For many decades, clinical decisions about the management of patients with Wolff-Parkinson-White (WPW) syndrome have essentially been based on the distinction between asymptomatic and symptomatic presentations rather than on intrinsic electrophysiological properties of accessory pathways (APs), considering the asymptomatic condition quite a benign disease. However, the natural history of WPW syndrome, particularly in the era of radiofrequency catheter ablation (RFA), is still poorly defined and in all probability is destined to remain undefined. The risk of sudden death has been mostly extrapolated from scattered and limited data on symptomatic patients and only occasionally from asymptomatic subjects fortuitously discovered by ECG testing or after episodes of syncope or aborted sudden cardiac arrest. Among a large series of WPW patients resuscitated from a sudden cardiac death, more than a half had ventricular fibrillation (VF) as the sentinel event, which suggests that the risk of sudden death in the asymptomatic population is indeed underrecognized. The earliest alarming reports of sudden cardiac death were published in the late 1930s, but the clinical manifestations typically range from an abnormal ECG finding without symptoms to cardiac arrest or sudden cardiac death. Anecdotal case series on the asymptomatic population typically stop short of recommending prophylactic ablation. However, RFA performed during the same procedure after electrophysiological testing is of benefit in improving the long-term outcomes. (Circulation. 2014;130:811-819.)

**Key Words:** death, sudden **ventricular fibrillation** **Wolff-Parkinson-White syndrome**

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**Methods and Results**—The Wolff-Parkinson-White registry was an 8-year prospective study of either symptomatic or asymptomatic WPW patients referred to our Arrhythmology Department for evaluation or ablation. Inclusion criteria were a baseline electrophysiological testing with or without RFA. Primary end points were the percentage of patients who experienced ventricular fibrillation (VF) or potentially malignant arrhythmias and risk factors. Among 2169 enrolled patients, 1001 (550 asymptomatic) did not undergo RFA (no-RFA group) and 1168 (206 asymptomatic) underwent ablation (RFA group). There were no differences in clinical and electrophysiological characteristics between the 2 groups except for symptoms. In the no-RFA group, VF occurred in 1.5% of patients, virtually exclusively (13 of 15) in children (median age, 11 years), and was associated with a short accessory pathway antegrade refractory period (P<0.001) and atrioventricular reentrant tachycardia initiating atrial fibrillation (P<0.001) but not symptoms. In the RFA group, ablation was successful in 98.5%, and after RFA, no patients developed malignant arrhythmias or VF over the 8-year follow-up. Untreated patients were more likely to experience malignant arrhythmias and VF (log-rank P<0.001). Time-dependent receiver-operating characteristic curves for predicting VF identified an optimal anterograde effective refractory period of the accessory pathway cutoff of 240 milliseconds.

**Conclusions**—The prognosis of the Wolff-Parkinson-White syndrome essentially depends on intrinsic electrophysiological properties of AP rather than on symptoms. RFA performed during the same procedure after electrophysiological testing is of benefit in improving the long-term outcomes. (Circulation. 2014;130:811-819.)
WPW population reported minimal or no risk of sudden death, but individually, they were not adequately powered because of the preponderance of adults, small case numbers, and short follow-up periods. Recent data have challenged the assumption that the asymptomatic WPW population is at minimal or no risk of sudden death and that RFA can be of benefit in asymptomatic subjects at risk.21–27 The purpose of this study was to evaluate the long-term outcomes and predictors in a large cohort of symptomatic or asymptomatic WPW patients undergoing electrophysiological testing (EPT) using a prospective patient registry.

Methods

WPW Registry and Data Collection
The WPW registry was a single-center, prospective, observational, 8-year study designed to provide information about long-term outcomes among WPW patients with either symptomatic or asymptomatic WPW syndrome who were referred to our Arrhythmology Department for EPT evaluation. From May 2005 to May 2010, we enrolled consecutive asymptomatic and symptomatic patients without prior RFA or documented life-threatening arrhythmias who consented to undergo a baseline EPT. The last patient was enrolled in May 2010. The observation period ended on May 2013 to allow a minimum follow-up time of 3 years. Patients were divided into 2 groups according to their decision to undergo ablation (RFA group) or not (no-RFA group). As described previously,22–27 data collection includes prior clinical history, physical examination, 12-lead ECG, chest x-ray and echocardiography, invasive procedural data, and serial follow-up visits with 24-hour ECG monitoring. The registry has been updated regularly with the use of electronic clinical records and by telephone encounters. The study protocol was approved by the institutional review board, and each subject, parent, or child’s legal guardian provided written and verbal informed consent for the study.

EPT Protocol
The EPT protocol has previously been described in detail.22–24 Briefly, atrial and ventricular extrastimulation with progressively shorter coupling intervals was performed to induce atrioventricular reentrant tachycardia (AVRT) until the effective refractory periods of the atrium and ventricle were achieved. Patients with concomitant atrioventricular nodal reentrant tachycardia were excluded from the study. If atrial fibrillation (AF) was not induced by atrial extrastimuli, induction of AF was attempted by ramp pacing starting at a cycle length of 300 milliseconds up to 200 milliseconds for 20 seconds 3 times. Inducible arrhythmias were defined as sustained if they lasted >1 minute. Tachyarrhythmia inducibility was defined as reproducible induction of sustained AVRT or AF. The anterograde effective refractory period of the AP (AP-AERP) was defined as the longest coupling interval at which anterograde block in the bypass tract was observed. Multiple pathways were diagnosed by accurate endocardial mapping during EPT. Isoproterenol was not infused at the time of EPT.

Catheter Ablation Procedure
The RFA procedure has previously been described in detail.22–24 A 7F deflectable electrode catheter was introduced through the femoral or by transseptal approach for left ablation or by the femoral vein for right side ablation. Irrigated-tip catheter ablation was usually performed with the temperature control mode (target temperature, 40°C) and a power limit of 40 W at the best endocardial or epicardial sites. If no effect was seen within 5 seconds, radiofrequency energy delivery was terminated, and the catheter was moved to a different site. The catheter ablation procedure was terminated if antegrade and retrograde conduction over the AP was permanently eliminated and arrhythmias could not be induced either with or without isoproterenol infusion. An additional 60-second lesion was delivered at the successful site to minimize the possibility of recurrent AP conduction. Catheter ablation was offered to all patients after EPT.

Definitions
The following definitions of events were used. A potentially malignant arrhythmia (MA) was considered an episode of documented sustained (>1 minute) AF with the shortest pre-excited RR interval of ≤250 milliseconds. Cardiac arrest was defined as a condition requiring cardiopulmonary resuscitation or electric defibrillation, which was not associated with an acute myocardial infarction or other transient factors. According to the new nomenclature, APs were classified as left-sided, right-sided, septal, and paraseptal APs.

Study End Points
The primary end points of the study were the characteristics and percentage of patients who, after EPT with or without catheter ablation during the same procedure, experienced MA or VF and predictors.

Long-Term Follow-Up
The follow-up began at the time of EPT and ended if arrhythmias developed or in May 2013. Patients were followed up without medical therapy or with medical or ablation therapy at the discretion of the referring physicians once arrhythmias occurred or recurred during follow-up. They were seen in our outpatient clinic at 6 and 12 months after EPT and every 12 months thereafter. Physical examination, 12-lead ECG, and 24-hour Holter monitoring were performed at each visit, whenever clinical circumstances required unscheduled visits, or whenever patients experienced symptoms suggestive of arrhythmias.

Statistical Analysis
We compared categorical outcomes by the χ² test unless the expected number of observations in any cell of a contingency table was <5, in which case we used the Fisher exact test. Continuous data were expressed as median and 25th to 75th percentile and compared by the Mann-Whitney U test. The cumulative risk of developing VF or MAs during follow-up was estimated by the Kaplan–Meier method, with log-rank tests used to identify differences in outcomes across asymptomatic and symptomatic untreated patients and between untreated and treated patients. Factors that predicted MA or VF after EPT were identified by univariable and multivariable models using the Cox proportional hazards model by backward-stepwise model selection with the removal testing based on the probability of the Wald statistic. Covariates included in the model were age, sex (female/male=0/1), multiple pathways (no/yes=0/1), inducibility of AVRT-AF (no/yes=0/1), AP-AERP, and symptoms (no/yes=0/1). Time-dependent receiver-operating curve analysis was performed to find the cut-point value of AP-AERP, associated with its better discriminant ability for separating WPW patients at low and high risk of developing VF. Time-dependent estimates of sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve and relative 95% confidence limits have been calculated with the inverse probability of censoring weighting method, computed from a Kaplan–Meier estimator at 48 and 96 months. Statistical analysis was performed with IBM SPSS Statistics version 21 and R software version 3.1.0. Significance was accepted at P<0.05. All tests of significance were 2 sided.

Results

Characteristics of the Patient Population
Among 2174 patients meeting the eligibility criteria, a total of 2169 patients were enrolled. Of them, 1001 patients did
not undergo RFA (no-RFA group) according to the referring physician’s or patient’s choice, and 1168 patients underwent ablation (RFA group). Some patients, particularly younger subjects or children, accepted EPT but declined RFA during the same procedure after reading the informed consent on potentially higher complications of RFA compared with EPT, and many others declined according to the decision of referring physicians who suggested postponing RFA to arrhythmia recurrence. The study population thus comprised a total of 2169 patients divided into 2 parallel cohorts distinguished primarily by treatment with RFA.

Comparison Between the 2 Groups of Patients
The electrophysiological characteristics of the 2 groups are summarized in Table 1. Age, sex, structural heart diseases, AP-AERP, AVRT-AF, multiple APs, and length of follow-up did not differ significantly between the 2 groups of patients, with a preponderance of symptomatic patients in the RFA group (Table 1).

No-RFA Group
Among the 1001 patients who did not undergo RFA, 550 were totally asymptomatic and 451 were symptomatic for sustained supraventricular tachycardia, but no MAs were recorded in any of them. Complete EPT data were available with a preponderance of symptomatic patients in the RFA group (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untreated (n=1001)</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Age at enrollment, y</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
</tr>
<tr>
<td>SHD, n (%)</td>
</tr>
<tr>
<td>AP-AERP, ms</td>
</tr>
<tr>
<td>Symptomatic, n (%)</td>
</tr>
<tr>
<td>AVRT-AF, n (%)</td>
</tr>
<tr>
<td>Multiple APs, n (%)</td>
</tr>
<tr>
<td>MAs, n (%)</td>
</tr>
<tr>
<td>VF, n (%)</td>
</tr>
<tr>
<td>Follow-up, mo</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as median (25th–75th percentile). AP indicates accessory pathway; AP-AERP, accessory pathway antegrade effective refractory period at baseline; AVRT-AF, inducible atrioventricular reentrant tachycardia triggering atrial fibrillation at electrophysiological testing; MA, potentially malignant arrhythmia; SHD, structural heart disease; and VF, ventricular fibrillation.

RFA Group
Among the 1168 patients who underwent RFA, 206 were asymptomatic and 962 symptomatic for sustained supraventricular tachycardia. Common symptoms included palpitations, chest discomfort, dyspnea, weakness, neck pulsations, and syncope or presyncope occurred in 75 patients, but no MAs or VFs were recorded in any of them. At the time of the EPT, symptomatic patients had inducible tachyarrhythmias, including orthodromic AVRT (85.0%), antidromic AVRT (5.0%), or both orthodromic and antidromic AVRT or AF (9.9%). Of note, AVRT degenerating into AF occurred in as many as 73 patients (6.3%). Compared with the asymptomatic subjects, the symptomatic subjects were older (P<0.001) with less inducibility of AVRT triggering AF (P<0.001), fewer multiple APs (P<0.001), and longer AP-AERPs (P<0.001). Overall, a total of 1270 APs were found and successfully ablated. A total of 698 APs (55.0%) were located on the left, 190 (15.0%) on the right, and 254 (20.0%) in the paraseptal space, and 127 (10.0%) presented with a septal or para-hisian localization. Overall, EPT-related complications included pneumothorax (5 patients), femoral hematomas at the catheter entry site (25 patients), and fistulas (2 patients). RFA-related complications included right bundle-branch block in 10 patients, left bundle-branch block in 3 patients with anterosetal APs, and a small asymptomatic pericardial effusion requiring prolongation of hospital stay in 2 children with left and right APs. Serious complications included a third-degree atrioventricular block in 1 patient. No fatality occurred after RFA.

Long-Term Follow-Up Outcome
The median follow-up for both groups was 96 months with no difference between the no- RFA and RFA patients (P=0.525).

No-RFA Group
The completeness of follow-up was 99.8% at 1 year and 92.3% at the end of the study. The mean clinic visits per patient were 8.3±0.7. The median follow-up period was 96 months (50–96 months). Asymptomatic patients had shorter follow-up than symptomatic patients (P<0.001). VF occurred during a median follow-up of 22 months (15–41 months) in 15 patients (13 asymptomatic and 2 symptomatic subjects), whereas during a median follow-up of 46.5 months (36–58.5 months), 78 additional patients (48 asymptomatic and 30 symptomatic) experienced MAs as documented by paramedics or at emergency facilities. VF resulted in a resuscitated cardiac arrest without neurological sequelae in all patients and developed a few minutes before warning symptoms, allowing a prompt successful resuscitation without the use of drugs potentially contributing to VF. Warning symptoms including presyncope in 10 patients and dizziness in 5 others, which occurred out of hospital (7 patients) or in hospital (8 patients) directly before VF. Cardiac arrest occurred while running in 4 patients, of whom 2 were initially symptomatic, and at rest in the remaining 11 patients. Life-threatening arrhythmias were attributable to pre-excited AF with a rapid response resulting in palpitations (25 patients), chest pain (5 patients),
headache (5 patients), dizziness (35 patients), or lightheadedness (8 patients). Rapid pre-excited AF occurred at rest in 65 patients, during sleep in 3 subjects, and while running in 10 additional patients. No patients with MAs or VF were taking antiarrhythmic drugs at the time of the event. All of them were successfully ablated immediately after arrhythmia occurrence. The clinical and electrophysiological characteristics of the 15 patients experiencing VF are shown in Table 2. Of note, all but 1 patient showed an AP-AERP ≤230 milliseconds, most of them (73.3%) had inducible AVRT triggering AF, and multiple APs were found in only a minority of cases (26.7%). Compared with the asymptomatic patients, asymptomatic patients had higher rates of VF (P=0.01) with similar rates of MAs (P=0.22). A comparison of clinical and electrophysiological characteristics of patients with MAs and those with VF showed that patients experiencing VF had shorter median AP-AERPs than those with MAs (220 milliseconds [210–230 milliseconds] versus 240 milliseconds [240–240 milliseconds]; P<0.001) with no difference in age, sex, and multiple APs and more inducible AVRTs triggering AF (73.3% versus 44.9%; P=0.04).

### No Life-Threatening Arrhythmias

During a median follow-up of 43 months (40–63.3 months), 216 patients with a median age of 17 years (10–39 years) experienced benign recurrences, including AVRT or AF, and all were successfully ablated after arrhythmia occurrence. Of them, 86 patients (39.8%) with a median age of 10 years (8–53 years) had been initially asymptomatic, and 130 (60.2%) with a median age of 19 years (10–39) had been initially symptomatic. Overall, the baseline median AP-AERP was 280 milliseconds (260–300), but we found significant differences between asymptomatic and symptomatic patients with benign recurrences because initially asymptomatic subjects were younger with longer AP-AERPs (280 milliseconds [270–300 milliseconds] versus 270 milliseconds [250–280 milliseconds]; P=0.002). During a median follow-up of 96 months (55–96 months), 285 patients with a median age of 39 years (32.5–42 years) definitively lost ventricular pre-excitation on the ECG, remaining asymptomatic. Of them, 119 with a median age of 42 years (31–52 years) were asymptomatic and 166 with a median age of 38 years (33–41 years) were symptomatic. Compared with patients who did not lose ventricular pre-excitation, those who did were older with a median age of 39 years (32.5–42 years) versus 13 years (10–29 years; P<0.001) and had longer baseline AP-AERP (300 milliseconds [280–310 milliseconds] versus 270 milliseconds [250 to 280 milliseconds]; P<0.001). No patient was taking antiarrhythmic drug therapy during the follow-up.

### Risk Profile of Untreated WPW Patients

In the whole population, the incidence rate of cardiac arrest/ VF was estimated at 2.4 per 1000 person-years (95% confidence interval [CI], 1.3–3.9).

### RFA Group

The completeness of follow-up was 95.5% at 1 year and 90.2% at the end of the study. The mean clinic visits per patient were 8.4±0.6. The median follow-up period was 96 months (48–96 months; Table 1). RFA was successful in 1150 patients (98.5%), whereas 18 initially symptomatic patients (8 male patients) over a median follow-up of 8 months (3–11.5 months) after the index procedure required a repeat RFA procedure for recurrent supraventricular tachycardia (10 patients, 55.6%), supraventricular tachycardia and the reappearance of pre-excitation (4 patients, 22.2%), AF and the reappearance of pre-excitation (2 patients, 11.1%), or reappearance of pre-excitation alone (2 patients, 11.1%). The median patient age was 18.5 years (14–27.7 years), and the median AP-AERP was 280 milliseconds (235–302.5 milliseconds). Inducibility of AVRT-AF and multiple APs were observed in 11.1% and 22.2%, respectively. The highest reintervention rate was

### Table 2. Characteristics of the 15 Untreated WPW Patients Experiencing VF During Follow-Up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Asymptomatic/Symptomatic</th>
<th>Age at Enrolment, y</th>
<th>Sex</th>
<th>SHD</th>
<th>Multiple</th>
<th>AP Location</th>
<th>AP-AERP, ms</th>
<th>AVRT-AF</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic</td>
<td>11</td>
<td>Male</td>
<td>−</td>
<td>−</td>
<td>PS</td>
<td>230</td>
<td>+</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Asymptomatic</td>
<td>32</td>
<td>Male</td>
<td>−</td>
<td>−</td>
<td>PS</td>
<td>200</td>
<td>−</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>Asymptomatic</td>
<td>32</td>
<td>Female</td>
<td>−</td>
<td>−</td>
<td>LFW</td>
<td>200</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>Asymptomatic</td>
<td>10</td>
<td>Male</td>
<td>−</td>
<td>−</td>
<td>PS</td>
<td>220</td>
<td>+</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Asymptomatic</td>
<td>10</td>
<td>Male</td>
<td>−</td>
<td>+</td>
<td>LFW+PS</td>
<td>220</td>
<td>+</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>Asymptomatic</td>
<td>12</td>
<td>Male</td>
<td>−</td>
<td>+</td>
<td>LFW+PS</td>
<td>210</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Asymptomatic</td>
<td>8</td>
<td>Male</td>
<td>−</td>
<td>−</td>
<td>PS</td>
<td>220</td>
<td>+</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>Asymptomatic</td>
<td>10</td>
<td>Male</td>
<td>−</td>
<td>+</td>
<td>LFW+PS</td>
<td>220</td>
<td>−</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>Asymptomatic</td>
<td>10</td>
<td>Male</td>
<td>−</td>
<td>−</td>
<td>PS</td>
<td>210</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>Asymptomatic</td>
<td>14</td>
<td>Male</td>
<td>−</td>
<td>−</td>
<td>RFW</td>
<td>220</td>
<td>−</td>
<td>28</td>
</tr>
<tr>
<td>11</td>
<td>Asymptomatic</td>
<td>14</td>
<td>Male</td>
<td>−</td>
<td>+</td>
<td>LFW+PS</td>
<td>220</td>
<td>+</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>Asymptomatic</td>
<td>10</td>
<td>Male</td>
<td>−</td>
<td>−</td>
<td>PS</td>
<td>240</td>
<td>+</td>
<td>55</td>
</tr>
<tr>
<td>13</td>
<td>Asymptomatic</td>
<td>11</td>
<td>Male</td>
<td>−</td>
<td>−</td>
<td>PS</td>
<td>230</td>
<td>−</td>
<td>53</td>
</tr>
<tr>
<td>14</td>
<td>Asymptomatic</td>
<td>9</td>
<td>Female</td>
<td>−</td>
<td>−</td>
<td>PS</td>
<td>230</td>
<td>+</td>
<td>12</td>
</tr>
<tr>
<td>15</td>
<td>Symptomatic</td>
<td>11</td>
<td>Male</td>
<td>−</td>
<td>+</td>
<td>LFW+PS</td>
<td>230</td>
<td>+</td>
<td>65</td>
</tr>
</tbody>
</table>

AP-AERP indicates baseline accessory pathway antegrade effective refractory period; AVRT-AF, atrioventricular reentrant tachycardia triggering atrial fibrillation; LFW, left free wall; PS, posteroseptal; RFW, right free wall; VF, ventricular fibrillation; and WPW, Wolff-Parkinson-White.
observed in the septal APs (35%); the lowest was observed in the left-sided APs.

Predictors of Potential MAs and VF
Kaplan–Meier estimates showed that asymptomatic untreated patients were more likely to develop VF than the untreated symptomatic patients (log-rank \(P=0.008\); Figure 1) with no difference in cumulative risk of MA (log-rank \(P=0.087\)). Univariable analysis showed that many variables were associated with both MAs and VF, including age, multiple APs, AVRT-AF, and AP-AERP (Tables 3 and 4), whereas the absence of symptoms at univariable analysis was associated with the development of VF (Table 4). Cox proportional hazards model showed that VF and MAs were independently associated with short AP-AERPs and AVRT-AF (Tables 3 and 4), whereas multiple APs were associated only with MAs (Table 3). Neither MAs nor VF was predicted by the presence of symptoms. Time-dependent receiver-operating curves for predicting VF showed at 48 months an AP-AERP cutoff point of 240 milliseconds with a sensitivity of 100% (95% CI, 100–100), specificity of 69% (95% CI, 56–81), area under the curve of 99.04% (95% CI, 98.39–99.69), positive predictive value of 28.1% (95% CI, 14.1–42.1), and negative predictive value of 100% (95% CI, 100–100). At 96 months, the AP-AERP cutoff point was 240 milliseconds with a sensitivity of 91.7% (95% CI, 76.2–100), specificity of 82% (95% CI, 71–93), area under the curve of 99.17% (95% CI, 98.4–99.9), positive predictive value of 46.0% (95% CI, 25.8–66.2), and negative predictive value of 99.9% (95% CI, 99.6–100). Untreated patients were more likely to experience MAs (Figure 2) or VF (Figure 3) than patients who underwent RFA during a follow-up period of 96 months.

Discussion
The present study is one of the largest and longest contemporary follow-up registry studies to examine the long-term outcomes and correlates of treated and untreated WPW patients. The results of this study provide new additional information on the management of the whole WPW population in the era of RFA. Among 1001 untreated WPW patients, despite an overall very low annual rate of VF, we have found higher rates of VF in the asymptomatic group than the symptomatic group. However, it may be that most symptomatic patients are ablated and that the subgroup of patients choosing not to be ablated after EPT could not be representative of the universe of symptomatic patients. Regardless of symptoms, only a shorter AP-AERP and degeneration of AF after AVRT were associated with VF development. These findings are clinically important, indicating that in the entire WPW population, the ERP of AP is a critical determinant of MAs, which also supports the recent recommendations of the Pediatric and Congenital Electrophysiology Society and the Heart Rhythm Society expert consensus statement concerning the young asymptomatic WPW population. Of note, in the present study, among 1168 treated WPW patients, no patients experienced MAs or VF after RFA, with only a minority presenting arrhythmia occurrence or recurrence (1.5%), which suggests that RFA improves the patient’s long-term outcomes and thus can be considered a primary end point.

The Natural History of WPW Syndrome in the Era of RFA
In the current era of the widespread use of RFA, it is reasonable that having a defined natural history of WPW syndrome

### Table 3. Factors Associated With MAs Among Untreated WPW Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Hazard Ratio</th>
<th>95% CI</th>
<th>(P)</th>
<th>Multivariable Hazard Ratio</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVRT-AF</td>
<td>58.84</td>
<td>36.25–95.48</td>
<td>&lt;0.001</td>
<td>18.91</td>
<td>11.18–31.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AP-AERP</td>
<td>0.94</td>
<td>0.93–0.95</td>
<td>&lt;0.001</td>
<td>0.95</td>
<td>0.93–0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple APs</td>
<td>9.45</td>
<td>5.93–15.08</td>
<td>&lt;0.001</td>
<td>1.73</td>
<td>1.03–2.89</td>
<td>0.04</td>
</tr>
<tr>
<td>Age at enrollment</td>
<td>0.95</td>
<td>0.93–0.97</td>
<td>&lt;0.001</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Sex</td>
<td>2.54</td>
<td>1.47–4.40</td>
<td>0.001</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.67</td>
<td>0.43–1.06</td>
<td>0.09</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

AP indicates accessory pathway; AP-AERP, accessory pathway antegrade effective refractory period at baseline; AVRT-AF, atrioventricular reentrant tachycardia triggering atrial fibrillation; CI, confidence interval; MA, potentially malignant arrhythmia; and WPW, Wolff-Parkinson-White.
in the whole WPW population with which to make decisions is challenging. Currently, the choice to provide RFA or not has reasonably been based on the presence or absence of symptoms rather than on a specific clinical or electrophysiological algorithm to prevent sudden death.\(^1\) The accumulating recent clinical evidence shows that in the WPW syndrome MAs, aborted sudden death, and sudden death can be the first clinical manifestation of the syndrome in previously asymptomatic subjects, representing a tragic unpredictable event, particularly in the young asymptomatic population.\(^2\)

At present, it is estimated that \(\approx 65\%\) of adolescents with a WPW pattern on a resting ECG are asymptomatic.\(^1,2\) ECG recordings by recent intensive screening programs before sports participation or before medical and surgical procedures have identified an increasing number of asymptomatic individuals with a WPW ECG pattern who are increasingly referred to electrophysiology laboratories worldwide for EPT evaluation and risk stratification. Patients with ventricular pre-excitation on the ECG, regardless of whether they have symptoms, have an unpredictable lifetime risk of sudden cardiac death, but only a minority of them are actually at risk, which poses considerable clinical challenges to physicians for identifying the few at risk, particularly children.\(^1-3\)

Because many patients who experienced VF have had previous episodes of both AF and paroxysmal supraventricular tachycardia,\(^9\) attention has focused for many decades on symptomatic patients, and guidelines have constantly recommended liberal indication for catheter ablation as a \textit{Class IA} recommendation only for the symptomatic patients.\(^1\) In the present study, over an 8-year follow-up period, only 2 of 451 symptomatic patients (0.4\%) experienced cardiac arrest, whereas as many as 13 of 550 initially asymptomatic patients (2.4\%) had cardiac arrest as first clinical manifestation of the syndrome, but none of them died. These data are not surprising if one considers that in a similar large retrospective series of patients (690 patients) with WPW syndrome, 15 patients (2.2\%) had aborted sudden death, and 8 previously asymptomatic patients had VF as the first manifestation of the disease.\(^4\) In the present study, cardiac arrest occurred a

![Figure 2](image_url)

**Figure 2.** Kaplan–Meier survival plot for malignant arrhythmias (MAs) in untreated patients (no radiofrequency catheter ablation [RFA]) and patients treated with RFA. Patients treated with RFA were less likely to experience MAs than those who did not undergo RFA.

![Figure 3](image_url)

**Figure 3.** Survival analysis up to 96 months of follow-up shows that untreated patients (no radiofrequency catheter ablation [RFA]) were more likely to experience ventricular fibrillation (VF) than those who underwent RFA.

### Table 4. Factors Associated With VF Among Untreated WPW Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>(P)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVRT-AF</td>
<td>102.51</td>
<td>30.33–346.39</td>
<td>(&lt;0.001)</td>
<td>27.16</td>
<td>5.29–139.40</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>AP-AERP</td>
<td>0.90</td>
<td>0.87–0.92</td>
<td>(&lt;0.001)</td>
<td>0.86</td>
<td>0.82–0.91</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Multiple APs</td>
<td>6.05</td>
<td>1.93–19.02</td>
<td>0.002</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Age at enrollment</td>
<td>0.92</td>
<td>0.87–0.98</td>
<td>0.01</td>
<td>0.91</td>
<td>0.81–1.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Sex</td>
<td>4.33</td>
<td>0.98–19.18</td>
<td>0.05</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.18</td>
<td>0.04–0.78</td>
<td>0.02</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

\(AP\) indicates accessory pathway; AP-AERP, accessory pathway antegrade effective refractory period at baseline; AVRT-AF, atrioventricular reentrant tachycardia triggering atrial fibrillation; CI, confidence interval; VF, ventricular fibrillation; and WPW, Wolff-Parkinson-White.
few minutes after the warning symptoms began, thus allowing more time for prompt treatment by direct current shock. Fortunately, cardiac arrest occurred in places where having cardiopulmonary resuscitation and defibrillation available was mandatory or in small cities near the hospital emergency room, thus avoiding death. Other contributing factors to successful resuscitation were the very young age (median age, 11 years) and the absence of structural heart disease among almost all resuscitated WPW patients.4,30 Finally, we should emphasize that patients and parents have been well educated and instructed to immediately reach the hospital or emergency services when symptoms began. In this study, all patients were successfully resuscitated, strongly suggesting a better education of and training for cardiopulmonary resuscitation, particularly among family members of asymptomatic WPW patients found to be at risk declining RFA. After RFA, no resuscitated patients had arrhythmia recurrence or cardiac arrest, confirming that, unlike primary VF, cardiac arrest in WPW can be prevented by sole RFA of APs.30

Taken together, these data, while confirming an overall very low annual rate of VF in the entire WPW population,3-5,8 have found significantly higher rates among asymptomatic subjects, predominantly in the pediatric population. Why asymptomatic status would confer higher risk of VF is unclear, but it may be that minimally or moderately symptomatic patients were enrolled, excluding those who had life-threatening arrhythmias. It is conceivable that the small number of VF events does not allow us to conclude that the asymptomatic population as a whole is at higher risk. In contrast, our data further emphasize the need for more intensive screening programs and risk stratification, particularly in the young asymptomatic WPW population, as recently recognized by a Pediatric and Congenital Electrophysiology Society/Heart Rhythm Society expert consensus document2 and 2 European surveys.31,32 In addition, the results of a recent meta-analysis including 1869 asymptomatic WPW patients confirmed that children have higher malignant event rates than adults.33

In the present study, subjects who developed VF had a characteristic electrophysiological profile. Compared with patients experiencing MAs, they showed more inducible pre-excited sustained AF triggered by AVRT (73.3% versus 44.9%) and shorter median AP-AERP (220 versus 240 milliseconds). A posteroseptal location of APs was found in almost all patients with VF, whereas the rate of multiple APs was similar in patients with VF or MAs, as reported by Timmermans et al. Of note, Kaplan–Meier estimates showed that over the 8-year follow-up period asymptomatic subjects were more likely to experience VF than the symptomatic subjects. Multivariable analysis demonstrated that the presence of symptoms was not an independent risk factor of outcome, whereas shorter AP-AERP and AVRT triggering AF were associated with both VF and MAs. Analysis of time-dependent receiver-operating curves for the prediction of VF showed an optimal AP-AERP cutoff point at 240 milliseconds, which confirms the key role of very short AP-AERPs to facilitate degeneration of AF into VF.

Although a shortest pre-excited RR interval of 250 milliseconds has been considered the widely accepted cutoff to define the risk of sudden death, our data suggest that shorter values are required, confirming previous observations from a series of patients resuscitated from VF. Therefore, our data suggest that, regardless of symptoms, to prevent sudden death, AVRT-AF and short AP-AERP should be considered a specific algorithm for routine use of RFA in the entire WPW population.

The Impact of RFA on the Natural History of WPW Syndrome
Since the introduction of RFA in the early 1990s, RFA has completely revolutionized our approach to the management of WPW syndrome, becoming the method of choice potentially available to all WPW patients. In the present study, a total of 1168 patients underwent RFA and 1001 additional patients with similar electrophysiological characteristics did not. The long-term results demonstrated that there was a striking difference in outcomes between ablated and nonablated patients because, over the 8-year follow-up, no ablated symptomatic or asymptomatic patients experienced MAs or VF. Of note, the very high success rates after RFA, as observed in the present study, were associated with very low rates of minor complications (<2%), which include just 1 complete third-degree atrioventricular block (0.08%). These data on the efficacy and safety of RFA across all locations of APs confirm the significant increase in ablation success rates from 90% in the early era to >95% in the later era of RFA, as recently reported by many electrophysiology laboratories worldwide.34 However, complications should always be balanced and discussed, particularly in asymptomatic patients found to be at low risk or when all asymptomatic WPW patients are ablated regardless of the risk.

Study Limitations
As limitations, we recognize that this was a single-center study and that a natural history study of patients with WPW syndrome requires a randomized trial to establish the role of RFA. However, we enrolled from all over Italy a significant number of symptomatic and asymptomatic WPW individuals with no significant differences in their electrophysiological characteristics who, only for ethical reasons, were not randomized. Our results have been obtained at a high-volume center with extensive experience in performing RFA of all AP locations and thus cannot be representative of all centers performing RFA. Although we have collected the largest number of documented VF cardiac arrests than previously reported, this number may be still relatively low, limiting multivariable models and time-dependent receiver-operating curve analysis. Finally, the possibility of fluctuations in autonomic tone could be another potential limitation. Despite these limitations, this prospective study registry has several strengths, including its very large size with complete clinical and electrophysiological data over an extensive follow-up without missing data.

Conclusions
This is the largest and longest prospective follow-up study to confirm that the vast majority of the WPW population has
an excellent prognosis and clearly indicates that the natural history of the syndrome and the risk of sudden death essentially depend on intrinsic electrophysiological properties of APs rather than on symptoms. Regardless of the presence or absence of symptoms, it is likely that RFA performed at the time of EPT in patients found to be at risk can definitively change the patient’s natural history, eliminating the risk of VF and sudden death.

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Disclosures
None.

References
Currently, in the era of radiofrequency catheter ablation (RFA), the management of Wolff-Parkinson-White is based on the distinction between asymptomatic and symptomatic presentations. However, whether symptomatic subjects are at higher risk of ventricular fibrillation is still unclear. The purpose of this prospective, single-center registry study was to evaluate the long-term outcomes and predictors of ablated and nonablated Wolff-Parkinson-White patients. Among 2169 enrolled patients, 1001 (550 asymptomatic and 451 symptomatic) did not have RFA (no-RFA group) and 1168 (206 asymptomatic and 962 symptomatic) did (RFA group). Primary end points were the percentage of patients who experienced ventricular fibrillation (VF) and predictors. During a median follow-up of 96 months, nonfatal cardiac arrest/VF occurred in 15 no-RFA patients, of whom 13 were originally asymptomatic (2.4%; median age, 11 years), and in none of the RFA group. The risk of cardiac arrest/VF was estimated at 2.4 per 1000 person-years (95% confidence interval, 1.3–3.9). Independent risk factors of VF were the induction of atrioventricular reentrant tachycardia degenerating into atrial fibrillation (P<0.001) and short effective refractory period of the accessory pathway (P<0.001), whereas time-dependent receiver-operating characteristic curves identified an optimal cutoff point at 240 milliseconds. These data, while confirming that the vast majority of the Wolff-Parkinson-White population have an excellent prognosis, indicate for the first time that the risk of VF/cardiac arrest essentially depends on intrinsic electrophysiological properties of accessory pathways. In a small percentage of patients found to be at risk after electrophysiological testing, predominantly children and regardless of symptoms, RFA can definitively change the patient’s natural history, eliminating the risk of VF and sudden death.

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