Risk of Arrhythmia and Sudden Death in Patients With Asymptomatic Preexcitation
A Meta-Analysis

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Background—The incidence of sudden cardiac death (SCD) and the management of this risk in patients with asymptomatic preexcitation remain controversial. The purpose of this meta-analysis was to define the incidence of SCD and supraventricular tachycardia in patients with asymptomatic Wolff-Parkinson-White ECG pattern.

Methods and Results—We performed a systematic search of prospective, retrospective, randomized, or cohort English-language studies in EMBASE and Medline through February 2011. Studies reporting asymptomatic patients with preexcitation who did not undergo ablation were included. Twenty studies involving 1869 patients met our inclusion criteria. Participants were primarily male with a mean age ranging from 7 to 43 years. Ten SCDs were reported involving 11 722 person-years of follow-up. Seven studies originated from Italy and reported 9 SCDs. The risk of SCD is estimated at 1.25 per 1000 person-years (95% confidence interval [CI], 0.57–2.19). A total of 156 supraventricular tachycardias were reported involving 9884 person-years from 18 studies. The risk of supraventricular tachycardia was 16 (95% CI, 10–24) events per 1000 person-years of follow-up. Children had numerically higher SCD (1.93 [95% CI, 0.57–4.1] versus 0.86 [95% CI, 0.28–1.75]; P=0.07) and supraventricular tachycardia (20 [95% CI, 12–31] versus 14 [95% CI, 6–25]; P=0.38) event rates compared with adults.

Conclusion—The low incidence of SCD and low risk of supraventricular tachycardia argue against routine invasive management in most asymptomatic patients with the Wolff-Parkinson-White ECG pattern. (Circulation. 2012;125:2308-2315.)

Key Words: death, sudden ▪ meta-analysis ▪ tachycardia, supraventricular ▪ Wolff-Parkinson-White syndrome

The prevalence of preexcitation on ECG (ie, the Wolff-Parkinson-White [WPW] ECG pattern) is estimated to be between 0.1% and 0.3%. The risk of sudden cardiac death (SCD) in symptomatic patients with WPW syndrome is estimated to be ~0.25%/y or 3% to 4% over a lifetime. However, SCD may be the first event in patients with asymptomatic preexcitation. Precise quantification of this risk has been debated, and management of the asymptomatic individual remains controversial.

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Clinical Perspective on p 2315

Some studies that report a higher incidence of SCD also report that prophylactic radiofrequency ablation of the accessory pathway (AP) in asymptomatic patients is favorable compared with routine follow-up. These studies advocate routine diagnostic electrophysiological study (EPS) to guide management and to proceed with ablation in high-risk patients. Ablation in patients with symptomatic WPW syndrome is well established with agreement that the benefits outweigh the procedural risks. This is less clear in asymptomatic individuals, and current guidelines do not favor an invasive approach but favor medical follow-up with individualized decision making in regard to ablation. In particular, the positive predictive value of invasive EPS to predict SCD is considered too low to justify routine use in asymptomatic patients.

Amid this controversy, a critical issue is to confidently establish the SCD rate associated with asymptomatic preexcitation. Most studies in asymptomatic patients are relatively small, uncontrolled observational trials with limited geographic scope. Given the controversies that surround the reported SCD rates in patients with asymptomatic preexcitation and the management of this risk, we performed a meta-analysis of patients with asymptomatic WPW to define the incidence of SCD and supraventricular tachycardia (SVT).
Methods

Search Strategy and Eligibility Criteria
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used for the meta-analysis.9 We performed a comprehensive search of prospective, retrospective, randomized, or cohort English-language studies in EMBASE and Medline through February 2011 using the MeSH terms “asymptomatic or incidental” and “preexcitation or Wolff-Parkinson-White or WPW or delta wave or accessory pathway.” The search was limited to humans. Bibliographies of the retrieved articles, including systematic reviews, were searched by hand for other relevant studies. The search was conducted in the third week of January 2011.

Two authors (M.O. and J.M.) independently performed the searches and reviewed all identified publications and abstracts for inclusion using predetermined criteria. The inclusion criteria were the presence of asymptomatic preexcitation on ECG and clinical follow-up of these patients with reporting of SCD and SVT events. The exclusion criteria were asymptomatic preexcitation on ECG and clinical follow-up of these patients with reporting of SCD and SVT events. The exclusion criteria were the presence of asymptomatic preexcitation on ECG and clinical follow-up of these patients with reporting of SCD and SVT events. The exclusion criteria were asymptomatic preexcitation on ECG and clinical follow-up of these patients with reporting of SCD and SVT events.

Data Synthesis and Analysis
Agreement between the 2 data extractors was assessed with the Cohen κ statistic. The principal summary measure was event rate expressed per 1000 patient-years of follow-up and is presented with 95% confidence intervals (CIs). Studies reporting median length of follow-up were converted to means and variances by use of the method described by Hozo and colleagues.10 Unweighted overall rates were estimated by use of crude numerator and denominators. Weighted meta-analytic prevalence estimates for outcomes were calculated with the variance-stabilizing Freeman-Tukey double-arc-sine transformation with an inverse-variance random-effects model.12 I² can be interpreted as the percentage of variability resulting from heterogeneity between studies rather than sampling error. We applied DerSimonian-Laird weights for the random-effects model in which heterogeneity between studies was found.13 In addition, because the CIs based on random-effects models are wider than those from fixed-effects models, random-effects results are reported as conservative or “worst-case scenario” estimates. Demographic statistical analyses were performed with IBM SPSS Statistics software (IBM Corp, Armonk, NY). The weighted meta-analysis was performed with Excel 2007. A 2-sided value of P<0.05 was considered statistically significant.

Results

Search Results
Among a total of 585 studies identified with the search terms and 5 other studies selected from bibliographies, 219 studies were reviewed by hand after the application of search engine filters (Figure 1). Of these 219, 43 studies were selected by review of abstract and/or titles, of which 23 studies were excluded after assessment of the full text. Agreement between the 2 reviewers was 99.5% (Cohen κ statistic, 0.96; 95% CI, 0.89–1.00). Two studies potentially reported on overlapping cohorts.7,14 The study with the longer follow-up was included in the analysis (study 6), and the other was excluded (Table 1 in the online-only Data Supplement).

Twenty published studies involving 1869 asymptomatic WPW patients with 11 722 person-years of follow-up met our inclusion criteria.2,5–7,14–30 Follow-up ranged from a mean of 15 months to 21.8 years (Tables 1 and 2). The studies included 1 randomized controlled clinical trial and 14 prospective and 5 retrospective observational studies. Partici-
Incidence of SCD

All 20 studies reported on SCD. Ten SCD episodes were reported in 6 studies. Five of the 6 studies originated from Italy. Rates of SCD in individual studies ranged from 0.7 to 4.5 per 1000 person-years. No events were seen in 14 studies with a total follow-up of 7813 person-years.

When all patients were considered, the unadjusted SCD rate was 0.85 events per 1000 person-years. We found mild statistical heterogeneity ($P=0.20$; $I^2$, 20%). In a random-effects model, the risk of SCD was 1.25 (95% CI, 0.57–2.19) per 1000 person-years (Figure 2).

Of the 10 SCDs, details on sex were available in 9. Eight of the 9 patients were male. Therefore, the SCD risk in female patients is markedly lower than in male patients.

SDC in Children

Five SCD episodes were reported in 2900 person-years of follow-up (Table 3). No events were seen in 3 studies with a total follow-up of 1492 person-years. Two of the 3 studies with SCD events in children originated from Italy (studies 3 and 6). There was mild statistical heterogeneity ($P=0.30$; $I^2$, 17.9%). The risk of SCD was 1.93 (95% CI, 0.57–4.14) per 1000 person-years.

SCD in Adults

Five SCD episodes were reported with 8822 person-years of follow-up in the 14 studies involving adults. No events were seen in 11 studies with a total follow-up of 6321 person-years. All 3 studies with SCD events in adults originated from Italy (studies 17—19). We found mild statistical heterogeneity ($P=0.33$; $I^2$, 11.1%). The risk of SCD was 0.86 (95% CI, 0.28–1.75) per 1000 person-years. The risk of SCD was numerically higher in children compared with adults, although the test of interaction was not conventionally significant ($P=0.07$; Table 3).

SCD in Italian Versus Non-Italian Studies

Seven studies originated from Italy and reported 9 SCD episodes. No events were seen in 2 studies. There was mild statistical heterogeneity ($P=0.25$; $I^2$, 23.9%). In a random-effects model, the overall risk of SCD in the Italian population was estimated at 2.16 (95% CI, 0.88–4.01) per 1000 person-years. Italian adults had a marginally higher SCD event rate compared with children, although this difference was not significant (interaction $P=0.71$; Table 3).

Only 1 SCD episode was reported involving 6990 person-years of follow-up from 13 non-Italian studies.
non-Italian studies were considered, the unadjusted rate was 0.14 SCD events per 1000 person-years, and there was mild statistical heterogeneity ($P = 0.8; I^2 = 0\%$). In a random-effects model, the overall SCD risk from non-Italian studies was estimated at 0.36 (95% CI, 0.05–0.94) per 1000 person-years (Table 3).

The risk of SCD was statistically significantly lower in the non-Italian compared with the Italian studies ($P = 0.004$). The difference in SCD rate between Italian and non-Italian studies was significant for adults ($P = 0.008$) but not for children ($P = 0.97$).

Two Italian studies reported 7 patients who were lost to follow-up. Three non-Italian studies also reported patients lost to follow-up: 4% of 157 cases (which included 78 asymptomatic cases), 5% of 113 cases (which included 53 asymptomatic cases), and 1 additional patient were lost to follow-up (Table 1). If all patients lost to follow-up were presumed to be asymptomatic, a total of 13 asymptomatic patients were lost to follow-up in the non-Italian studies. Assuming an SCD for each patient lost to follow-up, the overall SCD rate was 3.66 (95% CI, 1.73–6.29) per 1000 person-years ($P < 0.0001; I^2 = 83.4\%$). The risk of SCD was 16 (95% CI, 10–24) events per 1000 person-years of follow-up (Table 3).

### Incidence of SVT

SVT was described as an outcome in 18 studies (Figure 2 and Tables 2 and 3) involving 9884 person-years. There were 156 patients who developed SVT events. Rates in individual studies varied from 0 to 50 events per 1000 person-years with evidence of large statistical heterogeneity ($P < 0.0001; I^2 = 83.4\%$). The risk of SVT was 16 (95% CI, 10–24) events per 1000 person-years of follow-up (Table 3).

### Mortality Data on Asymptomatic Patients Undergoing Catheter Ablation

A total of 57 asymptomatic patients from 2 Italian studies with follow-up ($n = 37, n = 20$) underwent prophylactic catheter ablation. No deaths (95% CI, 0–6.3% deaths) were reported in these studies after a median follow-up of 27 months (range, 9–60 months) and 34 months (range, 19–44 months), respectively. Three patients represented with SVT (atrioventricular nodal reentrant tachycardia in 2 and atrioventricular reentrant tachycardia in 1).

### Discussion

The controversy related to the incidence of SCD among patients with asymptomatic preexcitation is grounded in part on the divergent event rates that have been reported, with
studies from this meta-analysis demonstrating SCD rates between 0 and 4.5 events per 1000 person-years of follow-up. The main findings of this meta-analysis are that (1) the overall risk of SCD in adults and children is low at 2.5 per 1000 person-years of follow-up, (2) the overall risk of SVT is low at 25 per 1000 person-years of follow-up, (3) children have a numerically higher event rate of SCD compared with adults, and (4) Italian studies reported all but 1 SCD event. The low incidence of SCD and SVT may be due to a number of potential electrophysiological characteristics predominantly related to the AP. In asymptomatic patients, the absence of arrhythmias may be due to poor antegrade AP conduction and/or poor retrograde conduction. Up to 46% of asymptomatic patients may not have retrograde conduction. Autonomic tone can also modulate conduction properties of the AP and facilitate SVT.

**Event Rates in Children Versus Adults**

Reported data suggest that some patients become symptomatic over time with a gradual decrease in the asymptomatic

Table 3. Event Rates per 1000 Patient-Years of Follow-Up With Random-Effects Model for Sudden Cardiac Death and Supraventricular Tachycardia

<table>
<thead>
<tr>
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<th>Children</th>
<th>Adults</th>
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<tr>
<td></td>
<td>n</td>
<td>Events, Patient-y</td>
</tr>
<tr>
<td><strong>Sudden cardiac death</strong></td>
<td></td>
<td></td>
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<tr>
<td>Overall</td>
<td>6</td>
<td>5 (2,900)</td>
</tr>
<tr>
<td>Italian</td>
<td>4</td>
<td>4 (2,230)</td>
</tr>
<tr>
<td>Non-Italian</td>
<td>2</td>
<td>1 (670)</td>
</tr>
<tr>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Supraventricular tachycardia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>6</td>
<td>65 (2900)</td>
</tr>
</tbody>
</table>

n Indicates number of studies. Event rate is expressed per 1000 patient years of follow-up (95% confidence interval [CI]).

*Interaction P-value comparing studies of children and adults.
†Interaction P-value comparing Italian to non-Italian studies. The risk of SCD was statistically significantly lower in the non-Italian (0.36, 95% CI: 0.05 to 0.94) vs the Italian (2.16, 95% CI: 0.98 to 4.01) studies with an interaction p-value of 0.004.
‡Studies of children and adults reporting on supraventricular tachycardia demonstrated significant statistical heterogeneity (P=0.008; I², 67.9%; and P<0.0001; I², 84.7%, respectively).
state over years. It is intuitively reasonable that children have a higher incidence of events over their longer lifespan compared with adults.

Children pose a unique challenge related to the apparently nonspecific nature of arrhythmia symptoms in this population and poorer articulation of these symptoms. Therefore, it remains unclear whether the event rate observed accurately reflects rates in truly asymptomatic children. A higher index of suspicion for arrhythmia is warranted, and careful follow-up with monitoring for arrhythmia in children seems prudent.

Event Rates in Italian Versus Non-Italian Studies

The Italian population clearly demonstrated higher SCD event rates that may be due to a number of reasons. First, a wide ECG screening program is used in Italy but generally not in other countries. Sampling bias can therefore occur in non-Italian studies if the sample population is not reflective of the general population. This bias can lead to either increased or decreased estimations of the true SCD event rate. The presence of a broader screening program in Italy may provide a more reliable estimate of risk compared with selective sampling.

However, there are reasons why the Italian studies may reflect an overestimation of the true SCD event rate. For example, differences in the clinical definition of asymptomatic affect the reported rates. In 2 Italian studies that reported six total SCD events, all six patients had nonspecific symptoms that may have been attributable to arrhythmia before ventricular fibrillation. Therefore, at the time of their fatal or near-fatal event, they were likely not truly asymptomatic. Therefore, a challenging but critical clinical issue is the identification of truly asymptomatic patients for inclusion in the individual studies. Clearly, the inclusion of potentially symptomatic patients in the individual studies may result in overestimation of the presented SCD risk rates. Therefore, there is a need for better clinical definitions of asymptomatic patients and potentially the creation of a well-designed patient history questionnaire (ie, a semiquantitative scoring system). Furthermore, symptom-rhythm correlation with Holter monitoring would be critical when nonspecific symptoms are present.

Other possible explanations for the differences between Italian and non-Italian studies include the presence of a more malignant genetic WPW variant (as-yet unidentified). Two Italian studies reported the presence of multiple APs in all patients who presented with an SCD event (6 SCD events), and this may have a genetic basis. Familial WPW and sporadic WPW are likely characterized by genetic heterogeneity, variable penetrance, and expressivity. A high risk of SCD has been reported with preexcitation associated with mutation in the PRKAG2 gene, leading to familial WPW syndrome. None of the 20 studies reporting on SCD reported familial WPW. Unlike familial WPW, mutations in PRKAG2 are not commonly associated with sporadic WPW syndrome. Furthermore, there is no evidence that polymorphisms of PRKAG2 predispose to AP formation or a higher risk of SCD. Finally, a publication bias may explain the higher incidence with duplication of the same cohort (see Limitations).

Sudden Death as Determined by Population and Autopsy Studies

The incidence rates of sudden death from population studies of individuals between 0 and 49 years of age vary widely. These studies report incidence rates of 0.09 (0–35 years of age), 0.028 (1–35 years of age), 0.032 (14–35 years of age), and 0.13 (35–49 years of age) per 1000 person-years. This compares with this meta-analysis with a SCD incidence rate that ranged from 0.05 to 0.94 per 1000 person-years within a 95% CI (using all non-Italian studies). Autopsy series report the cause of sudden death to be “unascertained” in 2.8% to 39% of cases. These unascertained sudden deaths would encompass many primary arrhythmic disorders, with WPW expected to constitute only a small part of this eclectic group.

Complications and Death Associated With AP Ablation

The risks associated with an ablation procedure are likely at least similar to the risks of SCD in asymptomatic individuals. Death as a consequence of ablation in 3 large series has been reported to occur in 0.07%, 0.13%, and 0.19% of cases. Procedure-related complications in these series were reported to be 1.8%, 4.4%, and 8.2%. Recurrence rates of up to 8% after AP ablation may further temper the enthusiasm to ablate asymptomatic patients. The 2 largest series reporting on complication rates and death related to AP ablation included a total of 7649 patients. Seven deaths and 197 complications were reported (death rate, 0.9 per 1000 patients; complication rate, 26 per 1000 patients). The immediate and long-term risks of EPS and/or radiofrequency ablation in children are also well recognized. It is also probable that the incidence of complications is variable in the community and that those complications may be under reported.

Clinical Implications

Patients with WPW most susceptible to SCD are asymptomatic. Thus, the evolution of the clinical status from an asymptomatic state to symptoms likely portends a higher risk for SCD, and these patients should seek medical review.

In some asymptomatic patients, invasive risk stratification may identify a subgroup of patients with essentially no risk of SCD, which may assist in decision making for certain individuals. However, the very low event rates challenge the accuracy of EPS to predict SCD. The positive predictive value of the shortest preexcited RR interval to predict SCD remains very low. The negative predictive value of the shortest preexcited RR >250 milliseconds is well established (the effective refractory period of the AP may also be used for risk stratification). The inducibility of atrioventricular reentrant tachycardia has been reported to have positive predictive values that vary widely between 0% and 70% and negative predictive values >95% for predicting subsequent atrioventricular reentrant tachycardia.

The merits of ECG screening programs continue to be debated. Although a broad screening program may add validity to a study, the efficacy of an ECG screening program for the prevention of SCD is disputed. A number of variables contribute to assessing the efficacy of a screening program: sensitivity and specificity of the test, practicality, cost-effectiveness, known significant morbidity/mortality of the illness, potential for harm by screening, and subsequent further testing/interventions. The disease should also have a safe and effective treatment (far
superior to the natural history of the disease). Furthermore, treatment provided at the asymptomatic stage should produce outcomes far superior to those of early treatment at the symptomatic stage. Additionally, a high prevalence in the population is more likely to yield a cost-effective screening program. Thus, a screening program may not be efficacious in this population because of the relatively low prevalence of preexcitation in the general population and the already low sudden death rates within this population compared with the equally low risk associated with a routine invasive EPS-guided approach. Furthermore, the cost associated with routine screening and therapeutic intervention in asymptomatic patients would need to be evaluated. However, a systematic evaluation of the effects of a screening program may prove the utility of such an approach. Thus, studies that evaluate the utility of mass screening of the asymptomatic population are required. SCD especially in otherwise healthy individuals is always tragic, and the notion of insurance against it is very appealing. Whether this can be done at an acceptable cost without inadvertently hurting individuals not destined to have a problem is the critical challenge.

Limitations

This meta-analysis is limited by restricting studies to the English language and published articles. Nevertheless, it still yielded a significant population of 1869 patients with $\sim 12,000$ person-years of follow-up. It is also important to note that the included studies were conducted among children and adults with varied lengths of follow-up. Thus, the assumption that the risk of SCD and SVT over time is stable in these 2 populations is a potential limitation.

Two Italian studies reporting adult patients may have overlap of cohorts (studies 18 and 19). Therefore the presented SCD events risk rates may be an overestimate (Table II in the online-only Data Supplement).

Methodological differences in follow-up may contribute to underestimation of the overall event rates. In particular, event rates in the non-Italian studies may be an underestimate, given that the majority of patients lost to follow-up were in non-Italian studies (assuming that all these patients lost to follow-up were asymptomatic). However, these non-Italian studies did not distinguish between symptomatic versus asymptomatic patients.

A publication bias against case reports (and exclusion of case reports in the meta-analysis) may also result in underestimation of overall event rates. Finally, comprehensive individual patient data were not available from the studies; therefore, vetting of appropriate inclusion and study outcomes could not be performed. Furthermore, the lack of individual patient data limited further analysis such as meta-regression.

Conclusions

This meta-analysis demonstrates a low incidence of life-threatening arrhythmia in patients with asymptomatic preexcitation. The preference of the patient and the patient’s specific circumstances are important considerations. Ultimately, a carefully informed asymptomatic or symptomatic patient (or parent) needs to choose between the risk of arrhythmia and the success and complication rates associated with EPS and ablation.

Disclosures

None.

References

The incidence of sudden cardiac death (SCD) and the management of this risk in patients with asymptomatic preexcitation remain controversial. We performed a meta-analysis of 20 studies reporting on asymptomatic patients (n = 1869) with preexcitation who did not undergo ablation (11 722 person-years of follow-up). A total of 10 SCDs were reported with 9


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**Supplementary Table 1: Two studies potentially reported on overlapping cohorts.**

The study with the longer follow-up was included in the analysis (study 6) and the other excluded.

<table>
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<th>Pappone et al(^1)</th>
<th>Santinelli et al(^2) (Study 6)</th>
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<tr>
<td><strong>Title</strong></td>
<td>Radiofrequency ablation in children with asymptomatic Wolff-Parkinson-White syndrome.</td>
<td>The natural history of asymptomatic ventricular pre-excitation a long-term prospective follow-up study of 184 asymptomatic children.</td>
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<tr>
<td></td>
<td>The department of Pediatrics, University of Naples, Naples.</td>
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**Supplementary Table 2: Two Italian studies reporting on adult patients may have overlap of cohorts (studies 18³, 19⁴).**

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<tr>
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<th>Pappone et al³ (study 18)</th>
<th>Santinelli et al⁴ (study 19)</th>
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<td><strong>Title</strong></td>
<td>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.</td>
<td>Asymptomatic ventricular preexcitation: a long-term prospective follow-up study of 293 adult patients.</td>
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<td><strong>Enrollment period</strong></td>
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<tr>
<td><strong>Age</strong></td>
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