIRM enrolled only older patients with one or more risk factors for stroke, most of whom had persistent AF (20,21). Younger patients with structurally normal hearts and paroxysmal arrhythmia were disproportionately represented in these trials, and results could not be generalized to a broader AF population; thus, curing AF and maintaining SR may still be the goal, at least in some groups of patients.

On the other hand, it should be noted that it is intrinsically unlikely that SR is per se harmful to the patient's life, and one could argue that the warning trend toward a higher risk of death in the rhythm-control groups in both RACE and AFFIRM studies could be attributable to the means used to achieve SR or to the means used for its long-term maintenance (20,21). Thus, we believe that the quest for safer and more effective catheter ablation techniques for curing AF will, and should, continue. In the meantime, although this cohort follow-up study suggests that PV ablation could be attempted not only in patients with severe drug-refractory AF, the purpose it really serves is to provide

encouragement for a prospective multicenter randomized clinical trial to confirm our findings.

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