

ORIGINAL ARTICLE

# A Randomized Study of Prophylactic Catheter Ablation in Asymptomatic Patients with the Wolff–Parkinson–White Syndrome

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## ABSTRACT

### BACKGROUND

Young age and inducibility of atrioventricular reciprocating tachycardia or atrial fibrillation during invasive electrophysiological testing identify asymptomatic patients with a Wolff–Parkinson–White pattern on the electrocardiogram as being at high risk for arrhythmic events. We tested the hypothesis that prophylactic catheter ablation of accessory pathways would provide meaningful and durable benefits as compared with no treatment in such patients.

### METHODS

From 1997 to 2002, among 224 eligible asymptomatic patients with the Wolff–Parkinson–White syndrome, patients at high risk for arrhythmias were randomly assigned to radio-frequency catheter ablation of accessory pathways (37 patients) or no treatment (35 patients). The end point was the occurrence of arrhythmic events over a five-year follow-up period.

### RESULTS

Patients assigned to ablation had base-line characteristics that were similar to those of the controls. Two patients in the ablation group (5 percent) and 21 in the control group (60 percent) had arrhythmic events. One control patient had ventricular fibrillation as the presenting arrhythmia. The five-year Kaplan–Meier estimates of the incidence of arrhythmic events were 7 percent among patients who underwent ablation and 77 percent among the controls ( $P < 0.001$  by the log-rank test); the risk reduction with ablation was 92 percent (relative risk, 0.08; 95 percent confidence interval, 0.02 to 0.33;  $P < 0.001$ ).

### CONCLUSIONS

Prophylactic accessory-pathway ablation markedly reduces the frequency of arrhythmic events in asymptomatic patients with the Wolff–Parkinson–White syndrome who are at high risk for such events.

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**S**UDDEN DEATH FROM CARDIAC CAUSES in a healthy young person is a tragic event. Although ventricular fibrillation can be the presenting arrhythmia in asymptomatic patients with a Wolff–Parkinson–White electrocardiographic pattern, invasive electrophysiological testing for risk stratification and catheter ablation are not routinely recommended.<sup>1</sup> We recently reported that a particular subgroup of asymptomatic patients may be at risk for an arrhythmic event during follow-up.<sup>2</sup> We also demonstrated the value of electrophysiological testing for stratifying asymptomatic patients into high- and low-risk groups. In the present trial, we tested the hypothesis that prophylactic accessory-pathway ablation performed at the time of the initial electrophysiological testing would improve the long-term outcome of patients at high risk for arrhythmias.

## METHODS

### ELIGIBLE PATIENTS

Recruitment of patients began on June 1, 1997, and ended on June 1, 2002. The inclusion criteria were ventricular preexcitation documented by 12-lead electrocardiography and the absence of arrhythmia-related symptoms. The exclusion criteria were participation in other investigational protocols, an age of less than 13 years, pregnancy, and concomitant medical conditions (Fig. 1). The study design was approved by the ethics committees of the two centers involved, and written informed consent was obtained from all patients.

### ELECTROPHYSIOLOGICAL TESTING

All patients were hospitalized and underwent electrophysiological testing the same day to assess the inducibility of atrioventricular reciprocating tachycardia, atrial fibrillation, or both. The details of the electrophysiological testing have been described previously.<sup>2</sup> The stimulation protocol consisted of atrial and ventricular incremental pacing and extrastimulation to assess inducibility. Atrial and ventricular extrastimulation with progressively shorter coupling intervals was performed at drive-cycle lengths of 400 and 350 msec to induce atrioventricular reciprocating tachycardia until the effective refractory periods of the atrium and ventricle were achieved. An episode of atrioventricular reciprocating tachycardia was terminated by rapid pacing three minutes after its onset. The anterograde effective refractory period of the accessory pathway was defined as the longest coupling interval at which anterograde

block in the bypass tract was observed. If atrial fibrillation was not induced by atrial extrastimuli, atrial burst pacing at basic cycle lengths of 300, 200, and 100 msec for 20 seconds was performed. Atrial fibrillation was considered an abnormal response if it lasted more than 30 seconds. Induced arrhythmias were considered sustained if they lasted for more than one minute. Preexcitation QRS morphology, the mean ventricular rate, and the shortest RR interval between two consecutive preexcited QRS complexes were determined during sustained atrial fibrillation when atrial fibrillation could be induced. Intravenous isoproterenol (1 to 4 µg per minute) or atropine (0.02 to 0.04 mg per kilogram of body weight) was used to facilitate the induction of arrhythmias.

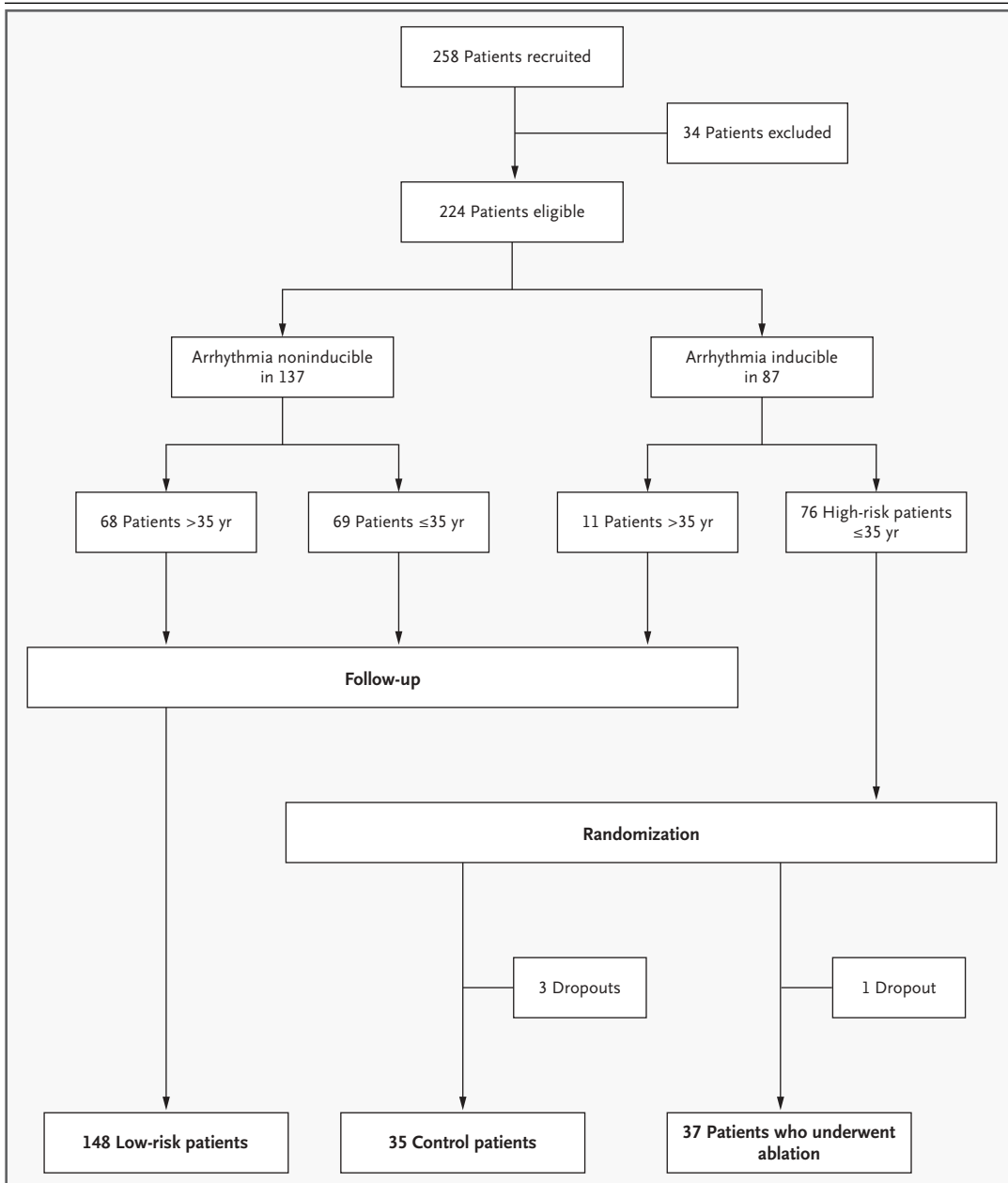
### RISK STRATIFICATION AND RANDOMIZATION

Once the results of their electrophysiological tests had been obtained, patients were classified as being at high or low risk for arrhythmias (Fig. 1). Patients at high risk were defined as those 35 years old or younger in whom arrhythmias were reproducibly induced. Once classified, these patients were randomly assigned to undergo radiofrequency catheter ablation of accessory pathways or to receive no treatment. Patients over 35 years of age, regardless of whether or not arrhythmias could be induced in them, and younger patients in whom arrhythmias could not be induced were considered to be at low risk and were followed up. Randomization was performed in a 1:1 fashion according to a computer-generated randomization scheme, in permuted blocks of four, to ensure a balance between groups in the two centers involved in this trial.

### ABLATION THERAPY

After electrophysiological evaluation had been performed, a 7-French, large-tipped, deflectable electrode catheter was introduced through the femoral artery for ablation of a left-sided accessory pathway or by the femoral vein for ablation of a right-sided pathway. Radio-frequency energy was delivered at a power of 30 to 50 W, and if conduction over the accessory pathway disappeared within 10 seconds the energy was maintained for 60 to 180 seconds with a maximal temperature of 65°C. If conduction persisted during the 10 seconds, the energy was not maintained. Multiple accessory pathways were defined as two or more distinct sites of early anterograde activation, retrograde activation, or both.

The full stimulation protocol was repeated after



**Figure 1. Study Protocol.**

The numbers of patients active in the study between recruitment and assignment to treatment group are shown. Thirty-four patients were excluded because of participation in other investigational protocols (3 patients), an age younger than 13 years (16 patients), pregnancy (2 patients), and concomitant medical conditions (13 patients).

a 30-minute waiting period, and the study was concluded if conduction in the accessory pathways was eliminated and arrhythmias could not be induced either with or without isoproterenol infusion. Major complications were defined as those that required intervention or prolonged the hospital stay.

**FOLLOW-UP EVALUATION**

For all 224 study patients, the intensity of follow-up was prespecified and included complete clinical examination with serial electrocardiography and 24-hour Holter monitoring that were uniformly scheduled and performed at one, three, and six

months; thereafter, the patients were seen once a year, or earlier if symptoms or arrhythmias occurred. No antiarrhythmic drug was given. The patients were asked to report any palpitations, asthenia, dyspnea (at rest, during effort, or both), dizziness, chest pain, blurred vision, or syncope.

The main prespecified end point was the occurrence of symptomatic arrhythmic events, including supraventricular tachycardia, atrial fibrillation, and ventricular fibrillation. Patients who underwent ablation were prescribed 100 mg of aspirin per day for four weeks after the procedure. To ensure uniformity in end-point ascertainment, the events were reviewed by an independent committee whose members were unaware of the patients' treatment assignments.

#### STATISTICAL ANALYSIS

The sample size for this study was determined on the basis of the anticipated frequency of arrhythmic events in the ablation and control groups. On the basis of our own experience, we predicted a 50 percent rate of arrhythmic events during a three-year observation period among high-risk patients with asymptomatic preexcitation. We also assumed that ablation would result in a 90 percent reduction in the frequency of arrhythmic events. On the basis of these assumptions, we predicted that 31 patients per group would be needed to give a power of 95 percent to detect an absolute difference of 40 percent with a two-sided  $\alpha$  value of 0.05. To allow for an unpredictable number of withdrawals, we decided to enroll a total of 76 patients in the expectation that at least 31 patients would be left in each group after a five-year observation period. Continuous variables were compared with use of the Mann-Whitney U test. For categorical variables, the chi-square test and the exact method were used. Event-free survival was calculated according to the Kaplan-Meier method, with the time of the first arrhythmic event as the outcome variable. The statistical significance of differences in outcome between the two randomized groups was assessed with use of the log-rank test. The data were censored if the patient died, reached the end of the follow-up period (June 2002), or was lost to follow-up without an occurrence of the outcome end point. In addition, covariate-adjusted analysis was performed with use of the Cox proportional-hazards model. The covariates included in this analysis were age, sex, the anterograde refractory period of the accessory pathways before and after isoproterenol treatment, the number of

accessory pathways, and the type of inducible arrhythmia. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Statistical tests were performed with use of SPSS for Windows, version 11.0.1.

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## RESULTS

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#### PATIENTS

Thirty-four of 258 consecutive asymptomatic patients with Wolff-Parkinson-White syndrome were excluded. Among the remaining 224 eligible patients, 76 were classified as being at high risk and the other 148 were classified as being at low risk (Fig. 1). Thirty-eight of the high-risk patients were randomly assigned to the ablation group, and 38 to the control group. Four patients withdrew consent immediately after randomization (one in the ablation group and three in the control group) and were excluded from the study. These dropouts left 37 in the ablation group and 35 in the control group. No patient died or was lost to follow-up.

#### ELECTROPHYSIOLOGICAL TESTING AND ABLATION

No significant differences were observed between the two groups of patients at high risk (Table 1). Among the 37 patients in the ablation group, atrioventricular reciprocating tachycardia was inducible in 15. In eight additional patients, atrioventricular reciprocating tachycardia degenerated into sustained atrial fibrillation. In the remaining 14 patients, nonsustained atrial fibrillation alone was induced by burst pacing. Ablation was successful in all patients. The median number of radio-frequency applications was 9 (range, 5 to 22). Among the 224 patients who underwent electrophysiological testing, major complications developed in 4 patients, for an overall rate of 2 percent. Complications related to electrophysiological testing (two pneumothoraxes and one large femoral hematoma) developed in 3 patients (1 percent), and an ablation-related complication (permanent right bundle-branch block) developed in 1 of the 37 patients (3 percent) in the ablation group; this patient had an anteroseptal accessory pathway.

#### ARRHYTHMIC EVENTS

##### *Ablation Group*

The 37 patients who underwent ablation were followed for a median of 27 months (range, 9 to 60). Two patients had an arrhythmic event, one at 9 months and the other at 26 months. Repeated

**Table 1. Characteristics of the 72 Asymptomatic Patients with the Wolff-Parkinson-White Syndrome at High Risk for Arrhythmias.\***

Variable	Ablation Group (N=37)	Control Group (N=35)
Age (yr)		
Median	23	22
Interquartile range	15-30	15-30
Male sex (%)	53	47
Structural heart disease (%)	0	0
Anterograde refractory period of accessory pathways (msec)		
Median	240	240
Interquartile range	225-260	230-260
Anterograde refractory period of accessory pathways after isoproterenol (msec)		
Median	200	200
Interquartile range	200-210	200-210
Multiple accessory pathways (%)	35	31
Location of single accessory pathways (%)†		
Left free wall	50	38
Right free wall	38	42
Posteroseptal	8	17
Anteroseptal	4	4
Location of multiple accessory pathways (%)‡		
Left free wall and posteroseptal	31	36
Left free wall and right free wall	39	27
Right free wall and posteroseptal	31	36
Inducibility (%)		
Nonsustained atrial fibrillation	38	37
Atrioventricular reciprocating tachycardia	41	40
Atrioventricular reciprocating tachycardia triggering atrial fibrillation	22	23
Length of atrioventricular reciprocating tachycardia cycle (msec)§		
Median	290	283
Interquartile range	260-300	260-300
Shortest preexcited RR interval during atrial fibrillation (msec)¶		
Median	250	240
Interquartile range	230-260	225-250
Shortest preexcited RR interval during sustained atrial fibrillation (msec)		
Median	230	225
Interquartile range	212-245	210-230
Hospital stay (days)		
Median	2	2
Range	2-5	2-5

\* Because of rounding, not all percentages total 100. There were no significant differences between the groups.

† Data are from 24 patients who underwent ablation and 24 controls.

‡ Data are from 13 patients who underwent ablation and 11 controls.

§ Data are from 23 patients who underwent ablation and 22 controls.

¶ Data are from 22 patients who underwent ablation and 21 controls.

|| Data are from 8 patients who underwent ablation and 8 controls.

electrophysiological testing revealed an atrioventricular-node reentrant tachycardia in both patients, who underwent successful slow-pathway ablation.

*Control Group*

The 35 controls were followed for a median of 21 months (range, 8 to 60). All patients continued to exhibit ventricular preexcitation during follow-up.

After a median follow-up of 15 months (range, 8 to 53), 21 patients (60 percent) had had arrhythmic events. The arrhythmic event was supraventricular tachycardia in 15 patients (leading to severe presyncope in 1 patient), atrial fibrillation in 5 patients (1 with syncope and 3 with presyncope), and ventricular fibrillation as the presenting symptom in 1 patient (a 22-year-old man). This man became

unconscious during jogging. In the emergency department, he was found to be in cardiac arrest due to ventricular fibrillation that was successfully cardioverted only after six shocks of up to 300 J. Base-line electrophysiological testing had induced an atrioventricular reciprocating tachycardia triggering atrial fibrillation; the shortest preexcited RR interval had been 200 msec. Multiple septal accessory pathways were found on both the right and the left sides.

#### Patients at Low Risk

The characteristics of the 148 patients at low risk are shown in Table 2. Symptoms of supraventric-

ular tachycardia developed in six patients. All but 1 of the 148 had single accessory pathways. Twenty patients stopped having ventricular preexcitation during follow-up.

#### LONG-TERM OUTCOME

Figure 2 shows a cumulative plot of arrhythmic events according to the characteristics of the induced arrhythmias among controls. Arrhythmic events occurred earlier in patients with induced atrioventricular reciprocating tachycardia, whether or not it triggered atrial fibrillation, than in patients with induced nonsustained atrial fibrillation. Within the first 2.5 years of follow-up, all of the former group of patients had arrhythmic events. On the other hand, 53 percent of the patients with inducible nonsustained atrial fibrillation remained asymptomatic over a five-year follow-up period.

Among the high-risk controls, the five-year rate of arrhythmic events was 77 percent. The corresponding rate for the patients assigned to ablation was 7 percent ( $P < 0.001$ ; relative risk, 0.08; 95 percent confidence interval, 0.02 to 0.33), representing a risk reduction of 92 percent (Fig. 3).

The event-free survival benefit associated with ablation remained significant after adjustment in a Cox regression analysis. As compared with the controls, the patients undergoing ablation had a relative risk of arrhythmic events of 0.016 (95 percent confidence interval, 0.002 to 0.104;  $P < 0.001$ ).

#### DISCUSSION

Prophylactic radio-frequency catheter ablation of accessory pathways in asymptomatic patients with a Wolff-Parkinson-White pattern at high risk for arrhythmias resulted in a risk reduction of 92 percent over a five-year follow-up period. All arrhythmic events occurred within the first 2.5 years of follow-up in patients with inducible atrioventricular reciprocating tachycardia, whether or not it triggered atrial fibrillation, whereas more than half of those with inducible nonsustained atrial fibrillation remained asymptomatic at five years.

We found that the risk of spontaneous arrhythmias significantly and persistently decreased over time after ablation: the event-free survival curves for patients at high risk who underwent ablation and those who did not continued to diverge as the duration of follow-up increased. At the end of the study, there were substantial differences between the two groups. The only two patients who had symptoms

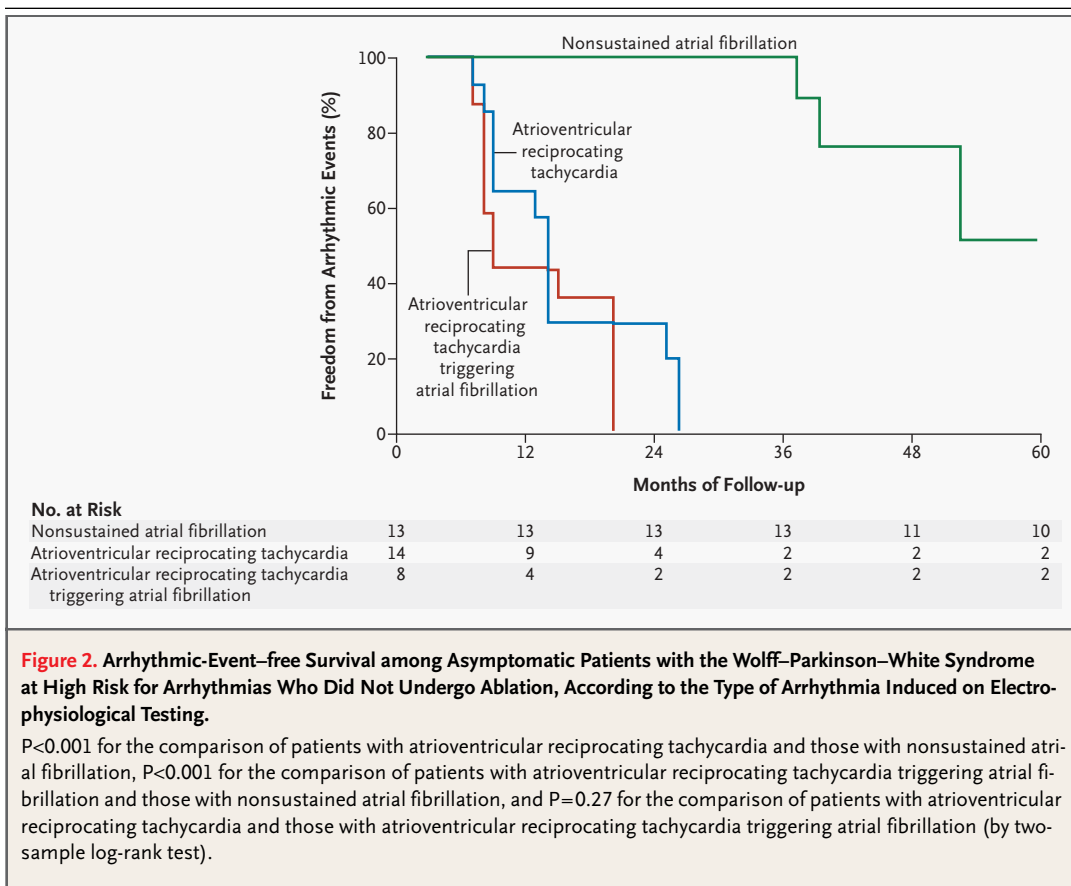
Variable	Value
Age (yr)	
Median	36
Interquartile range	27–48
Male sex (%)	59
Structural heart disease (%)	7
Anterograde refractory period of accessory pathways (msec)	
Median	280
Interquartile range	270–300
Anterograde refractory period of accessory pathways after isoproterenol (msec)	
Median	220
Interquartile range	210–240
Multiple accessory pathways (%)	0.7
Location of single accessory pathways (%)*	
Left free wall	53
Right free wall	20
Posteroseptal	25
Anteroseptal	2
Location of multiple accessory pathways (%)†	
Left free wall and posteroseptal	100
Left free wall and right free wall	0
Right free wall and posteroseptal	0
Inducibility (%)‡	
Nonsustained atrial fibrillation	91
Atrioventricular reciprocating tachycardia	9
Atrioventricular reciprocating tachycardia triggering atrial fibrillation	0
Length of atrioventricular reciprocating tachycardia cycle (msec)†	310
Shortest preexcited RR interval during nonsustained atrial fibrillation (msec)§	
Median	265
Interquartile range	260–280

\* Data are from 147 patients.

† Data are from 1 patient.

‡ Data are from 11 of the 87 patients with inducible arrhythmia.

§ Data are from 10 patients.

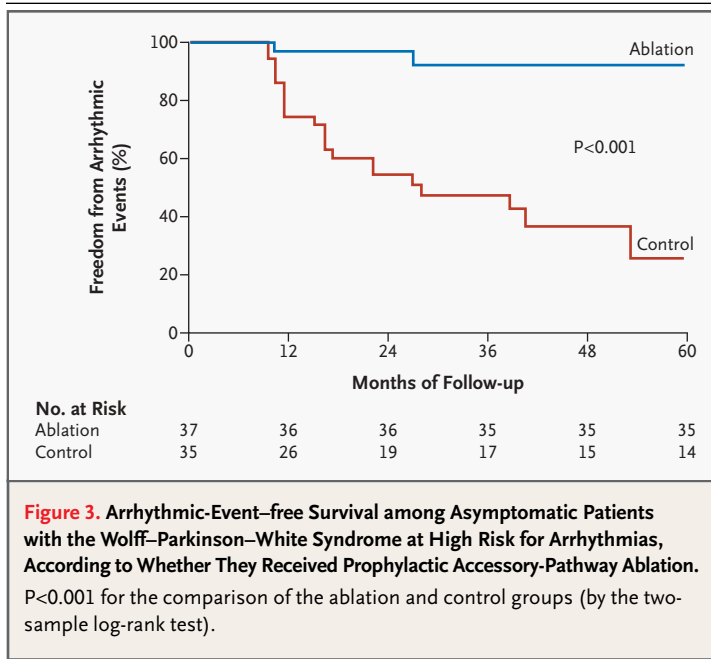


after undergoing ablation had an atrioventricular-nodal reentrant tachycardia, which may occur in patients with the Wolff-Parkinson-White syndrome after spontaneous disappearance of accessory-pathway conduction.<sup>3,4</sup>

Although the exact incidence of sudden death among asymptomatic patients with the Wolff-Parkinson-White syndrome is unknown, both electrophysiological and population-based studies suggest that it is low.<sup>5-8</sup> In contrast to these studies, we recently reported that ventricular fibrillation occurred in 3 of 162 asymptomatic subjects (1.85 percent) and sudden death from cardiac causes in 1 of them.<sup>2</sup> In the present study, one patient (0.46 percent) had a potentially fatal ventricular fibrillation. Overall, among 345 asymptomatic patients we studied from 1993 to 2002, including the 224 patients in the current study, ventricular fibrillation occurred in 4, but only 1 of them died. Thus, the rates of successful resuscitation from ventricular fibrillation and fatal ventricular fibrillation were 0.3 and 0.08 percent per year, respectively, a result suggesting that

in the asymptomatic population with the Wolff-Parkinson-White syndrome, the incidence of resuscitation from cardiac arrest due to ventricular fibrillation is markedly higher than that of sudden death. The rate of spontaneous arrhythmia that we found (17 percent) is similar to those reported by others in patients with asymptomatic ventricular preexcitation, which range from 8 to 21 percent.<sup>5-8</sup>

The fact that sudden death from cardiac causes can be the presenting symptom in some patients with the Wolff-Parkinson-White syndrome provides the rationale for routine electrophysiological testing and prophylactic ablation of accessory pathways in asymptomatic patients. In the three largest series of patients with the Wolff-Parkinson-White syndrome and documented ventricular fibrillation, the arrhythmia was the presenting symptom in 3 of 25 patients,<sup>9</sup> 6 of 23 patients,<sup>10</sup> and 8 of 15 patients,<sup>11</sup> and these findings were rarely observed in patients over 30 years of age.<sup>10,11</sup> An important observation in our prior study is that we found multiple accessory pathways in all patients who subse-



quently had ventricular fibrillation, a finding in agreement with those of other studies.<sup>2,12</sup> Indeed, in the present study, ventricular fibrillation occurred in a patient with multiple pathways in both the right and the left sides of the septum; thus, multiple pathways are an important target for ablation to prevent ventricular fibrillation and sudden death. In addition, we have shown that ventricular fibrillation or sudden death may be preceded by only minimally symptomatic atrial fibrillation, despite an extremely rapid ventricular response over accessory pathways.<sup>2</sup> Taken together, these findings provide a compelling argument for prophylactic ablation in such patients.

Our previous experience<sup>2</sup> and the present study contrast with previous studies that have found the Wolff-Parkinson-White electrocardiographic pattern in asymptomatic patients to be associated with a good prognosis.<sup>5-8,13-17</sup> Our results thus emphasize the importance of readdressing the issue of catheter ablation in this setting.<sup>18</sup> Since catheter ab-

lation is now being routinely and safely performed by skilled operators, asymptomatic persons are referred more commonly for invasive risk stratification and potential ablation, but the decision to perform ablation should also take into account the risk of a fatal complication. Although the risk of fatal complications has been reported to be as high as 0.3 percent in older patients with structural heart disease,<sup>18</sup> no patient in our study died, and we believe that the risk of death in young, otherwise healthy patients can be considered virtually nil.

Thus, we suggest expanding recommendations for invasive evaluation of asymptomatic patients with the Wolff-Parkinson-White syndrome. Patients without inducible arrhythmias do not require prophylactic ablation, since they remain asymptomatic for many years. Young patients with inducible arrhythmias may be divided into two subgroups. In those with inducible atrioventricular reciprocating tachycardia, whether or not it triggers sustained atrial fibrillation, ablation is mandatory, since arrhythmic events usually occur earlier. On the other hand, in patients with inducible, nonsustained atrial fibrillation, ablation may be deferred, because arrhythmic events are rare and usually develop later in life.

Our observations and conclusions should be interpreted in the light of the limitations imposed by an unblinded randomization. Our results were obtained at two institutions with high volumes of ablation procedures; therefore, these results may not be directly applicable to all institutions performing ablation therapy. Because none of our patients were younger than 13 years of age, these results are not applicable to children or infants, who represent a critical group for catheter ablation because of their low body weight, which has been shown to be a major risk factor for complications. Furthermore, the true rate of multiple accessory pathways might be higher, because we did not include children. Finally, the choice of an age cutoff of 35 years was arbitrary. However, our recently published data<sup>2</sup> and the data from this study confirm that the use of this cutoff may identify patients with inducible arrhythmias who will become symptomatic.

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