WPW Syndrome in the Era of Catheter Ablation: Insights from a Registry Study of 2169 Patients

Running title: Pappone et al.; Natural history of WPW syndrome in the era of RFA

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Abstract

Background—The management of Wolff-Parkinson-White (WPW) is based on the distinction between “asymptomatic” and “symptomatic” presentations but evidence is limited in the asymptomatic population.

Methods and Results—WPW registry was an 8-year prospective study of either symptomatic or asymptomatic WPW patients referred to our Arrhythmology Department for evaluation and/or ablation. Inclusion criteria were a baseline electrophysiological testing with or without catheter ablation (RFA). Primary endpoints were the percentage of patients who experienced ventricular fibrillation (VF) or potentially malignant arrhythmias (MA) 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 was no difference in clinical and electrophysiological characteristics between the 2 groups except for symptoms. In 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 AP antegrade refractory period ($P<0.001$), and AVRT initiating AF ($P<0.001$), but not symptoms. In RFA group, ablation was successful in 98.5% and, after RFA no patients developed MA or VF over 8-year follow-up. Untreated patients were more likely to experience MA and VF (log-rank, $P<0.001$). Time-dependent ROC curves for predicting VF identified an optimal AP-AERP cut-off at 240ms.

Conclusions—Prognosis of WPW syndrome essentially depends on intrinsic electrophysiological properties of AP rather than on symptoms and RFA performed during the same procedure after EPT is of benefit in improving the long-term outcomes.

Key words. Wolff-Parkinson-White syndrome, sudden death, ventricular fibrillation
Introduction

Since many decades, clinical decisions about the management of patients with Wolff–Parkinson-White (WPW) syndrome have been essentially based on the distinction between “asymptomatic” and “symptomatic” presentations, rather than on intrinsic electrophysiological properties of accessory pathways (AP), considering the asymptomatic condition quite a benign disease.1 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.1-11

Among a large series of WPW patients resuscitated from a sudden cardiac death, more than a half had VF as the sentinel event,4 which suggests that the risk of sudden death in the asymptomatic population is indeed under-recognized.9,10 The earliest alarming reports of sudden cardiac death were published in the late 1930s,6,7 but the clinical manifestations typically range from an abnormal ECG finding without symptoms to cardiac arrest or sudden cardiac death. Anecdotal case series studies on the asymptomatic WPW population reported minimal or no risk of sudden death, but individually they were not adequately powered because of the preponderance of adults with small case numbers and short follow-up periods.12-21 Recent data have challenged the assumption that asymptomatic WPW population is at minimal or no risk of sudden death and that radiofrequency ablation (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 more 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 electrophysiological testing. The last patient was enrolled on May 2010. The observation period ended on May 2013 to allow a minimum follow-up time of 3 years. Patients were divided in two 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 regularly updated using electronic clinical record 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.

Electrophysiological study protocol

EPT protocol has been previously described in details.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 AVNRT were excluded from the study. If atrial fibrillation was not induced by atrial extrastimuli, induction of atrial fibrillation was
attempted by ramp pacing starting at a cycle length of 300ms up to 200ms for 20 seconds three times. Inducible arrhythmias were defined as sustained if they lasted more than one minute. Tachyarrhythmia inducibility was defined as reproducible induction of sustained AVRT and/or atrial fibrillation (AF). The anterograde effective refractory period of the accessory pathway (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 electrophysiological study. Isoproterenol was not infused at the time of EPT.

**Catheter ablation procedure**

RFA procedure has been previously described in details.22–24 A 7 French deflectable electrode catheter was introduced through the femoral artery or by transseptal approach for left ablation or by the femoral vein for right side ablation. Irrigated-tip catheter ablation was usually performed with 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, RF energy delivery was terminated and catheter was moved to a different site. Catheter ablation procedure terminated if antegrade and retrograde conduction over AP was permanently eliminated and arrhythmias could not be induced either with or without isoproterenol infusion. An additional 60-s lesion was delivered at the successful site to minimize the possibility of recurrent AP conduction. Catheter ablation to be was offered to all patients after EPT.

**Definitions**

The following definitions of events were used. A potentially malignant arrhythmia (MA) was considered as an episode of documented sustained (>1 minute) AF with shortest preexcited RR interval (SPRRI) of ≤250ms. Cardiac arrest was defined as a condition requiring cardiopulmonary resuscitation and/or electrical 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 endpoints of the study were the characteristics and percentage of patients who after EPT with or without catheter ablation performed 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 up to May 2013. Patients were followed 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. At each visit, physical examination, 12-lead ECG, 24-hour Holter monitoring or whenever clinical circumstances required unscheduled visits or whenever they experienced symptoms suggestive of arrhythmias.

**Statistical analysis**

We compared categorical outcomes by $\chi^2$ test unless the expected number of observations in any cell of a contingency table was lower than five, in which case we used Fisher’s exact test. Continuous data were expressed as median and 25th-75th percentile, and compared by using the Mann-Whitney U test. Cumulative risk of developing ventricular fibrillation or MA 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, as well as 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 (F/M=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 ROC analysis was performed to find the cutpoint value of AP-AERP, associated with its better discriminant ability in separating WPW patients at low and high risk of developing VF. Time-dependent estimates of sensitivity, specificity, positive predictive value, negative predictive value and AUC, 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 using 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 or patient’s choice while 1168 patients underwent ablation (RFA-group). Some patients, particularly younger subjects or children, while accepting EPT declined RFA to be performed during the same procedure after reading informed consent on potentially higher complications of RFA as compared with EPT and many others declined according to the decision of referring physicians who suggested to post-pone RFA to arrhythmia recurrence. The study population thus comprised a total of 2169 patients divided into two parallel cohorts, primarily distinguished by treatment with RFA.
Comparison between the two groups of patients.

The electrophysiological characteristics of the two groups are summarized in Table 1. Age, sex, structural heart diseases, AP-AERP, AVRT-AF, multiple AP 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 MA were recorded in any of them. Complete EPT data were available for all patients. Orthodromic AVRT was reproducibly inducible in all symptomatic patients. Table 1 shows the clinical and electrophysiological characteristics of the study population at enrolment. There was an overall male preponderance that was unchanged when stratified by asymptomatic or symptomatic subjects (62.9% vs. 56.3%; P=0.034). Structural heart diseases were more frequently found in the symptomatic subgroup (10.4% vs. 1.5%; P<0.001) while the electrophysiological profile of asymptomatic subjects was characterized by a preponderance of multiple AP (7.6% vs. 3.8%; P=0.01) as compared with the symptomatic ones (Table 1).

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 while syncope-presyncope occurred in 75 patients, but no MA or VF were recorded in any of them. At the time of EPT symptomatic patients had inducible tachyarrhythmias, including orthodromic (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%). As compared with the asymptomatic subjects, the symptomatic ones were older ($P<0.001$), with less inducibility of AVRT triggering AF ($P<0.001$), less multiple accessory pathways ($P<0.001$) and longer AP-AERP ($P<0.001$).

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, 254 (20.0%) in the paraseptal space and 127 (10.0%) presented with a septal or para-hisian localization, respectively. Overall, EPT-related complications included pneumothorax (5 patients), femoral hematomas at the catheter entry (25 patients) and fistula (2 patients). RFA-related complications included right bundle branch block in 10 patients, left bundle branch block in 3 patients with antero-septal AP, a small asymptomatic pericardial effusion requiring prolongation of hospital stay in 2 children with left and right AP. Serious complications included a third-degree AV block in one patient. No fatality occurred after RFA.

**Long-term follow-up outcome**

The median follow-up for both groups was 96 months without difference between 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). Asymptomatic patients had shorter follow-up than symptomatic patients did ($P<0.001$).

Ventricular fibrillation occurred during a median follow-up of 22 months (15-41) in 15 patients (13 asymptomatic and 2 symptomatic subjects) while during a median follow-up of 46.5 months (36-58.5), 78 additional patients (48 asymptomatic and 30 symptomatic) experienced MA as documented by paramedics or at emergency facilities. Ventricular fibrillation 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 use of drugs potentially contributing to VF. Warning symptoms including pre-syncope 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 four patients of whom two were initially symptomatic, and at rest in the remaining 11 patients. Life-threatening arrhythmias were due to preexcited AF with a rapid response resulting in palpitations (25 patients), chest pain (5 patients), headache (5 patients), dizziness (35 patients), or light headedness (8 patients). Rapid preexcited AF was tolerated occurring at rest in 65 patients, during sleep in three subjects and while running in ten additional patients. No patients with MA 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 ventricular fibrillation are shown in Table 2. Of note, all but one showed an AP-AERP ≤230ms, most of them (73.3%) had inducible AVRT triggering AF and only in a minority of cases (26.7%) multiple APs were found. As compared with the symptomatic ones, asymptomatic patients had higher rates of ventricular fibrillation (P=0.01) with similar rates of MA (P=0.22). Comparison of clinical and electrophysiological characteristics of patients with MA and those with VF showed that patients experiencing VF had shorter median AP-AERP than those with MA (220ms, 210-230 vs. 240ms, 240-240; P<0.001) without difference in age, sex, multiple APs and more inducible AVRT triggering AF (73.3% vs. 44.9%; P=0.04).

**No life-threatening arrhythmias**

During a median follow-up of 43 months (40-63.3), 216 patients with a median age of 17 years (10-39) 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) 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 280ms (260-300), but we found significant differences between asymptomatic and symptomatic patients with benign recurrences since initially asymptomatic subjects were younger with longer AP-AERP [280ms (270-300) vs. 270ms (250-280); \( P=0.002 \)]. During a median follow-up of 96 months (55-96), 285 patients with a median age of 39 years (32.5-42) definitively lost ventricular preexcitation on the ECG remaining asymptomatic. Of them, 119 were asymptomatic with a median age of 42 years (31-52), and 166 were symptomatic with a median age of 38 years (33-41). As compared with patients who did not lose ventricular preexcitation, they who did were older with a median age of 39 years (32.5-42) vs. 13 years (10-29) \( (P<0.001) \), and had longer baseline AP-AERP (300ms, 280-310) vs. 270ms, 250-280) \( (P<0.001) \). 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 1,000 person-years (95% 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 of 96 months (48-96) \( (Table 1) \). RFA was successful in 1150 patients (98.5%) while 18 initially symptomatic patients (8 males) over a median follow-up of 8 months (3-11.5) after the index procedure required a repeat RFA procedure for recurrent SVT (10 patients, 55.6%), SVT and reappearance of preexcitation (4 patients, 22.2%), AF and reappearance of preexcitation (2 patients, 11.1%) or
reappearance of preexcitation alone (2 patients, 11.1%). The median patients’ age was 18.5 years (14-27.7) and the median AP-AERP was 280 ms (235-302.5). Inducibility of AVRT-AF and multiple AP were observed in 11.1% and 22.2%, respectively. The highest re-intervention rate was observed in the septal APs (35%) while the lowest was observed in the left-sided APs.

**Predictors of potentially malignant arrhythmias and ventricular fibrillation**

K-M estimates showed that asymptomatic untreated patients were more likely to develop VF than the untreated symptomatic ones (log-rank, \( P=0.008 \)) (Figure 1) without difference in cumulative risk of MA (log-rank, \( P=0.087 \)). Univariable analysis showed that many variables were associated with both MA and VF including age, multiple APs, AVRT-AF and AP-AERP (Tables 3 and 4) while absence of symptoms at univariable analysis was associated with VF development (Table 4). Cox proportional hazards model showed that VF and MA were independently associated with short AP-AERP and AVRT-AF (Tables 3 and 4) while multiple APs were only associated with MA (Table 3). Neither MA nor VF was predicted by the presence of symptoms. Time-dependent ROC curves for predicting VF showed at 48 months an AP-AERP cut-off point of 240ms with sensitivity (95% CI) of 100% (100% to 100%), specificity 69% (56% to 81%), AUC 99.04% (98.39% to 99.69%), positive predictive value 28.1% (14.1%-42.1%) and negative predictive value 100% (100% to 100%). At 96 months, the AP-AERP cut-off point was 240ms with sensitivity (95% CI) of 91.7% (76.2% to 100%), specificity 82% (71% to 93%), AUC 99.17% (98.4% to 99.9%), positive predictive value 46.0% (25.8%-66.2%) and negative predictive value 99.9% (99.6% to 100%). Untreated patients were more likely to experience MA (Figure 2) or VF (Figure 3) than those who underwent RFA during a follow-up period of 96 months.
Discussion

The current 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 one. However, it may be that the most symptomatic patients get ablated and 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 whole WPW population the ERP of AP is a critical determinant of malignant arrhythmias, which also support the recent recommendations of the PACES/HRS expert consensus statement among the young asymptomatic WPW population.\(^2\) Of note, in the present study, among 1168 treated WPW patients, no patients experienced MA or VF after RFA with only a minority presenting arrhythmia occurrence/recurrence (1.5%), which suggests that RFA improves the patient’s long-term outcomes and thus can be considered as a primary endpoint.

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 it is challenging to have a defined natural history of WPW syndrome in the whole WPW population with which make decisions. Currently, the choice to provide RFA or not has been reasonably made 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
WPW syndrome malignant arrhythmias, aborted sudden death or 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. At present, it is estimated that approximately 65% of adolescents with a WPW pattern on a resting ECG are asymptomatic. ECG recordings by recent intensive screening programs prior to sports participation or prior to 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 preexcitation on the ECG, regardless of whether they have symptoms or not, have an unpredictable lifetime risk of sudden cardiac death but only a minority of them is actually at risk, which poses considerable clinical challenges to physicians for identifying the few at risk, particularly in children. Because many patients who experienced VF have had previous episodes of both AF and paroxysmal supraventricular tachycardia, the attention has been focused for many decades on symptomatic patients and guidelines have constantly recommended liberal indication to catheter ablation as Class IA only for the symptomatic ones. In the present study, over 8-year follow-up period only 2 of 451 symptomatic patients (0.4%) experienced cardiac arrest while 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 actually died. These data are not surprising if one considers that in a similar large retrospective series of patients (690 patients) with Wolff- Parkinson White syndrome, 15 (2.2%) had ‘aborted’ sudden death, and that VF was the first manifestation of the disease in 8 previously asymptomatic patients. In the present study cardiac arrest occurred a few minutes after beginning of warning symptoms thus allowing a more time for prompt treatment by DC shock. Fortunately, cardiac arrest occurred in
places where availability of CPR and defibrillation was mandatory, or in small cities near to the hospital emergency avoiding death. Other contributing factors to successful resuscitation were the very young age (median age 11 years) and absence of structural heart disease, as it was among almost all resuscitated WPW patients.\(^4\,30\) Finally, we should emphasize that patients and parents have been well educated and alarmed to immediately reach hospital or emergency services at beginning of symptoms. In this study, all patients were successfully resuscitated strongly suggesting a better future education and training for CPR particularly among family members of asymptomatic WPW patients found 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 accessory pathways.\(^30\)

These data taken together while confirming an overall very low annual rate of VF in the whole WPW population,\(^1,5,8\) 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 concluding that the asymptomatic population as a whole is at higher risk. By 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 PACES/HRS expert consensus document\(^2\) and two 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 rate than adults.\(^33\)

In the present study, subjects who developed VF had a characteristic electrophysiological profile. As compared with patients experiencing MA, they showed more inducible preexcited
sustained AF triggered by AVRT (73.3% vs. 44.9%), and shorter median AP-AERP (220 ms vs. 240 ms). A postero-septal location of AP was found in almost all patients with VF while the rate of multiple accessory pathways was similar in patients with VF or MA, as reported by Timmermans et al.4 Of note, KM estimates showed that over 8-year follow-up period asymptomatic subjects were more likely to experience VF than the symptomatic ones. Multivariable analysis demonstrated that presence of symptoms was not an independent risk factor of outcome while shorter AP-AERP and AVRT triggering AF were associated with both VF and MA. Analysis of time-dependent ROC curve for prediction of VF showed an optimal AP-AERP cut-off point at 240ms, which confirms the key role of very short AP-AERRP to facilitate degeneration of AF into VF.

Although a shortest preexcited RR interval (SPRRI) of 250 ms has been considered as the widely accepted cut-off 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.9 Therefore, our data suggest that regardless of symptoms to prevent sudden death AVRT-AF and short AP-AERP should be considered as a specific algorithm for routine use of RFA in the whole 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 non-ablated patients since over 8-year follow-up no ablated symptomatic or asymptomatic patients
experienced MA 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 one complete third-degree AV block (0.08%). These data on 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. However, complications should be always balanced and discussed, particularly in the asymptomatic patients found at low risk or when ablating all asymptomatic WPW 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 or asymptomatic WPW individuals without 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 then cannot be representative of all centers performing RFA. Although we have collected the largest number of documented VF/cardiac arrest than previously reported, this number may be still relatively low limiting multivariable models and time dependent ROC 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 which confirms 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 at risk can definitively change the patient's natural history eliminating the risk of VF and sudden death.

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Conflict of Interest Disclosures: None.

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Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Untreated (n=1001)</th>
<th>Treated (n=1168)</th>
<th>P</th>
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<tr>
<td>Age, years</td>
<td>19 (10-37.5)</td>
<td>19 (12-35)</td>
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<tr>
<td>Sex, M (%)</td>
<td>600 (59.9)</td>
<td>701 (60.0)</td>
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<td>SHD, n (%)</td>
<td>55 (5.5)</td>
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<td>AP-AERP, ms</td>
<td>280 (250-300)</td>
<td>280 (250-300)</td>
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<td>Symptomatic, n (%)</td>
<td>451 (45.1)</td>
<td>962 (82.4)</td>
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<td>AVRT-AF, n (%)</td>
<td>47 (4.7)</td>
<td>73 (6.3)</td>
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<td>Multiple AP, n (%)</td>
<td>59 (5.9)</td>
<td>80 (6.8)</td>
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<td>MA, n (%)</td>
<td>78 (7.8)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
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<td>VF, n (%)</td>
<td>15 (1.5)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
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<td>Follow-up (months)</td>
<td>96 (50-96)</td>
<td>96 (48-96)</td>
<td>0.525</td>
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</table>

Continuous variables are expressed as median (25th-75th percentile).
Age= Age at enrolment; AP-AERP = Accessory Pathway Antegrade Effective Refractory Period at baseline; AVRT-AF= Inducible Atrioventricular Reentrant Tachycardia triggering Atrial Fibrillation at EPT; MA= potentially malignant arrhythmias; Multiple AP = Multiple accessory pathways; SHD = Structural Heart Disease; VF= ventricular fibrillation.
### Table 2. Characteristics of the 15 untreated WPW patients experiencing VF during the follow-up

<table>
<thead>
<tr>
<th>Patient</th>
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<th>AP-AERP</th>
<th>AVRT-AF</th>
<th>Follow-up</th>
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Age= Age at enrollment (years); AP-AERP (ms) = Baseline Accessory Pathway Antegrade Effective Refractory Period; AVRT-AF= Atrioventricular Reentrant Tachycardia triggering Atrial Fibrillation; Follow-up in months; LFW= Left free wall; PS= Postero-septal; RFW= Right free wall.
### Table 3. Factors associated with potentially malignant arrhythmias among untreated WPW patients.

<table>
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<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
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<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
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<td>AVRT-AF</td>
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<td>36.25-95.48</td>
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<td>AP-AERP</td>
<td>0.94</td>
<td>0.93-0.95</td>
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<tr>
<td>Multiple AP</td>
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<tr>
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<tr>
<td>Sex</td>
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<td>1.47-4.40</td>
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<tr>
<td>Symptoms</td>
<td>0.67</td>
<td>0.43-1.06</td>
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CI = Confidence Interval; AVRT-AF = Atrioventricular Reentrant Tachycardia triggering Atrial Fibrillation; AP-AERP = Accessory Pathway Antegrade Effective Refractory Period at baseline; Multiple AP = Multiple Accessory Pathways; Age = Age at enrollment.

### Table 4. Factors associated with ventricular fibrillation among untreated WPW patients.

<table>
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<th>Multivariable</th>
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<td>Multiple AP</td>
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<td>Age</td>
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<td>Sex</td>
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<tr>
<td>Symptoms</td>
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CI = Confidence Interval; AVRT-AF = Atrioventricular Reentrant Tachycardia triggering Atrial Fibrillation; AP-AERP = Accessory Pathway Antegrade Effective Refractory Period at baseline; Multiple AP = Multiple Accessory Pathways; Age = Age at enrollment.
Figure Legends:

**Figure 1.** Survival analysis stratified by symptoms after excluding MA shows that more VF episodes were observed in asymptomatic patients.

**Figure 2.** Kaplan-Meier survival plot for MA in untreated (no-RFA) and treated with RFA (RFA patients). Patients treated with RFA were less likely to experience MA than those who did not undergo RFA.

**Figure 3.** Survival analysis up to 96 months of follow-up shows that untreated (no-RFA) patients were more likely to experience VF than those who underwent RFA.
Symptomatic
Asymptomatic

Freedom from VF

Follow-up (months)

P=0.008

Number at risk

Asymptomatic 502 500 495 493 492 490 489 489 489
Symptomatic 421 421 420 419 419 419 419 419 419

Figure 1
Figure 2

Number at risk

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</table>

Freedom from MA

Follow-up (months)

RFA

No-RFA

\( P < 0.001 \)
Figure 3

Freedom from VF

Follow-up (months)

P<0.001

Number at risk

<table>
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RFA vs No-RFA
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Carlo Pappone, Gabriele Vicedomini, Francesco Manguso, Massimo Saviano, Mario Baldi, Alessia Pappone, Cristiano Ciaccio, Luigi Giannelli, Bogdan Ionescu, Andrea Petretta, Raffaele Vitale, Amarild Cuko, Zarko Calovic, Angelica Fundaliotis, Mario Moscatiello, Luigi Tavazzi and Vincenzo Santinelli

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