Risk of Arrhythmia and Sudden Death in Patients with Asymptomatic Pre-Excitation: A Meta Analysis

Running title: Obeyesekere et al.; Sudden death in asymptomatic pre-excitation

Manoj N. Obeyesekere, MBBS; Peter Leong-Sit, MD; David Massel, MD; Jaimie Manlucu, MD; Simon Modi, MBBS; Andrew D. Krahn, MD; Allan C. Skanes, MD; Raymond Yee, MD; Lorne J. Gula, MSc, MD; George J. Klein, MD

University of Western Ontario, Division of Cardiology, London, Ontario, Canada

Correspondence:
Manoj N Obeyesekere, MBBS  Peter Leong-Sit, MD
Division of Cardiology  Division of Cardiology
University of Western Ontario  University of Western Ontario
339 Windermere Road, C6-110  339 Windermere Road, C6-110
London - N6A 5A5, Ontario, Canada  London - N6A 5A5, Ontario, Canada
Tel: 519-663-3746  Tel: 519-663-3746
Fax: 519-663-3782  Fax: 519-663-3782
E-mail: manojobey@yahoo.com  E-mail: Peter.LeongSit@LHSC.ON.CA

Journal Subject Codes: [8] Epidemiology, [106] Electrophysiology
Abstract:

**Background** - The incidence of sudden cardiac death (SCD) and the management of this risk in patients with asymptomatic pre-excitation remains controversial. The purpose of this meta-analysis was to define the incidence of SCD and supraventricular tachycardia (SVT) 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 to February 2011. Studies reporting on asymptomatic patients with pre-excitation who did not undergo ablation were included. Twenty studies involving 1,869 patients met our inclusion criteria. Participants were primarily male with mean age ranging from 7 to 43 years. Ten SCDs were reported involving 11,722 person-years (PYrs) of follow-up. Seven studies originated from Italy and reported 9 SCDs. The risk of SCD is estimated at 1.25 per 1,000 PYrs (95% Confidence Interval (CI): 0.57 to 2.19). 156 SVT’s were reported involving 9,884 PYrs from 18 studies. The risk of SVT was 16 (95% CI: 10 to 24) events per 1,000 PYrs of follow-up. Children had numerically higher SCD (1.93 (95% CI: 0.57 to 4.1) vs. 0.86 (95% CI: 0.28 to 1.75), p=0.07) and SVT event rates (20 (95% CI: 12 to 31) vs. 14 (95% CI: 6 to 25), p=0.38) compared to adults.

**Conclusions** - The low incidence of SCD and low risk of SVT argues against routine invasive management in most asymptomatic patients with the Wolff-Parkinson-White ECG pattern.

**Key words:** meta-analysis; sudden death; supraventricular tachycardia; Wolff-Parkinson-White syndrome

**Abbreviations:**

AF - Atrial Fibrillation
AVRT - Atrio-Ventricular Re-entry Tachycardia
ECG – Electrocardiogram
ERP - Effective Refractory Period
PPV - Positive Predictive Value
RFA - Radio-Frequency Ablation
SVT - Supra ventricular tachycardia
VF - Ventricular Fibrillation
AP - Accessory Pathway
CI - Confidence Interval
EPS - Electrophysiology study
NPV - Negative Predictive Value
PYrs - Patient Years
SCD - Sudden Cardiac Death;
SPRR - Shortest Pre-excited RR interval
WPW - Wolf-Parkinson-White
Introduction

The prevalence of pre-excitation on ECG (i.e., the Wolff-Parkinson-White (WPW) ECG pattern) is estimated to be between 0.1 to 0.3%\(^1\). The risk of sudden cardiac death (SCD) in symptomatic patients with WPW syndrome is estimated to be approximately 0.25% per year or 3-4% over a lifetime\(^2,3\). However SCD may be the first event in patients with asymptomatic pre-excitation\(^4\). Precise quantification of this risk has been debated and management of the asymptomatic individual remains controversial.

Some studies that report a higher incidence of SCD also report that prophylactic radiofrequency ablation (RFA) of the accessory pathway (AP) in asymptomatic patients is favorable compared to routine follow-up\(^5\)\(^7\). These studies advocate routine diagnostic electrophysiological study (EPS) to guide management and to proceed with ablation in high-risk patients\(^6\). Ablation in patients with symptomatic WPW syndrome is well established with agreement that the benefits outweigh the procedural risks\(^8\). 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 regarding ablation\(^8\). In particular, the positive predictive value (PPV) of invasive EPS to predict SCD is considered too low to justify routine use in asymptomatic patients\(^8\).

Amidst this controversy, a critical issue is to confidently establish the SCD rate associated with asymptomatic pre-excitation. 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 pre-excitation 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 utilized for the meta-analysis. We performed a comprehensive search of prospective, retrospective, randomized or cohort, English-language studies in EMBASE and Medline through to February 2011, using the MeSH terms “asymptomatic or incidental” and “pre-excitation 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 hand-searched for other relevant studies. The search was conducted in the third week of January 2011.

Two authors (MO and JM) independently performed the searches and reviewed all identified publications and abstracts for inclusion using predetermined criteria. The inclusion criteria were (1) the presence of asymptomatic pre-excitation on ECG (2) clinical follow-up of these patients with (3) reporting of SCD and SVT events. The exclusion criteria were (1) prophylactic ablation of the AP or (2) absence of follow-up data. Review articles, letters to editors, case reports and studies with no follow-up were excluded. When studies reported on asymptomatic WPW patients undergoing ablation that also included an asymptomatic control group that did not undergo ablation, the asymptomatic non-ablation cohort was eligible for inclusion. Disagreements were resolved by consensus with a third investigator (PL).

Data extraction and quality assessment

Data from included studies were extracted independently by two authors (MO and JM) and confirmed by each. Extracted data included baseline patient characteristics, number of patients enrolled, gender, follow-up data, SCD/aborted SCD/ventricular fibrillation (VF) events and SVT events. The primary meta-meter was the incidence rate of SCD/aborted SCD/VF. The secondary
meta-meter was the incidence rate of SVT events.

The following criteria were utilized to assess for risk of bias and methodological quality: Study design, Inclusion criteria, Length of follow-up, Definition of SCD/aborted SCD/VF, Definition of SVT, Loss to follow-up. Studies were reviewed to identify duplicate reports from the same cohort by reviewing the country and institute of origin, authorship, inclusion/exclusion criteria, enrollment period and outcomes.

**Data synthesis and analysis**

Agreement between the two data extractors was assessed with Cohen’s kappa statistic. The principal summary measure was event rate expressed per 1,000 patient years of follow-up (PYrs) and presented with 95% confidence intervals (CIs). Studies reporting median length of follow-up were converted to means and variances using the method described by Hozo and colleagues. Unweighted overall rates were estimated by use of crude numerator and denominators. Weighted meta-analytical prevalence estimates for outcomes were calculated using the variance stabilising Freeman-Tukey double arcsine transformation with an inverse variance random effects model. We evaluated the presence of heterogeneity across trials with the Cochrane’s Q and Higgins’s and Thompson’s I² statistics. I² can be interpreted as the percentage of variability due to heterogeneity between studies rather than to sampling error. We applied DerSimonian-Laird weights for the random effects model where heterogeneity between studies was found. In addition, as the CIs based on random effects models are wider than fixed effects models, random effects results are reported as conservative or ‘worst case scenarios’ estimates. Demographic statistical analyses were performed using IBM SPSS Statistics software (IBM Corporation, Armonk, NY-USA). The weighted meta-analysis was performed using Excel 2007. A two-sided P-values <0.05 was considered statistically significant.
Results

Search results

Among a total of 585 studies identified using the search terms and five other studies selected from bibliographies, 219 studies were hand-reviewed following the application of search engine filters (Figure 1). Out 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 two reviewers was 99.5% (Cohen-Kappa statistic 0.96, 95% CI: 0.89-1.00). Two studies potentially reported on overlapping cohorts7, 14. The study with the longer follow-up was included in the analysis (study 6) and the other excluded (Supplemental Table 1).

Twenty published studies involving 1,869 asymptomatic WPW patients with 11,722 PYrs of follow-up met our inclusion criteria2, 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, 14 prospective and 5 retrospective observational studies. Participants were primarily male (weighted average 67%) and young with mean ages in the studies ranging from 7 to 43 years (weighted mean age was 26.5 years). When only considering studies that reported on children (i.e., studies that reported on patients with a mean age plus 1 standard deviation <18 years or studies that reported on patients with an age <18 within the 75% quartile14, 21, 23-25, 28), 6 studies were identified (studies 1-6). Thus 14 studies reported on adults (studies 7-20).

Incidence of Sudden Cardiac Death

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 per 1,000 PYrs to 4.5 per 1,000 PYrs. No events were seen in 14 studies with a total follow-up of 7,813
Considering all patients, the unadjusted SCD rate was 0.85 events per 1,000 PYrs. We found mild statistical heterogeneity (p=0.20, I^2 20%). Using a random effects model the risk of SCD was 1.25 (95% CI: 0.57-2.19) per 1,000 PYrs (Figure 2).

Of the 10 SCDs, gender details were available in 9. Eight of the 9 patients were male. Therefore, the SCD risk in females is markedly lower than in males.

**Sudden Cardiac Death in Children**

Five SCD episodes were reported in 2,900 PYrs of follow-up (Table 3). No events were seen in 3 studies with a total follow-up of 1,492 PYrs. 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 1,000 PYrs).

**Sudden Cardiac Death in Adults**

Five SCD episodes were reported with 8,822 PYrs of follow-up in the 14 studies involving adults. No events were seen in 11 studies with a total follow-up of 6,321 PYrs. All 3 studies with SCD events in adults originated from Italy (studies 17, 18, 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 1,000 PYrs. The risk of SCD was numerically higher in children compared to adults, although the test of interaction was not conventionally significant (p=0.07, Table 3).

**Sudden Cardiac Death in Italian versus non-Italian studies**

Seven studies originated from Italy and reported nine SCD episodes. No events were seen in 2 studies. There was mild statistical heterogeneity (p=0.25, I^2 23.9%). Using a random effects model the overall risk of SCD in the Italian population is estimated at 2.16 (95% CI: 0.88-4.01)
per 1,000 PYrs. Italian adults had a marginally higher SCD event rate compared to children, although this difference was not significant (interaction p=0.71) (Table 3).

Only 1 SCD episode was reported involving 6,990 PYrs of follow-up from 13 non-Italian studies. Considering all non-Italian studies the unadjusted rate was 0.14 SCD events per 1000 PYrs and there was mild statistical heterogeneity (p=0.8, I² 0%). Using a random effects model the overall SCD risk from non-Italian studies was estimated at 0.36 (95% CI: 0.05-0.94) per 1,000 PYrs (Table 3).

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

Two Italian studies reported 7 patients that 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) and 5% of 113 cases (which included 53 asymptomatic cases) and one additional patient were lost to follow-up (Table 1). If all lost to follow-up patients were presumed to be asymptomatic, a total of 13 asymptomatic patients were lost to follow-up in the non-Italian studies. Assuming a SCD for each lost to follow-up, the overall SCD rate was 3.66 (95% CI: 1.73 to 6.29) per 1,000 PYrs (p<0.0001, I² 70.1%) and in non-Italian studies was 3.98 (95% CI: 1.00 to 8.93) per 1,000 PYrs (p<0.0001, I² 66%).

Incidence of Supra-ventricular Tachycardia

Supra-ventricular tachycardia was described as an outcome in 18 studies (Figure 2, Tables 2 and 3) involving 9,884 PYrs. There were 156 patients who developed SVT events. Rates in individual studies varied from 0 to 50 events per 1,000 PYrs with evidence of large statistical heterogeneity (p<0.0001, I² 83.4%). The risk of SVT was 16 (95% CI: 10 to 24) events per 1,000
PYrs 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\(^6\), n=20\(^7\)) underwent prophylactic catheter ablation. No deaths (95% CI: 0 to 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), respectively. Three patients re-presented with SVT (atrio-ventricular nodal re-entrant tachycardia in 2 and atrio-ventricular re-entrant tachycardia (AVRT) in 1).

**Discussion**

The controversy related to the incidence of SCD among patients with asymptomatic pre-excitation is grounded in part on the divergent event rates that have been reported, with studies from this meta-analysis demonstrating SCD rates of between 0 to 4.5 events per 1,000 PYrs of follow-up.

The main findings of this meta-analysis are: 1) The overall risk of SCD in adults and children is low at <2.5 per 1,000 PYrs of follow-up, 2) The overall risk of SVT is low at <25 per 1,000 PYrs of follow-up, 3) Children have a numerically higher event rate of SCD compared to 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\(^{31}\). These patients may not be as predisposed to atrial fibrillation (AF), which is generally triggered by SVT in individuals with no other heart disease\(^5\). Autonomic tone can also modulate conduction...
properties of the AP and facilitate SVT.\textsuperscript{32}

**Event rates in children versus adults**

Reported data suggest that some patients become symptomatic over time with a gradual decrease in the asymptomatic state over the years.\textsuperscript{2} It is intuitively reasonable that children have a higher incidence of events over their longer life span compared to adults.

Children pose a unique challenge related to the apparently non-specific nature of arrhythmia symptoms in this population and poorer articulation of these symptoms.\textsuperscript{7, 14} Therefore it remains unclear if 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 utilized in Italy, but generally not utilized 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 to 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” impacts the reported rates. In two of the Italian studies that reported six total SCD events, all six patients had non-specific symptoms that may have been attributable to arrhythmia prior to VF. Therefore at the time of their fatal or near-fatal event, they were likely not truly asymptomatic.\textsuperscript{5, 7, 14} A challenging but critical clinical issue, therefore, is the identification of truly asymptomatic
patients for inclusion into the individual studies. Clearly, 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 (i.e., a semi-quantitative scoring system). Furthermore, symptom-rhythm correlation with Holter monitoring would be critical when non-specific 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 a SCD event (6 SCD events) and this may have a genetic basis. Familial and sporadic WPW is likely characterized by genetic heterogeneity, variable penetrance and expressivity. A high risk of SCD has been reported with pre-excitation 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 of 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 ages zero to 49 years vary widely. These studies report incidence rates of 0.09 (ages 0-35), 0.028 (ages 1-35), 0.032 (ages 14-35) and 0.13 (ages 35-49) per 1,000 PYrs. This compares with this meta-analysis with a SCD incidence rate that ranged from 0.05 to 0.94 per 1,000 PYrs within a 95% confidence interval (utilizing all non-Italian studies). Autopsy series report that the etiology
of sudden death to be ‘unascertained’ in 2.8%\textsuperscript{39} to 39%\textsuperscript{40} of cases\textsuperscript{36}. These unascertainable 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 accessory pathway 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%\textsuperscript{41}, 0.13%\textsuperscript{42} and 0.19% of cases\textsuperscript{43}. Procedure related complications in these series were reported to be 1.8%\textsuperscript{41}, 4.4%\textsuperscript{42} and 8.2%\textsuperscript{43}. Recurrence rates of up-to 8% following AP ablation may further temper the enthusiasm to ablate asymptomatic patients\textsuperscript{43}. The 2 largest series\textsuperscript{41,42} reporting on complication rates and death due to AP ablation included a total of 7,649 patients. Seven deaths and 197 complications were reported (death rate of 0.9 per 1,000 patients, complication rate of 26 per 1,000 patients). The immediate and long-term risks of EPS and/or RFA in children are also well-recognized\textsuperscript{44}. It is also probable that the incidence of complications is variable in the community and those complications may be underreported.

**Clinical implication**

Patients with WPW most susceptible to SCD are symptomatic\textsuperscript{4}. 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 PPV of the shortest pre-excited RR (SPRR) interval\textsuperscript{4} to predict SCD remains very low\textsuperscript{15,17-19}. The negative predictive value (NPV) of a SPRR >250ms is well-established\textsuperscript{19,45} (the effective
refractory period of the AP may also be utilized for risk stratification). The inducibility of AVRT has been reported to have PPVs that vary widely between 0%\textsuperscript{19} to 70%\textsuperscript{5} and NPVs >95%\textsuperscript{5,\textsuperscript{19}} at predicting subsequent AVRT.

The merits of ECG screening programs continue to be debated. While 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 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 due to 1) the relatively low prevalence of pre-excitation in the general population and 2) the already low sudden death rates within this population compared to the equally low risk associated with a routine invasive EPS guided approach. Furthermore, the cost associated with screening and therapeutic intervention as a routine in asymptomatic cases 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 are required that evaluate the utility of mass screening the asymptomatic population. Sudden cardiac death especially in otherwise healthy individuals is always tragic and the notion of "insurance" against it is very appealing. Whether this can be done at 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 manuscripts. Nevertheless this still yielded a significant population of 1,869 patients with approximately 12,000 PYrs 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 on adult patients may have overlap of cohorts (studies 185, 1926). Therefore the presented SCD events risk rates may be an overestimate (Supplemental Table 2).

Methodological differences in follow-up may contribute to under-estimation of the overall event rates. In particular event rates in the non-Italian studies may be an under estimate, given the majority of lost-to follow-up was observed in non-Italian studies (assuming that all these lost to follow-up patients 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 was not available from the studies and therefore vetting of appropriate inclusion and study outcomes could not be performed. Furthermore, the lack of individual patient data limited further analysis such as the use of meta-regression.

Conclusion

This meta-analysis demonstrates a low incidence of life threatening arrhythmia in patients with
asymptomatic pre-excitation. The preference of the patient and their specific circumstances is an important consideration. Ultimately in the asymptomatic patients (and also in the symptomatic patient) a carefully informed patient (or parent) needs to choose between the risk of arrhythmia versus the success and complication rates associated with EPS and ablation.

Conflict of Interest Disclosures: None

References:


Table 1: Study quality assessment (studies 1 to 6 reported on children and studies 7 to 20 reported on adults).

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Year</th>
<th>Author</th>
<th>Design</th>
<th>Country of study</th>
<th>Cases</th>
<th>Age (years)</th>
<th>Follow-up (months)</th>
<th>Lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2000</td>
<td>Vignati</td>
<td>Retrospective</td>
<td>Italy</td>
<td>64</td>
<td>7.1±5.6</td>
<td>108±48</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2000</td>
<td>Inoue</td>
<td>Prospective</td>
<td>Japan</td>
<td>52</td>
<td>Mean 10.5</td>
<td>91.2±48</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2003</td>
<td>Sarubbi</td>
<td>Prospective</td>
<td>Italy</td>
<td>57</td>
<td>9.7±5.4</td>
<td>Mean 48</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2007</td>
<td>BrembillaPerrot</td>
<td>Prospective</td>
<td>France</td>
<td>55</td>
<td>14±3</td>
<td>60±12</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2009</td>
<td>Fazio</td>
<td>Retrospective</td>
<td>Italy</td>
<td>124</td>
<td>7.8 (range 0.1-18)</td>
<td>50.4 (range 12-156)</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>2009</td>
<td>Santinelli</td>
<td>Prospective</td>
<td>Italy</td>
<td>184</td>
<td>10 (range 10-12)</td>
<td>57 (range 32-90)</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1964</td>
<td>Smith</td>
<td>Retrospective</td>
<td>Texas, USA</td>
<td>29</td>
<td>Not provided.</td>
<td>115 PYrs</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>1986</td>
<td>Milstein</td>
<td>Prospective</td>
<td>Canada</td>
<td>42</td>
<td>36±12</td>
<td>29±18</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>1989</td>
<td>Klein</td>
<td>Prospective</td>
<td>Canada</td>
<td>29</td>
<td>39±11</td>
<td>54.7±14</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>1989</td>
<td>Satoh</td>
<td>Prospective</td>
<td>Japan</td>
<td>34</td>
<td>32±19</td>
<td>15 (2-47)</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>1990</td>
<td>Beckman</td>
<td>Prospective</td>
<td>Chicago, USA</td>
<td>15</td>
<td>33±12.5</td>
<td>115.2±55.2</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>1990</td>
<td>Leitch</td>
<td>Prospective</td>
<td>Texas, USA</td>
<td>75</td>
<td>34±14</td>
<td>51.6 (range 12-108)</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>1993</td>
<td>Munger</td>
<td>Retrospective</td>
<td>Minneapolis, USA</td>
<td>53</td>
<td>33±16</td>
<td>537 PYrs</td>
<td>5% *</td>
</tr>
<tr>
<td>14</td>
<td>1993</td>
<td>BrembillaPerrot</td>
<td>Prospective</td>
<td>France</td>
<td>40</td>
<td>35±15</td>
<td>21.6 (range 6-36)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>2000</td>
<td>Goudevenos</td>
<td>Prospective</td>
<td>Greece</td>
<td>77</td>
<td>46.7±21.0</td>
<td>55 (range 20-108)</td>
<td>4% *</td>
</tr>
<tr>
<td>16</td>
<td>2001</td>
<td>Fitzsimmons</td>
<td>Retrospective</td>
<td>Texas, USA</td>
<td>187</td>
<td>34±8.9</td>
<td>261.6±140.4</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>2003</td>
<td>Pappone</td>
<td>RCT</td>
<td>Italy</td>
<td>183</td>
<td>36 (IQR 27-48)</td>
<td>36 (range 8-60)</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>2003</td>
<td>Pappone</td>
<td>Prospective</td>
<td>Italy</td>
<td>212</td>
<td>35.8±20.5</td>
<td>37.7±16.1</td>
<td>3</td>
</tr>
<tr>
<td>19</td>
<td>2009</td>
<td>Santinelli</td>
<td>Prospective</td>
<td>Italy</td>
<td>293</td>
<td>36 (IQR 28-47.5)</td>
<td>67 (range 8-90)</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>1990</td>
<td>Fukatani</td>
<td>Prospective</td>
<td>Japan</td>
<td>64</td>
<td>Not provided.</td>
<td>79.2±54</td>
<td>0</td>
</tr>
</tbody>
</table>

* 4% of 157 cases were lost to follow-up (which included 78 asymptomatic cases).
* 5% of 113 cases were lost to follow-up (which included 53 asymptomatic cases).
Follow-up presented as mean±SD or median (range) or patient years of follow up (PYrs) when reported as such or derived.
Age in years presented as mean±SD or median (range) or median (inter-quartile range, IQR).
Table 2: Sudden cardiac death and Supraventricular Tachycardia event rates utilizing random effects modeling.

<table>
<thead>
<tr>
<th>Study</th>
<th>Author</th>
<th>Patient Years</th>
<th>Sudden Cardiac Death</th>
<th>Supra-Ventricular Tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Event rate*</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Events</td>
<td>Lower</td>
</tr>
<tr>
<td>1†</td>
<td>Vignati21</td>
<td>576</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>Inoue28</td>
<td>395</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>3†</td>
<td>Sarubbi23</td>
<td>228</td>
<td>1</td>
<td>4.386</td>
</tr>
<tr>
<td>4</td>
<td>BrembillaPerrot24</td>
<td>275</td>
<td>1</td>
<td>3.636</td>
</tr>
<tr>
<td>5†</td>
<td>Fazio25</td>
<td>521</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>6†</td>
<td>Santinelli26</td>
<td>905</td>
<td>3</td>
<td>3.316</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td></td>
<td><strong>2,900</strong></td>
<td><strong>5</strong></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Smith20</td>
<td>115</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>8</td>
<td>Milstein21</td>
<td>102</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>9</td>
<td>Klein16</td>
<td>132</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>10</td>
<td>Satoh18</td>
<td>42</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>11</td>
<td>Beckman10</td>
<td>144</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>12</td>
<td>Leitch9</td>
<td>325</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>13</td>
<td>Munger8</td>
<td>537</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>14</td>
<td>BrembillaPerrot20</td>
<td>72</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>15</td>
<td>Goudevenos22</td>
<td>353</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>16</td>
<td>Fitzsimmons23</td>
<td>4077</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>17†</td>
<td>Pappone9</td>
<td>420</td>
<td>1</td>
<td>2.381</td>
</tr>
<tr>
<td>18†</td>
<td>Pappone9</td>
<td>666</td>
<td>3</td>
<td>4.504</td>
</tr>
<tr>
<td>19†</td>
<td>Santinelli26</td>
<td>1415</td>
<td>1</td>
<td>0.707</td>
</tr>
<tr>
<td>20</td>
<td>Fukatani29</td>
<td>422</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td></td>
<td><strong>8,822</strong></td>
<td><strong>5</strong></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>11722</strong></td>
<td><strong>10</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

* Event rates are per 1,000 Patient years of follow-up.
† Studies originating from Italy.
Table 3: Event rates (95% confidence interval) per 1,000 patient years of follow-up using random effects model for sudden cardiac death and supraventricular tachycardia.

### Sudden Cardiac Death

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th></th>
<th>Adults</th>
<th></th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Events (PYrs)</td>
<td>Event Rate (95% CI)</td>
<td>N Events (PYrs)</td>
<td>Event Rate (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>6 5 (2,900)</td>
<td>1.93 (0.57 to 4.14)</td>
<td>14 5 (8,822)</td>
<td>0.86 (0.28 to 1.75)</td>
<td>0.07</td>
</tr>
<tr>
<td>Italian</td>
<td>4 4 (2,230)</td>
<td>1.88 (0.28 to 4.90)</td>
<td>3 5 (2,501)</td>
<td>2.55 (0.59 to 5.88)</td>
<td>0.71</td>
</tr>
<tr>
<td>Non-Italian</td>
<td>2 1 (670)</td>
<td>2.12 (0 to 8.53)</td>
<td>11 0 (6,321)</td>
<td>0.26 (0.06 to 0.81)</td>
<td>0.16</td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td></td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Supra-ventricular Tachycardia

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th></th>
<th>Adults</th>
<th></th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Events (PYrs)</td>
<td>Event Rate (95% CI)</td>
<td>N Events (PYrs)</td>
<td>Event Rate (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>6 65 (2,900)</td>
<td>202 (119 to 306)</td>
<td>12 91 (6,984)</td>
<td>143 (65 to 250)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

N = number of studies.
PYrs = patient years of follow-up.
Event Rate = expressed per 1,000 patient years of follow-up with 95% confidence intervals in parentheses.
p* = interaction p-value comparing studies of children and adults.
p# = 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) versus the Italian (2.16, 95% CI: 0.88 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).
Figure Legends:

Figure 1. Flow diagram of literature search and study selection.

Figure 2. Random effects analysis for sudden cardiac death (top panel) and supraventricular tachycardia (bottom panel). X-axis represents event rate per 1,000 Patient-years of Follow-up with 95% Confidence Intervals for individual studies and overall summary rate. Y-axis represents individual studies (references).
Studies included in meta-analysis (n=20)

Records identified through database searching (n=585)

Total records identified (n=590)

Hand searching and Snowballing (n=5)

Duplicates (n=234)

Records after non-human and non-English studies excluded (n=356)

Non-Human (n=22)
Non-English (n=115)

Records excluded (n=176)
No follow up data - 18
Review articles - 45
Case reports - 24
Symptomatic and/or ablation/surgery studies - 42
Editorials/letters - 10
Unrelated topic - 37

English-only and human Abstracts and/or title screened (n=219)

Full text articles assessed for eligibility (n=43)

Full text articles excluded (n=23)
Letters - 2
Case reports - 1
Review articles - 6
No follow up - 13
Cohort duplication - 1

Studies included in meta-analysis (n=20)
Overall Risk of Sudden Cardiac Death

Event rate per 1,000 patient years = 1.25 (95% Confidence Interval 0.57 to 2.19). Heterogeneity p = 0.2, $I^2 = 20\%$.
Overall Risk of Supra-ventricular Tachycardia

Event rate per 1,000 patient years = 16 (95% Confidence Interval 10 to 24). Heterogeneity p < 0.0001, I² = 83%.

Study (reference)

Munger (2)
Pappone (5)
Pappone (6)
Santinelli (14)
Milstein (15)
Klein (16)
Satoh (17)
Beckman (18)
Leitch (19)
Brembilla-Perrot (20)
Vignati (21)
Goudevenos (22)
Sarubi (23)
Brembilla-Perrot (24)
Fazio (25)
Fitzsimmons (27)
Inoue (28)
Smith (30)

Summary

Event Rate per 1,000 Patient-Years of Follow-up with 95% Confidence Intervals
Risk of Arrhythmia and Sudden Death in Patients with Asymptomatic Pre-Excitation: A Meta Analysis
Manoj N. Obeyesekere, Peter Leong-Sit, David Massel, Jaimie Manlucu, Simon Modi, Andrew D. Krahn, Allan C. Skanes, Raymond Yee, Lorne J. Gula and George J. Klein

Circulation, published online April 24, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2012/04/19/CIRCULATIONAHA.111.055350

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2012/04/19/CIRCULATIONAHA.111.055350.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL.

Supplementary Table 1: Two studies potentially reported on overlapping cohorts\(^1,2\). The study with the longer follow-up was included in the analysis (study 6)\(^2\) and the other excluded.

<table>
<thead>
<tr>
<th></th>
<th>Pappone et al(^1)</th>
<th>Santinelli et al(^2) (Study 6)</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td><strong>Year</strong></td>
<td>2004</td>
<td>2009</td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td>Italy</td>
<td>Italy</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>5 to 12 years of age. Med. 10 (IQR 7 to 11)</td>
<td>5 to 18 years of age. Mean 10 +/- 2</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>165</td>
<td>184</td>
</tr>
<tr>
<td><strong>SCD’s or VF</strong></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Institutes</strong></td>
<td>Department of Cardiology, Electrophysiology and Cardiac Pacing Unit, San Raffaele University Hospital, Milan.</td>
<td>Department of Cardiology, Electrophysiology and Cardiac Pacing Unit, San Raffaele University Hospital, Milan.</td>
</tr>
<tr>
<td></td>
<td>The department of Pediatrics, University of Naples, Naples.</td>
<td></td>
</tr>
</tbody>
</table>


Supplementary Table 2: Two Italian studies reporting on adult patients may have overlap of cohorts (studies 18³, 19⁴).

<table>
<thead>
<tr>
<th></th>
<th>Pappone et al³ (study 18)</th>
<th>Santinelli et al⁴ (study 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</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>
</tr>
<tr>
<td>Year</td>
<td>2003</td>
<td>2009</td>
</tr>
<tr>
<td>Origin</td>
<td>Italy</td>
<td>Italy</td>
</tr>
<tr>
<td>Enrollment period</td>
<td>1993 to 1996</td>
<td>1995 to 2005</td>
</tr>
<tr>
<td>Age</td>
<td>Range 7 to 63. Mean 35.8 +/- 20.5.</td>
<td>Older than 18. Median 36 (IQR 28 to 47).</td>
</tr>
<tr>
<td>N</td>
<td>212</td>
<td>293</td>
</tr>
<tr>
<td>SCD’s or VF</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Institutes</td>
<td>Department of Cardiology, Electrophysiology and Cardiac Pacing Unit, San Raffaele University Hospital, Milan.</td>
<td>Department of Cardiology, Electrophysiology and Cardiac Pacing Unit, San Raffaele University Hospital, Milan.</td>
</tr>
</tbody>
</table>
