

Asymptomatic Ventricular Preexcitation A Long-Term Prospective Follow-Up Study of 293 Adult Patients

Vincenzo Santinelli, MD; Andrea Radinovic, MD; Francesco Manguso, MD;
Gabriele Vicedomini, MD; Giuseppe Ciconte, MD; Simone Gulletta, MD; Gabriele Paglino, MD;
Stefania Sacchi, MD; Simone Sala, MD; Cristiano Ciaccio, MD; Carlo Pappone, MD

Background—Sudden cardiac death can be the first clinical presentation of asymptomatic ventricular preexcitation.

Methods and Results—From 1995 to 2005, we prospectively collected clinical and electrophysiological data among 293 adults with asymptomatic ventricular preexcitation (61.4% males; median age, 36 years; interquartile range [IQR], 28 to 47.5). After electrophysiological testing, patients were prospectively followed, taking no drugs. The primary end point of the study was the occurrence of a first arrhythmic event. Predictors of arrhythmic events were analyzed by univariate and multivariate Cox models. Over a median follow-up of 67 months (minimum to maximum, 8 to 90), after electrophysiological testing, 262 patients (median age, 37 years; IQR, 30 to 48) did not experience arrhythmic events, remaining totally asymptomatic, whereas 31 patients (median age, 25 years; IQR, 22 to 29; median follow-up, 27 months; minimum to maximum, 8 to 55) had a first arrhythmic event, which was potentially life-threatening in 17 of them (median age, 24 years; IQR, 20 to 28.5; median follow-up, 25 months; minimum to maximum, 9 to 55). Potentially life-threatening tachyarrhythmias resulted in resuscitated cardiac arrest (1 patient), presyncope (7 patients) syncope (4 patients), or dizziness (5 patients). In multivariate analysis age ($P=0.004$), inducibility ($P=0.001$) and anterograde effective refractory period of the accessory pathway ≤ 250 ms ($P=0.001$) predicted potentially life-threatening arrhythmias.

Conclusions—These results indicate that prognosis of adults who present with asymptomatic ventricular preexcitation is good, and the risk of a significant event is small. Short anterograde effective refractory period of the accessory pathway and inducibility at baseline are independent predictors of potentially life-threatening arrhythmic events, and the risk decreases with increasing age. (*Circ Arrhythmia Electrophysiol.* 2009;2:102-107.)

Key Words: Wolff-Parkinson-White syndrome ■ death, sudden ■ syncope ■ catheter ablation

The natural history of asymptomatic ventricular preexcitation in the pediatric and adult population does not necessarily imply parity of disease in terms of pathophysiology, mechanisms, outcomes, predictors, and management. Children have a different electrophysiological function of both the accessory pathway and the atrioventricular (AV) node as well as a considerably higher incidence of multiple pathways than adults, and this can influence outcome and predictors.¹ Recently, we have demonstrated that in children aged between 5 and 18 years, incidentally found with asymptomatic ventricular preexcitation, the outcome is not as benign as previously supposed.² Multiple accessory pathways and short refractory periods were identified as independent predictors of potentially life-threatening arrhythmic events.² We report here additional data on outcome and predictors of arrhythmic events in asymptomatic patients older than 18 years to extend our knowledge on the natural history of asymptomatic ventricular preexcitation beyond childhood.

Editorial see p 97
Clinical Perspective see p 107

Methods

Study Design

Between July 1995 and December 2005, subjects older than 18 years with an incidental Wolff-Parkinson-White (WPW) syndrome on ECG, who were considered to be asymptomatic based on an accurate history, were enrolled and followed after electrophysiological testing (EPT) in the absence of antiarrhythmic drug therapy. Patients participating in other investigational protocols were excluded from the study. Patients provided written informed consent for participation after the study design had been approved by the ethics committee.

Electrophysiological Study

All patients underwent a baseline EPT, as described previously.²⁻⁵ Briefly, atrial and ventricular extrastimulation with progressively shorter coupling intervals was performed at drive-cycle lengths of

Received October 10, 2008; accepted January 27, 2009.

From the Department of Arrhythmology, Electrophysiology, and Cardiac Pacing Unit, San Raffaele Scientific Institute, Milan, Italy.

Correspondence to Vincenzo Santinelli, MD, Department of Electrophysiology, San Raffaele University Hospital, Via Olgettina 60, 20132, Milan, Italy. E-mail vincenzo.santinelli@hsr.it

© 2009 American Heart Association, Inc.

Circ Arrhythmia Electrophysiol is available at <http://circep.ahajournals.org>

DOI: 10.1161/CIRCEP.108.827550

Table 1. Characteristics of 293 Asymptomatic Adult Patients With Ventricular Preexcitation With and Without Arrhythmic Events

Variable	All Patients (n=293)	Arrhythmic Events			Potentially Life-Threatening Arrhythmias		
		Yes (n=31)	No (n=262)	P Value	Yes (n=17)	No (n=276)	P Value
Median age (IQR), y	36 (28–47.5)	25 (22–29)	37 (30–48)	<0.001	24 (20–28.5)	36 (29–48)	<0.001
Male sex, n (%)	180 (61.4)	21 (67.7)	159 (60.7)	0.445	11 (64.7)	169 (61.2)	0.775
Anterograde APERP \leq 250 ms, n (%)	39 (13.3)	22 (71)	17 (6.5)	<0.001	15 (88.2)	24 (8.7)	<0.001
Multiple accessory pathways, n (%)	13 (4.4)	4 (12.9)	9 (3.4)	0.037	2 (11.8)	11 (4.0)	0.169
Inducibility, n (%)	47 (16.0)	22 (71.0)	25 (9.5)	<0.001	14 (82.4)	33 (12.0)	<0.001

APERP indicates accessory pathway effective refractory period.

400 and 350 ms to induce AV reentrant tachycardia (AVRT) until the effective refractory periods of the atrium and ventricle were achieved. Induction of atrial fibrillation (AF) was attempted by ramp pacing starting at a cycle length of 300 ms over a period of 20 seconds; pacing was stopped once atrial refractoriness had been attained or AF induced. Inducible arrhythmias were defined as sustained if they lasted more than 1 minute. Inducibility was also assessed at baseline or after isoproterenol infusion (1 to 4 μ g/min) and defined as reproducible induction of sustained AVRT or AF. An episode of AVRT was terminated by rapid pacing 3 minutes after its onset. The anterograde effective refractory period of the accessory pathway (APERP) was defined as the longest coupling interval at which anterograde block in the bypass tract was observed. Multiple pathways were diagnosed by change in morphology during induced AF and accurate endocardial mapping by multiple catheters during induced tachyarrhythmias or ventricular pacing.

Definitions

A potentially life-threatening arrhythmia was defined as an episode of documented sustained (>1 minute) preexcited AF with a shortest preexcited RR interval \leq 250 ms. 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. Inducibility was defined as reproducible induction of sustained AVRT or AF.

End Point

The primary end point of the study was the occurrence of a first arrhythmic event. Predictors of arrhythmic events and potentially life-threatening arrhythmias were analyzed.

Follow-Up

The follow-up began after EPT and was conducted in an outpatient setting up to December 2007. Follow-up visits were scheduled every 6 months for a clinical evaluation, 12-lead ECG recording, and 24-hour Holter monitoring regardless of symptoms. Patients were instructed to immediately report any new symptom, conduct frequent follow-up visits with serial 24-hour Holter recording to evaluate potential arrhythmic events in the absence of symptoms. Subjects

were asked to report the following symptoms: palpitation, asthenia, nausea, resting or exercise dyspnea, dizziness, chest oppression, blurred vision, syncope, or any transient sensation of feeling unwell. The circumstances of arrhythmic events occurrence were accurately obtained.

Statistical Analysis

For continuous variables the Mann–Whitney *U* test was used to analyze differences between patients with or without arrhythmic or potentially life-threatening events. For discrete variables the χ^2 test was performed, unless the Fisher exact test was required for frequency tables when >20% of the expected values were $<$ 5. Factors that predicted time to total arrhythmic events and potentially life-threatening events were identified by univariate and multivariate analyses using the Cox proportional hazards models. In this analysis, independent variables for entry into the model were selected according to their weight on univariate testing ($P<0.001$): age, refractory period of the accessory pathways \leq 250 ms (no/yes=0/1), and tachyarrhythmia inducibility (no/yes=0/1). Two-sided probability values of less than 0.05 were considered to indicate statistical significance. Statistical tests were performed with SPSS software, version 17.0.0.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Population

The baseline characteristics of the study population are shown in Table 1. Among 343 screened subjects, 50 declined entry into the study and were lost to follow-up. Accordingly, a total of 293 patients (median age at diagnosis, 36 years; interquartile range [IQR], 28 to 47.5) were included into the study and prospectively followed after baseline EPT (Figure). Patients were referred for WPW electrocardiographic pattern found incidentally (n=180) or before starting sport activities

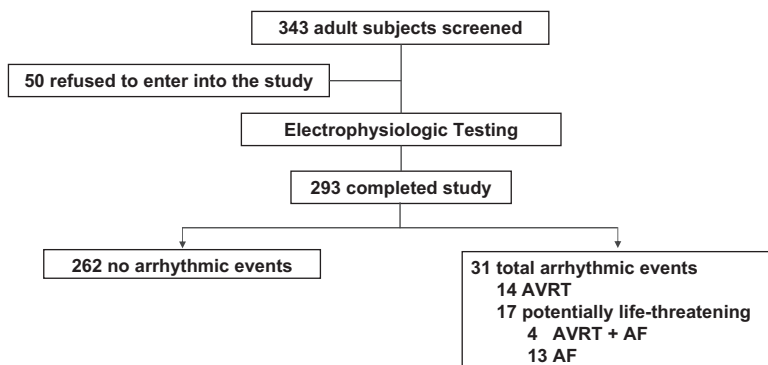


Figure. Patients enrollment and outcomes.

Table 2. Univariate Cox Regression Analysis in 293 Asymptomatic Adults With Ventricular Preexcitation

Variables	β Coefficient	Hazard Ratio (95% CI)	P Value
Total arrhythmic events			
Age, y*	-0.137	0.872 (0.825–0.921)	<0.001
Sex (male)	0.254	1.290 (0.607–2.739)	0.508
Multiple AP	1.358	3.887 (1.360–11.112)	0.011
Anterograde APERP			
≤250 ms	3.061	21.349 (9.800–46.505)	<0.001
Inducibility	2.838	17.079 (7.844–37.188)	<0.001
Potentially life-threatening arrhythmias			
Age, y*	-0.190	0.827 (0.753–0.907)	<0.001
Sex (male)	0.110	1.117 (0.413–3.020)	0.828
Multiple AP	1.240	3.457 (0.790–15.121)	0.100
Anterograde APERP			
≤250 ms	4.124	61.783 (14.083–271.046)	<0.001
Inducibility	3.437	31.084 (8.901–108.548)	<0.001

AP indicates accessory pathway; APERP, accessory pathway effective refractory period.

*The hazard ratio for age is per 1-year increase.

(n=113). According to electrocardiographic criteria,⁶ 42% of patients had left-sided, 30.4% right-sided, 26.6% postero-septal, and 1% antero-septal accessory pathways. Associated diseases were found in 34 patients (11.6%), and there was a predominance of male subjects (61.4%).

Follow-Up After EPT

The baseline clinical and electrophysiological characteristics of the patients who did or did not experience arrhythmic events or potentially life-threatening arrhythmic events are listed in Table 1. Seventy-nine patients (27%; mean age, 48±5 years) had spontaneous disappearance of the δ wave during the follow-up. The median duration of follow-up after EPT for the entire study population was 67 months (minimum to maximum, 8 to 90). Among the 262 patients who did not experience arrhythmic events, the median follow-up duration was 69 months (minimum to maximum, 39 to 90). Total arrhythmic events occurred within a median follow-up of 27 months (minimum to maximum, 8 to 55) and potentially life-threatening during a median follow-up of 25 months (minimum to maximum, 9 to 55). The first arrhythmic event was documented as sustained atrioventricular reentrant tachycardia (18 patients), which degenerated into AF in 4 patients and AF (13 patients; Figure). As compared with patients who had no events, those who did were younger, had shorter anterograde refractory period of accessory pathways, and more frequently were found multiple pathways (Table 1). In addition, among patients who developed potentially life-threatening events, EPT showed that AF was triggered by AVRT in 12 patients and by burst pacing in 2 patients with a shortest preexcited RR interval of 227.5±8.7 ms (range, 215 to 240). By contrast, among patients who did not experience life-threatening events, AF was triggered by AVRT in 2 patients and by burst pacing in 5 patients with a shortest preexcited RR intervals of 234.2±9.7 ms (range, 220 to 250).

There was no difference in shortest preexcited RR intervals between patients with and without potentially life-threatening events ($P=0.899$). Isoproterenol facilitated tachyarrhythmias induction in 2 patients with potentially life-threatening events and in 6 without life-threatening events. Subjects who experienced arrhythmic events had baseline intact retrograde conduction over accessory pathways.

Potentially Life-Threatening Arrhythmias

Potentially life-threatening arrhythmias were attributable to a preexcited AF with a mean ventricular rate of 250±18 bpm and occurred at rest. Patients with potentially life-threatening arrhythmias were young adults (median age, 24 years), the majority of them were male, and most had inducible tachyarrhythmias with shorter APERP (Table 1). Inducible tachyarrhythmias were characterized by AVRT triggering AF in 12/14 patients without isoproterenol and AF in the remaining 2 patients after isoproterenol. No patient had inducible AVRT and ERP of accessory pathway >250 ms. Tachyarrhythmias led to ventricular fibrillation with a resuscitated cardiac arrest (1 subject), presyncope (7 patients), syncope (4 patients), or dizziness (5 patients). Transition from rapid preexcited AF to cardiac arrest was documented at the emergency room and was not preceded by symptoms. In most patients life-threatening arrhythmias were recorded during presentation to emergency room (13 patients) or incidentally during routine Holter (6 patients). All patients were successfully ablated.

Predictors of Total Arrhythmic Events and Life-Threatening Tachyarrhythmias

By univariate Cox analysis predictors of arrhythmic events or potentially life-threatening events were age, anterograde refractory period of accessory pathways ≤250 ms, and inducibility (Table 2). Moreover, multiple pathways were significantly associated with shorter time to event only for total arrhythmic events. Multivariate Cox analysis demonstrated that younger age, anterograde refractory period of accessory pathways ≤250 ms, and inducibility were predictors of total arrhythmic events and potentially life-threatening events (Table 3). Sensitivity and specificity, positive predictive values of risk factors, alone and in combination, are reported in Table 4. A high predictive positive value (80%) is obtained when all 3 factors are combined (Table 4).

Discussion

Main Findings

The results of the present long-term follow-up study demonstrate that among patients in whom ventricular preexcitation has been found incidentally at age of >18 years only a minority experienced arrhythmic events and almost all remained asymptomatic over a median follow-up of 67 months. These data suggest that in adult patients who present with asymptomatic ventricular preexcitation the prognosis is good and the risk of a significant event is small decreasing with increasing age. Younger age at diagnosis, tachyarrhythmia inducibility, and short refractory period of accessory pathways are independent risk factors for potentially life-

Table 3. Multivariate Cox Analysis in 293 Asymptomatic Adults With Ventricular Preexcitation

Variables	β Coefficient	Hazard Ratio (95% CI)	P Value
Total arrhythmic events			
Age, y*	-0.112	0.894 (0.838–0.953)	0.001
Inducibility	1.902	6.700 (2.893–15.515)	<0.001
Anterograde APERP \leq 250 ms	1.860	6.422 (2.771–14.884)	<0.001
Potentially life-threatening arrhythmias			
Age, y*	-0.161	0.851 (0.762–0.951)	0.004
Inducibility	2.180	8.850 (2.311–33.895)	0.001
Anterograde APERP \leq 250 ms	2.743	15.529 (3.290–73.287)	0.001

AP indicates accessory pathway; APERP, accessory pathway effective refractory period.

*The hazard ratio for age is per 1-year increase.

threatening arrhythmic events, and their combination results in a high positive predictive value.

The Natural History of Asymptomatic Ventricular Preexcitation From Childhood to Adulthood

Ventricular preexcitation has been noted in subjects of all ages and its clinical presentation and natural history is highly variable.^{2–5,7–18} The WPW ECG pattern may be incidentally found from childhood to adulthood, suggesting that initially asymptomatic subjects may have different ages at diagnosis, which may result in different prognosis and predictors. Prior electrophysiology or population-based studies^{19–29} have reported that asymptomatic population with ventricular preexcitation, as a whole, has a benign prognosis, although it is well known that sudden death can be the first clinical manifestation of the syndrome in previously asymptomatic subjects.^{2–5,8–11} Although the association of sudden death in the WPW syndrome with AF with a rapid response and short ERP has been reported, no clinical or electrophysiological variables have been demonstrated by univariate or multivariate analysis to predict which patients are at greater risk from within the larger pool of asymptomatic people with WPW pattern.^{19–29} In the present long-term electrophysiology-based study, a total of 293 adult patients (61.4% were male) with a median age of 36 years underwent a baseline electrophysiological study. Subjects were totally asymptomatic at the time of diagnosis, which was made incidentally either at a routine

medical examination or on a screening ECG before admission to competitive sports. During a median follow-up of 67 months after EPT, \approx 90% of them had no arrhythmic events remaining totally asymptomatic and 30% of them had δ wave disappearance. Only a minority of young adult patients (10%; median age, 25 years) developed a first arrhythmic event, which was potentially life-threatening in approximately 5% (median age, 24 years), but no one died. Although this relatively good prognosis suggests that an aggressive population-based ablative strategy may not be justified in the adult population who present with asymptomatic ventricular preexcitation, a close follow-up with prophylactic ablation in selected young subjects at risk may be considered as an acceptable option. Compared to patients who experienced potentially life-threatening events, those who did not showed a characteristic electrophysiological profile (ie, older age, lower tachyarrhythmia inducibility, longer anterograde refractory period of accessory pathways, and many of them had no baseline retrograde AP conduction or multiple accessory pathways). These data indicate that, unlike children,² only a minority of adults has multiple bypass tracts (4.4%), which suggests that from childhood to adulthood multiple pathways can disappear in many subjects, decreasing the risk of life-threatening events or alternatively, that children with multiple pathways are more likely to become symptomatic and therefore not present as an asymptomatic adult. Disappearance of ventricular preexcitation on the ECG occurred in as many as 30% of older subjects (>45 years), perhaps further decreasing the risk of life threatening events over years. These findings suggest that increasing age may be associated with changes of both number and electrophysiological properties of accessory pathways, which ultimately may expose adult older patients to less risk of life-threatening arrhythmias and sudden death. Understanding pathophysiology, mechanisms, and clinical course over years can better clarify the natural history of asymptomatic ventricular preexcitation from childhood to adulthood to find the most acceptable therapeutic option.

Predictors of Potentially Life-Threatening Tachyarrhythmias

Predicting clinical outcome is one of the major issues in patients incidentally found with asymptomatic ventricular preexcitation. At present, risk assessment in such population has not been well defined, remaining a considerable clinical challenge.⁷ In the present study, the event rate of potentially

Table 4. Diagnostic Accuracy of the Risk Factors for Potentially Life-Threatening Arrhythmic Events, Alone and in Combination, in Asymptomatic Adults With Ventricular Preexcitation

Variables	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)
Age*	88.24 (63.56 to 98.54)	74.28 (68.69 to 79.33)	17.44 (10.1 to 27.13)
Inducibility	82.35 (56.57 to 96.2)	88.04 (83.62 to 91.63)	29.79 (17.34 to 44.89)
Anterograde APERP \leq 250 ms	88.24 (63.56 to 98.54)	91.3 (87.34 to 94.35)	38.46 (23.36 to 55.38)
Age + Inducibility + Anterograde APERP	70.59 (44.04 to 89.69)	98.91 (96.86 to 99.78)	80 (51.91 to 95.67)

PPV indicates positive predictive value; APERP, accessory pathway effective refractory period.

*To categorize this variable, receiver operating characteristic curve defining an optimal age cut-off value to distinguish patients with potentially life-threatening arrhythmic events from those without these events was performed. The cut-off values obtained by receiver operating characteristic curve analysis was 29 years of age.

life-threatening events was low. Univariate and multivariate analysis demonstrated that younger age at diagnosis, tachyarrhythmia inducibility, and short refractory period of accessory pathways are independent risk factors for arrhythmic events as well as for potentially life-threatening arrhythmic events. The odds ratio of 0.851 indicates the protective effect per year of increase in the age at diagnosis. These findings demonstrate that the greater risk of potentially lethal events is limited to early adulthood, decreasing with increasing age. Inducibility and short refractory period of accessory pathways were important predictors, which confirms previous studies.²⁻⁵ Finally, potentially life-threatening tachyarrhythmias occurred ≈ 2 years after baseline EPT, which suggests that in young adults tachyarrhythmia inducibility is a marker of future serious arrhythmia occurrence.

Study Limitations

Patients who declined to enter into the study were lost to follow-up, which might result in a potential selection bias. A potential overfitting attributable to the low number of life-threatening arrhythmic events cannot be completely excluded.

Conclusions

The results of the present study increase our knowledge on the natural history of asymptomatic ventricular preexcitation and verify that the risk of potentially life-threatening tachyarrhythmias in adults incidentally found with asymptomatic ventricular preexcitation on the ECG is indeed small and decreases with increasing age. Young age at diagnosis, tachyarrhythmia inducibility, and short refractory period of accessory pathways at baseline are independent predictors of potentially life-threatening arrhythmic events. In young adults at risk, catheter ablation can offer lifetime benefits that overcome the minimal risk of the procedure.

Disclosures

None.

References

- Lee P, Hwang B, Chen Y, Tai C, Chen S, Chiang C. Electrophysiologic characteristics and radiofrequency catheter ablation in children with Wolff-Parkinson-White syndrome. *Pacing Clin Electrophysiol*. 2006;29:490-495.
- Santinelli V, Radinovic A, Manguso F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Ciconte G, Sacchi S, Sala S, Pappone C. The natural history of asymptomatic ventricular preexcitation. A long-term follow-up study of 184 asymptomatic children. *J Am Coll Cardiol*. 2009;53:275-280.
- Pappone C, Santinelli V, Rosanio S, Vicedomini G, Nardi S, Pappone A, Tortoriello V, Manguso F, Mazzone P, Gulletta S, Oreto G, Alfieri O. Usefulness of invasive electrophysiologic testing to stratify the risk of arrhythmic events in asymptomatic patients with Wolff-Parkinson-White pattern: results from a large prospective long-term follow-up study. *J Am Coll Cardiol*. 2003;41:239-244.
- Pappone C, Santinelli V, Manguso F, Augello G, Santinelli O, Vicedomini G, Gulletta S, Mazzone P, Tortoriello V, Pappone A, Dicandia C, Rosanio S. A randomized study of prophylactic ablation in asymptomatic patients with the Wolff-Parkinson-White syndrome. *N Engl J Med*. 2003;349:1803-1811.
- Pappone C, Manguso F, Santinelli R, Vicedomini G, Sala S, Paglino G, Mazzone P, Lang CC, Gulletta S, Augello G, Santinelli O, Santinelli V. Radiofrequency ablation in children with asymptomatic Wolff-Parkinson-White syndrome. *N Engl J Med*. 2004;351:1197-1205.
- Milstein S, Sharma AD, Guiraudon GN, Klein GJ. An algorithm for the electrocardiographic localization of accessory pathways in the Wolff-Parkinson-White syndrome. *Pacing Clin Electrophysiol*. 1987;10:555-563.
- Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaffer CW, Stevenson WG, Tomaselli GF, Antman EM, Smith SC Jr, Alpert JS, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Hiratzka LF, Hunt SA, Jacobs AK, Russell RO Jr, Priori SG, Blanc JJ, Budaj A, Burgos EF, Cowie M, Deckers JW, Garcia MA, Klein WW, Lekakis J, Lindahl B, Mazzotta G, Morais JC, Oto A, Smiseth O, Trappe HJ; European Society of Cardiology Committee, NASPE-Heart Rhythm Society. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. A report of the American college of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology committee for practice guidelines (writing committee to develop guidelines for the management of patients with supraventricular arrhythmias) developed in collaboration with NASPE-Heart Rhythm Society. *J Am Coll Cardiol*. 2003;42:1493-1531.
- Klein GJ, Bashore TM, Sellers TD, Pritchett EL, Smith WM, Gallagher JJ. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *N Engl J Med*. 1979;301:1080-1085.
- Montoya PT, Brugada P, Smeets J, Talajic M, Della Bella P, Lezaun R, vd Dool A, Wellens HJ, Bayés de Luna A, Oter R. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *Eur Heart J*. 1991;12:144-150.
- Timmermans C, Smeets JL, Rodriguez LM, Vrochous G, Van den Dool A, Wellens HJ. Aborted sudden death in the Wolff-Parkinson-White syndrome. *Am J Cardiol*. 1995;76:492-494.
- Russel MW, Dorostkar PC, Dick M. Incidence of catastrophic events associated with the Wolff-Parkinson-White syndrome in young patients: diagnostic and therapeutic dilemma. *Circulation* 1993;88:II-484. Abstract.
- Bremilla-Perrot B, Chometon F, Groben L, Ammar S, Bertrand J, Marcha C, Cloez JL, Tisserand A, Huttin O, Tatar C, Duhoux F, Yangni N'da O, Beurrier D, Terrier de Chaise A, Zhang N, Abbas M, Cedano J, Marçon F. Interest of non-invasive and semi-invasive testings in asymptomatic children with pre-excitation syndrome. *Europace*. 2007;9:837-843.
- Mantakas ME, McCue CM, Miller WW. Natural history of Wolff-Parkinson-White syndrome discovered in infancy. *Am J Cardiol*. 1978;41:1097-1103.
- Giardina AC, Ehlers KH, Engle MA. Wolff-Parkinson-White in infants and children: a longterm follow-up study. *Br Heart J*. 1972;34:839-846.
- Perry JC, Garson A Jr. Supraventricular tachycardia due to Wolff-Parkinson-White syndrome in childhood: early disappearance and late recurrence. *J Am Coll Cardiol*. 1990;16:1215-1220.
- Munger TM, Packer DL, Hammill SC, Feldman BJ, Bailey KR, Ballard DJ, Holmes DR Jr, Gersh BJ. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953-1989. *Circulation*. 1993;87:866-873.
- Teo WS, Klein GJ, Guiraudon GM, Yee R, Leitch JW, McLellan D, Leather RA, Kim YH. Multiple accessory pathways in the Wolff-Parkinson-White syndrome as a risk factor for ventricular fibrillation. *Am J Cardiol*. 1991;67:889-891.
- Sharma AD, Bashore TM, Sellers TD, Pritchett EL, Smith WM, Gallagher JJ. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *N Engl J Med*. 1979;301:1030-1035.
- Klein GJ, Yee R, Sharma AD. Longitudinal electrophysiologic assessment of asymptomatic patients with the Wolff-Parkinson-White electrocardiographic pattern. *N Engl J Med*. 1989;320:1229-1233.
- Satoh M, Aizawa Y, Funazaki T, Niwano S, Ebe K, Miyajima S, Suzuki K, Aizawa M, Shibata A. Electrophysiologic evaluation of asymptomatic patients with the Wolff-Parkinson-White pattern. *Pacing Clin Electrophysiol*. 1989;12:413-420.
- Beckman KJ, Gallastegui JL, Bauman JL, and Hariman RJ. The predictive value of electrophysiologic studies in untreated patients with Wolff-Parkinson-White syndrome. *J Am Coll Cardiol*. 1990;15:640-647.
- Leitch JW, Klein GJ, Yee R, Murdock C. Prognostic value of electrophysiology testing in asymptomatic patients with Wolff-Parkinson-White pattern. *Circulation*. 1990;82:1718-1723.
- Flensted-Jensen E. Wolff-Parkinson-White syndrome: A long-term follow-up of 47 cases. *Acta Med Scand*. 1969;186:65-74.
- Orini E. Pre-excitation: studies on criteria, prognosis and heredity. *Acta Medi Scand Suppl*. 1966;465:1-55.

25. Berkman NL, Lamb LE. The Wolff-Parkinson-White electrocardiogram: A follow-up study of five to twenty-eight years. *N Engl J Med.* 1968; 278:492-494.
26. Soria R, Guize L, Chretien JM, Le Heuzey JY, Lavergne T, Desnos M, Hagege A, Guerre Y. The natural history of 270 cases of Wolff-Parkinson-White syndrome in a survey of the general population. *Arch Mal Coeur Vaiss.* 1989;82:331-336.
27. Goudevenos JA, Katsouras CS, Graekas G, Argiri O, Giogiakas V, Sideris DA. Ventricular pre-excitation in the general population: a study on the mode of presentation and clinical course. *Heart.* 2000; 83:29-34.
28. Fitzsimmons PJ, McWhirter PD, Peterson DW, Kruyer WB. The natural history of Wolff-Parkinson-White syndrome in 228 military aviators: A long-term follow-up of 22 years. *Am Heart J.* 2001;142:530-536.
29. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of electrocardiographic preexcitation in men. The Manitoba follow-up study. *Ann Intern Med.* 1992;116:456-460.

CLINICAL PERSPECTIVE

Sudden cardiac death in asymptomatic ventricular preexcitation remains a compelling question because it can be the first clinical manifestation in young previously asymptomatic persons, and unfortunately, risk stratification may be inconclusive. In the present study, 293 asymptomatic subjects (median age, 36 years) incidentally found with ventricular preexcitation on ECG underwent a baseline electrophysiological study and were prospectively followed from 1995 to 2007. During a median follow-up of 67 months, most patients remained asymptomatic, although 5% developed potentially life-threatening events. Multivariate analysis demonstrated that younger age, tachyarrhythmia inducibility, and short refractory period of accessory pathways predicted such rare events. These results have important clinical implications and suggest that prophylactic catheter ablation can be appropriately offered to a minority of asymptomatic subjects who are at risk of potentially life-threatening events.