

ACC/AHA/HRS Systematic Review Report

Risk Stratification for Arrhythmic Events in Patients With Asymptomatic Pre-Excitation: A Systematic Review for the 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

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Objective—To review the literature systematically to determine whether noninvasive or invasive risk stratification, such as with an electrophysiological study of patients with asymptomatic pre-excitation, reduces the risk of arrhythmic events and improves patient outcomes.

Methods—PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (all January 1, 1970, through August 31, 2014) were searched for randomized controlled trials and cohort studies examining noninvasive or invasive risk stratification in patients with asymptomatic pre-excitation. Studies were rejected for low-quality design or the lack of an outcome, population, intervention, or comparator of interest or if they were written in a language other than English.

Results—Of 778 citations found, 9 studies met all the eligibility criteria and were included in this paper. Of the 9 studies, 1 had a dual design—a randomized controlled trial of ablation versus no ablation in 76 patients and an uncontrolled prospective cohort of 148 additional patients—and 8 were uncontrolled prospective cohort studies (n=1594). In studies reporting a mean age, the range was 32 to 50 years, and in studies reporting a median age, the range was 19 to 36 years. The majority of patients were male (range, 50% to 74%), and <10% had structural heart disease. In the randomized controlled trial component of the dual-design study, the 5-year Kaplan-Meier estimates of the incidence of arrhythmic events were 7% among patients who underwent ablation and 77% among patients who did not undergo ablation (relative risk reduction: 0.08; 95% confidence interval: 0.02 to 0.33; $P<0.001$). In the observational cohorts of asymptomatic patients who did not undergo catheter ablation (n=883, with follow-up ranging from 8 to 96 months), regular supraventricular tachycardia or benign atrial fibrillation (shortest RR interval >250 ms) developed in 0% to 16%, malignant atrial fibrillation (shortest RR interval ≤250 ms) in 0% to 9%, and ventricular fibrillation in 0% to 2%, most of whom were children in the last case.

Conclusions—The existing evidence suggests risk stratification with an electrophysiological study of patients with asymptomatic pre-excitation may be beneficial, along with consideration of accessory-pathway ablation in those deemed to be at high risk of future arrhythmias. Given the limitations of the existing data, well-designed and well-conducted studies are needed. (*Circulation*. 2016;133:e575-e586. DOI: 10.1161/CIR.000000000000309.)

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Introduction

Electrocardiographic pre-excitation affects about 0.1% to 0.3% of the general population.¹ When pre-excitation is accompanied by symptoms such as syncope or palpitations, the diagnosis of Wolff-Parkinson-White (WPW) syndrome is established.² Patients with WPW syndrome have an increased risk of sudden cardiac death (SCD) that may approach 4%

over a lifetime.³ Therefore, risk stratification of these symptomatic patients, particularly with an electrophysiological (EP) study, and catheter ablation of the accessory pathway are recommended⁴; however, when patients with electrocardiographic pre-excitation have no symptoms, it is not clear how to risk-stratify them for arrhythmic events. In such patients, the first arrhythmic event may lead to SCD.⁵ Therefore, how to accurately quantify the risk of SCD in asymptomatic patients has been debated for years, and management of such patients remains controversial.

The “2003 ACC/AHA/ESC Guidelines for the Management of Patients With Supraventricular Arrhythmias” designated “no treatment” as a Class I recommendation and catheter ablation as a Class IIa recommendation in patients with asymptomatic pre-excitation.⁴ The guideline writing committee based these recommendations on the facts that the positive predictive value of the EP study is too low to justify routine use in asymptomatic patients⁶ and that the potential value of EP study in identifying high-risk patients who may benefit from catheter ablation must be balanced against the approximately 2% risk of a major complication associated with catheter ablation.⁴ Although the guideline emphasized the importance of seeking medical expertise when patients with previously asymptomatic pre-excitation experience arrhythmia-related symptoms, it did not provide helpful information on the usefulness or comparative accuracy of invasive EP study and noninvasive EP study in predicting arrhythmic events or on the effectiveness of invasive EP study with catheter ablation of the accessory pathway, as appropriate, to prevent arrhythmic events, including SCD.⁴

On the basis of the “ACC/AHA Clinical Practice Guideline Methodology Summit Report”,⁷ the ACC/AHA Task Force

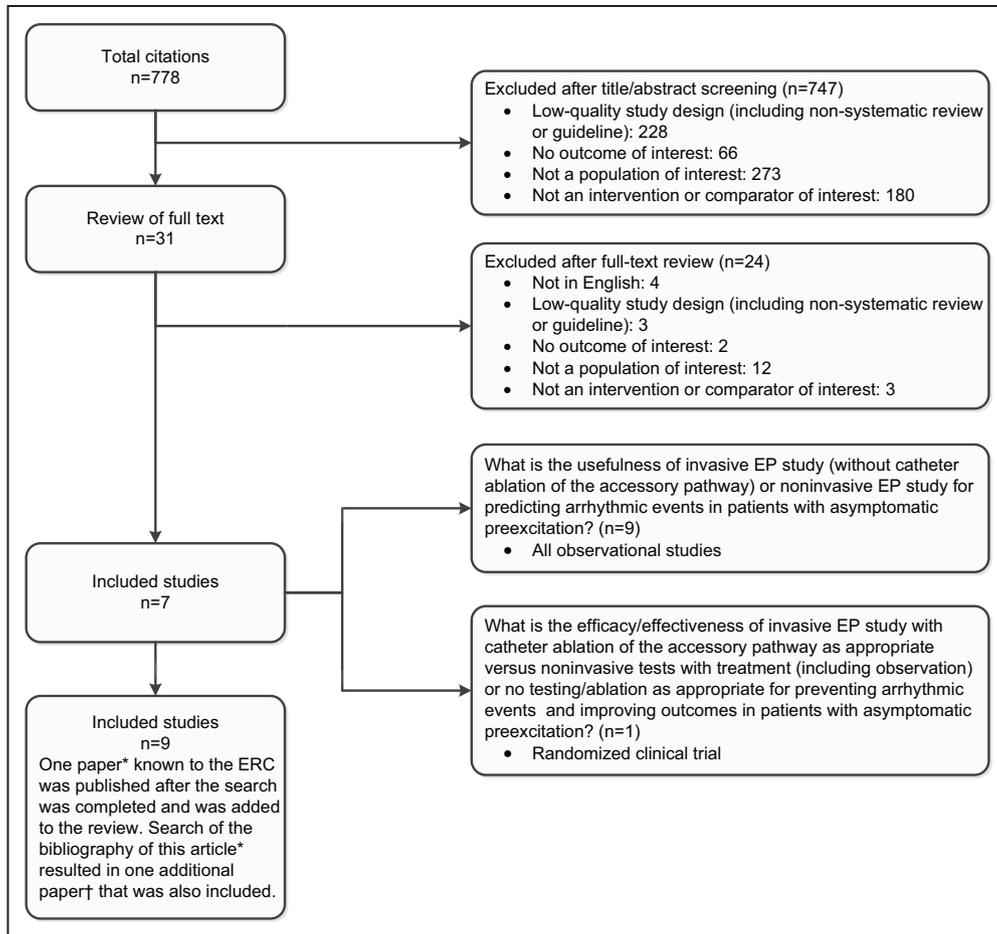


Figure 1. Search Strategy QUORUM Diagram. *Pappone et al, 2014.¹⁵ †Santinelli et al, 2009.¹⁶ EP indicates electrophysiologic and ERC, Evidence Review Committee.

on Practice Guidelines recognized the need for an objective review of the literature by an independent Evidence Review Committee (ERC) to inform recommendations about the evaluation and management of patients with asymptomatic pre-excitation in the “2015 ACC/AHA/HRS Guideline for the Management of Adults Patients With Supraventricular Tachycardia”.⁸

Methods

The ERC conducted this systematic review to address the following specific clinical questions posed by the guideline writing committee for this clinical practice guideline (with input from the ERC):

1. What is the comparative accuracy of invasive EP study (without catheter ablation of the accessory pathway) versus noninvasive testing for predicting arrhythmic events (including SCD) in patients with asymptomatic pre-excitation?;
2. What is the usefulness of invasive EP study (without catheter ablation of the accessory pathway) versus no testing for predicting arrhythmic events (including SCD) in patients with asymptomatic pre-excitation?;
3. What is the usefulness of invasive EP study (without catheter ablation of the accessory pathway) or noninvasive

EP study for predicting arrhythmic events (including SCD) in patients with asymptomatic pre-excitation?

4. What are the efficacy and effectiveness of invasive EP study with catheter ablation of the accessory pathway as appropriate versus noninvasive tests with treatment (including observation) or no testing/ablation as appropriate for preventing arrhythmic events (including SCD) and improving outcomes in patients with asymptomatic pre-excitation?

This systematic review complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement⁹ and with the recommendations of the “ACC/AHA Clinical Practice Guideline Methodology Summit Report”.⁷

Search Strategy

Eligible studies were identified by using PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (all January 1, 1970, through August 31, 2014). The following search terms were used: “asymptomatic or incidental” and “pre-excitation or “Wolff-Parkinson-White or WPW” or “delta wave” or “accessory pathway.” The ERC also searched bibliographies of previous relevant systematic reviews.^{10–12}

Table 1. Summary of Included Studies

Study (Author, Year)	Study Design	Sample Size (N)	Participant Characteristics	Inclusion Criteria	Exclusion Criteria
Pappone C, et al, 2003 ¹⁷ 14602878	Combined RCT and prospective observational cohort study. All pts underwent EP study. Pts with inducible arrhythmia on EP study who were ≤35 y were randomized to ablation vs. no ablation. The remaining pts were followed as an observational cohort.	224 (EP study identified 76 high-risk pts who were then enrolled in an RCT and 148 low-risk pts enrolled in a prospective observational cohort study)	<ul style="list-style-type: none"> • Median (IQR) age 23 y (15–30 y) for ablation group and 22 y (15–30 y) for no-ablation group. Male sex 53% in ablation arm and 47% in no-ablation group. No structural heart disease in either group. • Median (IQR) age for observational cohort 36 y (27–48 y). Male sex 59% in this cohort. Structural heart disease 7%. 	<ul style="list-style-type: none"> • Ventricular pre-excitation documented by 12-lead ECG • Absence of arrhythmia-related symptoms 	<ul style="list-style-type: none"> • Participation in other investigational protocols • Age <13 y • Pregnancy • Concomitant medical conditions
Brembilla-Perrot B, et al, 2001 ¹⁸ 11707045	Uncontrolled prospective observational study. All pts underwent testing with transesophageal stimulation.	92	<ul style="list-style-type: none"> • Mean age (±SD): 34 y (±15 y), age range 11–69 y • 68 men, 24 women • No structural heart disease 	<ul style="list-style-type: none"> • Asymptomatic WPW pattern on the ECG • No documented tachycardia and no history of sustained tachycardia 	<ul style="list-style-type: none"> • Documentation of SVT at any time
Klein GJ, et al, 1989 ¹⁹ 2710202	Uncontrolled prospective observational study. All pts underwent an EP study.	29	<ul style="list-style-type: none"> • Age (±SD): 50 y (±18 y) in the pre-excitation–lost subgroup 39 y (±11 y) in the pre-excitation–persistent subgroup • Sex: 17/29 (58.6%) men, 12/29 (41.4%) women • Structural heart disease: — 	<ul style="list-style-type: none"> • Asymptomatic WPW pattern on the ECG • No documented tachycardia and no history of sustained tachycardia 	—
Leitch JW, et al, 1990 ²⁰ 2225373	Uncontrolled prospective observational study. All pts underwent an EP study.	75	<ul style="list-style-type: none"> • Mean age (±SD) 34 y (±13 y), age range 7–77 y • Male pts 44 (59%) • Structural heart disease 5/75 (7%): (1 with CAD, 2 with cardiomyopathy, 1 with valvular heart disease, 1 with Ebstein anomaly) 	<ul style="list-style-type: none"> • Asymptomatic with WPW pattern on the ECG 	<ul style="list-style-type: none"> • All pts underwent symptom-limited exercise stress testing and 24-h Holter monitoring and were excluded from the study if SVT was documented at any time. • Other specific exclusions were intermittent pre-excitation either at rest or during exercise testing and EP study.
Milstein S, et al, 1986 ²² 3706161	Uncontrolled prospective cohort study. All pts underwent an EP study.	42	<ul style="list-style-type: none"> • Mean age (±SD) 36 y (±12 y); age range 7–77 y • Sex: 21 (50%) men and 21 (50%) women • Structural heart disease: — 	<ul style="list-style-type: none"> • WPW pattern seen on a routine ECG. These pts were considered asymptomatic because they had neither documented arrhythmias nor a history of sustained palpitations 	—

(Continued)

Table 1. Continued

Study (Author, Year)	Study Design	Sample Size (N)	Participant Characteristics	Inclusion Criteria	Exclusion Criteria
Pappone C, et al, 2003 ²¹ 12535816	Uncontrolled prospective observational study. All pts underwent an EP study.	212	<ul style="list-style-type: none"> • Mean age of overall population (\pmSD): 35.8 y (\pm20.5 y), age range 7–63 y. Sex in overall population: N/A. Structural heart disease in overall population was present in 10/212 (5%) (5 with MVP, 2 with HCM, 3 with hypertension) • Mean age (\pmSD) of the 162 patients with complete f/u 33.6 y (\pm14.3 y), age range 7–63 y. Male 105/162 (65%). Structural heart disease was present in 4/162 (3 with MVP, 1 with HCM) 	<ul style="list-style-type: none"> • Asymptomatic WPW pattern was found either incidentally at routine examination or during a medical check-up before admission to a competitive sport or a high-risk occupation 	—
Sato M, et al, 1989 ²³ 2466266	Uncontrolled observational cohort study. All pts underwent an EP study.	95 (34 asymptomatic and 61 symptomatic pts)	<ul style="list-style-type: none"> • Mean age (\pmSD) 32 y (\pm19 y) • Male 73% • Structural heart disease 13% • Intermittent pre-excitation 23% 	<ul style="list-style-type: none"> • WPW pattern • Asymptomatic (neither documented tachycardia, nor a history of palpitations suggestive of paroxysmal tachycardia) 	—
Santinelli V, et al, 2009 ¹⁶ 19808453	Uncontrolled prospective observational study. All pts underwent an EP study.	293	<ul style="list-style-type: none"> • Median age (IQR) 36 y (28–48 y) • Male 61% 	<ul style="list-style-type: none"> • Incidental WPW pattern on the ECG • Asymptomatic based on an accurate history 	<ul style="list-style-type: none"> • Participation in other research studies
Pappone C, et al, 2014 ¹⁵ 25052405	Uncontrolled prospective observational study. All pts underwent an EP study. They reported data by treatment with catheter ablation.	2169 (756 asymptomatic, 550 asymptomatic and with no ablation, and 1413 symptomatic pts)	<ul style="list-style-type: none"> • Median age 19 y, male preponderance among asymptomatic pts (63%). • Structural heart diseases were found in 1.5% of asymptomatic pts 	<ul style="list-style-type: none"> • Asymptomatic and symptomatic pts without prior ablation or documented life-threatening arrhythmias who consented to undergo a baseline EP study 	—

CAD indicates coronary artery disease; ECG, electrocardiogram; EP, electrophysiological; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; MVP, mitral valve prolapse; pt, patient; RCT, randomized controlled trial; SD, standard deviation; SVT, supraventricular tachycardia; WPW, Wolff-Parkinson-White; and —, not available.

Eligibility Criteria

Randomized controlled trials (RCTs) and nonrandomized comparative studies were included that compared invasive EP study with noninvasive testing, including resting ECG, stress testing, electrocardiographic monitoring, and esophageal pacing for predicting or preventing arrhythmic events in adults (\geq 18 years of age) with asymptomatic pre-excitation. Studies that allowed children were included only if the mean age of enrolled patients was \geq 18 years of age. Studies were excluded if they enrolled only patients with WPW syndrome or if they enrolled patients with WPW syndrome and patients with asymptomatic pre-excitation but did not report results for the latter group separately. Case series and single-group (uncontrolled) observational studies were included if they had a minimum of 20 patients and follow-up of at least 80%. Eligible studies had to report on any of the following 7 prespecified outcomes: SCD or arrhythmic death, atrial fibrillation [AF], regular supraventricular tachycardia [SVT], all-cause mortality, quality of life, hospitalization or readmission for cardiovascular events, and ablation-related

complications. The review was restricted to articles published in English. Unpublished studies were not sought.

Methods of Review

To determine the studies’ eligibility for inclusion in the systematic review, 2 members of the ERC independently reviewed each abstract and full citation. Disagreements were resolved by consensus or by involving a third reviewer (S.M. Al-Khatib). Abstracted data were entered into the Indico Clinical Guideline Platform (Indico Solutions Pty. Ltd., Melbourne, Victoria, Australia), a Web-based software platform. For each included study, the ERC members abstracted data on the study author; year of publication; sample size; inclusion and exclusion criteria; study design; setting (outpatient versus inpatient); participant characteristics (age, sex, presence of structural heart disease); the tests/procedures and their results or acute outcomes; long-term outcomes, including SCD or arrhythmic death, AF, regular SVT, all-cause mortality, quality of life, hospitalization/readmission for cardiovascular events, and ablation-related

Table 2. Comparators and Outcomes

Study (Author, Year)	Study Groups	Results of Noninvasive Testing	Results of Invasive EP Study	Acute Outcome of Catheter Ablation	Clinical Outcomes of Interest	Duration of Follow-Up	Loss to Follow-Up
Pappone C, et al, 2003 ¹⁷ 14602878	Group 1: Ablation Group 2: No ablation Group 3: Low-risk group followed as an observational cohort	N/A	15/37 (41%) pts in the ablation group had inducible AVRT. In 8 additional pts, AVRT degenerated into sustained AF. The median number of radiofrequency applications was 9 (range, 5–22).	Ablation was acutely successful in all pts. Complications related to EP study (2 pneumothoraxes and 1 large femoral hematoma) developed in 3 (1%) pts. An ablation-related complication (permanent right bundle-branch block) developed in 1/37 (3%) pt with an anteroseptal accessory pathway.	2/37 (5%) pts in the ablation group had an arrhythmic event, found on EP study to be due to AVNRT in both pts. Within a mean of 15 mo, 21/35 (60%) pts in the no-ablation group had an arrhythmic event, which was SVT in 15 pts, AF in 5 pts, and VF (not preceded by symptoms) in 1 pt. Among the high-risk controls (group 2), the 5-y rate of arrhythmic events was 77% vs. 7% in the ablation group. In the observational cohort, symptoms of SVT developed in 6 pts and 20 pts lost ventricular pre-excitation.	Ablation group median f/u 27 mo, range 9–60 mo. Control group median f/u 21 mo, range 8–60 mo.	None
Brembilla-Perrot B, et al, 2001 ¹⁸ 11707045	Group 1: Transesophageal stimulation	All patients had 24-h Holter and stress test performed before study entry and only those without supraventricular arrhythmia were included	The number of accessory pathways found was not reported. The ERPs of pathway(s) at baseline and during isoproterenol infusion were not reported. Shortest RR interval (<250 ms) during induced AF was present in 20/92 (22%) patients. Atrial tachyarrhythmia was induced in 27% of pts.	No ablation	3/92 (3%) pts developed symptomatic AF several years later. Of these 3 pts, 1 presented with AF and then VF 1 d after an aortic aneurysmectomy. Among the 42 pts considered to have a benign form of WPW syndrome, there was no clinical event, except a death related to an accident.	—	—
Klein GJ, et al, 1989 ¹⁹ 2710202	Group 1: Invasive EP study without catheter ablation	N/A	28/29 (97%) pts had only 1 accessory pathway, and 1/29 (3%) pts had >1 accessory pathway. The mean (\pm SD) ERP of pathway(s) at baseline was 334 ms (\pm 105 ms) on the initial study and 301 ms (\pm 78 ms) on the f/u study. The shortest RR interval (\pm SD) during induced AF was 266 ms (\pm 39 ms). Sustained AF was induced in 2/29 (7%) pts on the initial study and 11/29 (38%) pts on the f/u study.	No ablation	Sustained paroxysmal SVT 2/29 (7%) (during 36–79 mo); 27/29 (93%) remained asymptomatic; 9/29 (31%) lost WPW pattern on the ECG.	36–79 mo	None
Leitch JW, et al, 1990 ²⁰ 2225373	Group 1: Invasive EP study without catheter ablation	N/A	At baseline, the median ERP of the accessory pathway was 293 ms (IQR 280–310 ms), and the median retrograde ERP of the accessory pathway was 288 ms (IQR 240–320 ms). The median shortest RR interval during preexcited AF was 274 ms (IQR 240–325 ms) in 72 pts, was \leq 250 ms in 23 pts, and was \leq 200 ms in 8 pts. AVRT was induced in 12/75 (16%), and sustained AF was induced in 23/75 (31%).	No ablation	3/75 (4%) died of noncardiac causes, and 1/75 (1%) pt died suddenly after initial consultation but before EP study was done. 5/75 (7%) developed symptomatic AVRT. 1/75 (1%) developed symptomatic AF. The presence of sustained AVRT at EP study did not differentiate pts who remained asymptomatic from pts who became symptomatic. Only 1 (4%) pt developed clinical AF of the 23 pts in whom AF was induced at EP study.	Median 4.3 y (range 1–9 y)	None

(Continued)

Table 2. Continued

Study (Author, Year)	Study Groups	Results of Noninvasive Testing	Results of Invasive EP Study	Acute Outcome of Catheter Ablation	Clinical Outcomes of Interest	Duration of Follow-Up	Loss to Follow-Up
Millstein S, et al, 1986 ²² 3706161	Group 1: Asymptomatic WPW pattern	N/A	43 accessory pathways in 42 asymptomatic pts. Mean (±SD) ERP of accessory pathway was 333±106 ms in asymptomatic pts vs. 298±42 ms in asymptomatic pts (P<0.025). Mean shortest RR interval during AF was 277±48 ms in the asymptomatic groups vs. 247±51 ms in the symptomatic group (P<0.025). Sustained AVRT could be induced in only 1 pt.	No ablation	1 pt died of metastatic carcinoma after 43 mo, and 1 pt died suddenly after he had agreed to participate in the study but before EP study could be performed. 4 pts received propranolol because of undocumented "skipped beats." All other pts remained asymptomatic.	29±18 mo	None
Pappone C, et al, 2003 ²¹ 12535816	Group 1: Invasive EP study without catheter ablation	N/A	17/162 (10%) had multiple accessory pathways. Baseline mean (±SD) ERP was 275.2 ms (±33.8 ms). Isoproterenol mean (±SD) ERP was 246.1 ms (±30.5 ms). Shortest RR in AF was not reported. 47/162 (29%) had inducible arrhythmia: nonsustained AF in 17, sustained AF in 19, and inducible AVRT that degenerated into totally pre-excited sustained AF in 11.	No ablation	129/209 (62%) remained asymptomatic at the end of f/u, whereas 33 (16%) developed arrhythmic events: SVT in 25, AF in 8, documented VF in 3/209 (aborted sudden death in 2, both of whom had developed symptoms due to AF), and sudden death in 1/209	37.7±16.1 mo; range 14 to 60 mo	3/212 (1.4%); 47/212 who refused the 5-y EP study were excluded from the analysis.
Satoh M, et al, 1989 ²³ 2466266	Group 1: Asymptomatic pts with WPW pattern	Intermittent pre-excitation on ECG recording 23%	Number of pts with multiple accessory pathways not reported. Baseline mean ERP of accessory pathway was 288±29 ms in asymptomatic pts. Shortest RR in AF not reported. AVRT was induced in 6/34 (18%) pts in the asymptomatic group, and sustained AF was induced in 2/34 (6%) of asymptomatic pts.	No ablation	Group 1: no events	Mean 15 mo (range 2 to 47 mo)	—
Santinelli V, et al, 2009 ¹⁶ 19808453	Group 1: Invasive EP study without catheter ablation	N/A	Anterograde ERP of accessory pathway ≤250 ms was present in 39/293 (13%) pts. Multiple accessory pathways were found in 13 (4%) pts. Inducible arrhythmia was found in 47 (16%) pts.	No ablation	262/293 (89%) pts did not experience arrhythmic events, remaining totally asymptomatic, whereas 31/293 (11%) pts had an arrhythmic event, which was potentially life threatening in 17 of them. Potentially life-threatening tachyarrhythmias resulted in resuscitated cardiac arrest (1 pt), presyncope (7 pts), syncope (4 pts), or dizziness (5 pts).	Median duration of f/u after EP study was 67 mo (range 8 to 90)	—

(Continued)

Table 2. Continued

Study (Author, Year)	Study Groups	Results of Noninvasive Testing	Results of Invasive EP Study	Acute Outcome of Catheter Ablation	Clinical Outcomes of Interest	Duration of Follow-Up	Loss to Follow-Up
Pappone C, et al, 2014 ¹⁵ 25052405	Group 1: Asymptomatic pts with WPW pattern (they presented data on symptomatic pts and by whether catheter ablation of the accessory pathway was done, but the groups were not matched and selection bias was not adjusted for)	—	No ablation: Multiple accessory pathways in 59 (6%), median (IQR) ERP of accessory pathway 280 ms (250–300 ms). Inducible AVRT triggering AF on EP study was found in 47 (5%) of pts. With ablation: Multiple accessory pathways in 80 (7%), median ERP (IQR) of accessory pathway 280 ms (250–300 ms). Inducible AVRT triggering AF on EP study was found in 73 (6%) of pts.	206/756 asymptomatic pts were treated with ablation; ablation was successful in 98.5%.	No ablation: during a median f/u of 22 mo, VF occurred in 13/550 (2%) asymptomatic pts (almost exclusively in children). During a median f/u of 46.5 mo, 48/550 (9%) additional asymptomatic pts experienced malignant arrhythmias, and 86/756 (11%) of the asymptomatic pts developed benign arrhythmias (AVRT and AF). With ablation: no pt developed malignant arrhythmias or VF over the 8 y of f/u.	Median 96 mo	No ablation: completeness of f/u was 99.8% at 1 y and 92.3% at the end of the study With ablation: completeness of f/u was 95.5% at 1 y and 90.2% at the end of the study

AF indicates atrial fibrillation; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reciprocating tachycardia; ECG, electrocardiogram/electrocardiographic; EP, electrophysiological; ERP, effective refractory period; f/u, follow-up; IQR, interquartile range; N/A, not applicable; pt, patient; SD, standard deviation; SVT, supraventricular tachycardia; VF, ventricular fibrillation; WPW, Wolf-Parkinson-White; and —, not available.

complications; duration of follow-up; and loss to follow-up. Overall study quality was assessed in terms of risk of bias, relevance to the study question, and fidelity of implementation.⁷ To evaluate risk of bias, the Cochrane Collaboration Risk of Bias Tool was used for RCTs,¹³ and the Newcastle-Ottawa Scale was used for cohort studies.¹⁴ An RCT was assigned an overall rating of low-to-intermediate risk of bias if the trial was not deemed to be at high risk of bias for any assessed domain of study quality.

Statistical Analysis

Given the major methodological differences between RCTs and cohort studies, the 2 study types were analyzed separately. For each outcome of interest, the feasibility of completing a quantitative synthesis (ie, meta-analysis) was assessed. Meta-analyses were considered when at least 3 studies reported the same outcome in similar populations, but because of incomplete data, they were not feasible. Counts/percentages of arrhythmic events were pooled from the observational cohort studies.

Results

Study and Patient Characteristics

We screened 778 abstracts, evaluated 31 full-text articles, and included 7 articles. In addition, 1 paper known to the ERC was published after the search was completed and was added to the review.¹⁵ A search of the bibliography of this article¹⁵ resulted in 1 additional paper¹⁶ that was also included. The search strategy used is shown in Figure 1.

Of the 9 eligible studies that were identified, 1 had a dual-study design—encompassing both an RCT of ablation versus no ablation in 76 patients and a separate, uncontrolled prospective cohort of 148 additional patients¹⁷—and 8 were uncontrolled prospective observational cohort studies.^{15, 16, 18–23} These 9 studies contributed data from 1818 participants (although some patients were included in >1 study), with sample sizes

ranging from 29 to 550 asymptomatic patients with no ablation of the accessory pathway and from 37 to 206 asymptomatic patients with ablation of the accessory pathway.^{17–23} All 9 studies addressed question 3, which examined the usefulness of either invasive EP study without catheter ablation of the accessory pathway or noninvasive EP study for predicting arrhythmic events in patients with asymptomatic pre-excitation.^{15–23} The RCT¹⁷ component of the dual-design study also addressed question 4, which examined the efficacy of invasive EP study with catheter ablation of the accessory pathway as appropriate versus noninvasive tests with treatment or no testing/ablation as appropriate for preventing arrhythmic events and improving outcomes in patients with asymptomatic pre-excitation.

The characteristics of the studies and the participants are presented in Table 1. In studies reporting a mean age, the range was 32 to 50 years,^{17–20,22,23} and in studies reporting a median age, the range was 19 to 36 years.^{15–17} The majority of patients were male (range 50% to 74%). Structural heart disease was reported to be present in a minority of patients (<10%).^{15,17,18,20,21,23} Intermittent pre-excitation was an exclusion criterion in 1 study²⁰ and was reported to be present in 23% of patients in another study.²³ The remaining studies did not report on whether pre-excitation was intermittent or persistent.

Study Results

Study comparators and outcomes are presented in Table 2. In the 2003 RCT component of the dual-design study by Pappone et al,¹⁷ during a median follow-up of 27 months, 2 (5%) of 37 patients in the ablation group had regular SVT, versus 21 (60%) of 35 patients in the no-ablation group (regular SVT in 15 patients, AF in 5 patients, and ventricular fibrillation [VF] in 1 patient). In the randomized comparison of ablation versus no ablation, the 5-year Kaplan-Meier estimates of the incidence of arrhythmic events were 7% among patients who underwent ablation and 77% among those who did not (relative risk reduction: 0.08; 95% confidence interval: 0.02 to 0.33; $P < 0.001$). The rates of different types of arrhythmic

Table 3. Quality Assessment of Included Studies

Study (Author, Year)	Representativeness of the Cohort	Selection of a Nonexposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Enrollment	Independent Blind Assessment of Outcomes	Was Follow-Up Long Enough for Outcomes to Occur?	Adequacy of Cohort Follow-Up (Including Loss to Follow-Up)	Precision of Findings
Pappone C, et al, 2003 ¹⁷ 14602878	Questionable	Yes	Yes	Reasonable, based on the absence of symptoms	The events were reviewed by an independent committee whose members were unaware of the pts' treatment assignments	Yes	Yes	Fairly precise with CI 0.02–0.33 for arrhythmic events and 0.002–0.104 for event-free survival
Brembilla-Perrot B, et al, 2001 ¹⁸ 11707045	Yes	N/A (no comparator group)	All pts underwent EP study	Reasonable, based on the absence of symptoms. Pts had to have a normal ECG, exercise stress test, and 24-h Holter monitor	—	Uncertain because duration of f/u was not reported	F/u and loss to f/u were not reported	N/A (no comparator group)
Klein GJ, et al, 1989 ¹⁹ 2710202	Yes	N/A (no comparator group)	All pts underwent EP study	2/29 had SVT between scheduling EP study and when EP study was performed	—	Yes	Yes	N/A (no comparator group)
Leitch JW, et al, 1990 ²⁰ 2225373	Questionable	N/A (no comparator group)	All pts underwent EP study	Yes	—	Yes	Yes	N/A (no comparator group)
Milstein S, et al, 1986 ²² 3706161	Yes	N/A (all pts underwent EP study)	All pts underwent EP study	Yes	—	Yes	Yes	Imprecise due to small sample size
Pappone C, et al, 2003 ²¹ 12535816	Questionable	N/A (no comparator group)	All pts underwent EP study	Yes	—	Yes	Questionable	N/A (no comparator group)
Satoh M, et al, 1989 ²³ 2466266	Yes	N/A (all pts underwent EP study)	All pts underwent EP study	Yes	—	Yes	—	Imprecise (no events)
Santinelli V, et al, 2009 ¹⁶ 19808453	Questionable	N/A (no comparator group)	All pts underwent EP study	Yes	—	Yes	—	N/A (no comparator group)
Pappone C, et al, 2014 ¹⁵ 25052405	Questionable	N/A (no comparator group)	All pts underwent EP study	Yes	—	Yes	—	N/A (no comparator group)

CI indicates confidence interval; ECG, echocardiogram; EP, electrophysiological; f/u, follow-up; N/A, not applicable; pt, patient; SVT, supraventricular tachycardia; and —, not available.

events occurring within 5 years were not reported in this paper.¹⁷ In the associated observational cohort, symptoms of SVT developed in 6 (4%) of 148 patients.¹⁷

In the 1986 study by Milstein et al,²² 4 (10%) of 42 patients started receiving propranolol because of palpitations of unclear etiology, whereas all other patients remained asymptomatic during a mean follow-up of 29 months.

In the 1989 study by Klein et al,¹⁹ sustained SVT occurred in 2 (7%) of 29 patients during 36 to 79 months of follow-up, with the other 27 (93%) patients remaining asymptomatic.

In the 1989 study by Satoh et al,²³ no events occurred during a mean follow-up of 15 months.

In the 1990 study by Leitch et al,²⁰ 5 (7%) of 75 patients developed symptomatic atrioventricular reentrant tachycardia, and 1 (1%) of 75 developed symptomatic AF over a median follow-up of 4.3 years. The presence of sustained atrioventricular reentrant tachycardia at EP study did not differentiate patients who remained asymptomatic from patients who became symptomatic during follow-up.

In the 2001 study by Brembilla-Perrot et al,¹⁸ which did not report duration of follow-up, 3 (3%) of 92 patients developed

a clinically significant atrial arrhythmia several years after initial enrollment. Of these 3 patients, 1 adult presented with AF and then VF 1 day after an aortic aneurysmectomy.

In another 2003 study by Pappone et al,²¹ 129 (62%) of 209 patients remained asymptomatic at the end of follow-up (mean follow-up, 38 months), whereas 33 (16%) experienced arrhythmic events. Of these 33 patients, 25 developed regular SVT, 8 developed AF, and 3 had documented VF (aborted SCD in 2, both of whom had AF, and death in 1 of 209).

In the 2009 study by Santinelli et al,¹⁶ during a median follow-up of 67 months (range, 8 to 90 months), 262 (89%) of 293 patients did not experience arrhythmic events, remaining totally asymptomatic, whereas 31 (11%) of 293 patients had an arrhythmic event, which was potentially life threatening in 17 patients (6%). Potentially life-threatening tachyarrhythmias resulted in resuscitated cardiac arrest (1 patient), presyncope (7 patients), syncope (4 patients), or dizziness (5 patients).

In a 2014 study by Pappone et al,¹⁵ during a median follow-up of 22 months (range, 15 to 41 months), VF occurred in 13 (2%) of 550 asymptomatic patients with no ablation, almost all of whom were children. During a median follow-up of 46.5 months (range, 36 to 58.5 months), 48 (9%) additional previously asymptomatic patients experienced malignant arrhythmias. In all patients, VF developed a few minutes after warning symptoms and resulted in a resuscitated cardiac arrest without neurological sequelae. These malignant arrhythmic events correlated with the electrophysiological properties of the accessory pathway. Eighty-six of the 756 (550 asymptomatic patients with no ablation plus 206 asymptomatic patients who underwent ablation) asymptomatic patients (11%) developed benign arrhythmias (atrioventricular reentrant tachycardia and AF). Ablation was reported to be successful in 98.5% of cases; after radiofrequency ablation, no patient developed malignant AF (shortest RR \leq 250 ms) or VF over the 8 years of follow-up.

Two studies reported on EP study- and ablation-related complications. In the first 2003 study by Pappone et al,¹⁷ complications related to EP study developed in 3 patients (1%) (2 pneumothoraxes and 1 large femoral hematoma). An ablation-related complication (permanent right bundle-branch block) developed in 1 (3%) of 37 patients. In the 2014 study by Pappone et al,¹⁵ complications of EP study consisted of pneumothorax in 5 patients (0.2%), femoral hematomas at the catheter entry site in 25 patients (1%), and fistulas in 2 patients (0.09%). Ablation-related complications included right bundle-branch block in 10 patients (0.9%); left bundle-branch block in 3 patients (0.3%) with anteroseptal accessory pathways; and a small, asymptomatic pericardial effusion requiring prolongation of hospital stay in 2 children (0.2%) with left and right accessory pathways. Serious complications included third-degree atrioventricular block in 1 patient (0.1%). No deaths occurred after ablation.

Evidence Synthesis

Because 4^{15-17, 21} of the 9 included papers were published by the same group and some of their patients were included in >1 study, only the most recent and inclusive study by that group was included in this part of the analysis.¹⁵ In the RCT

component of the dual-design study (n=76), estimates of the incidence of arrhythmic events were 7% among patients who underwent ablation and 77% among the controls ($P<0.001$).¹⁷ In the observational cohorts of asymptomatic patients who did not undergo catheter ablation (n=883) during follow-up that ranged from 8 to 96 months,^{15, 18-20, 23} regular SVT or benign AF (shortest RR >250 ms) developed in 0% to 16%, and malignant AF (shortest RR \leq 250 ms) developed in 0% to 9%. VF developed in 0 to 14 (2%) of 883 patients who, except for 3 (1 in the study by Brembilla-Perrot et al¹⁸ and 2 in Pappone et al, 2003²¹/Pappone et al, 2014¹⁵), were all children (n=11, all in Pappone et al, 2014¹⁵). None of the patients who died suddenly had undergone accessory-pathway ablation. In 2 studies,^{20, 22} 1 patient was reported to have died suddenly after consenting to undergo an EP study but before the EP study was performed. Given the ambiguity of these 2 deaths, they were not included in the estimates of VF.

Quality of Included Studies

Quality assessment of included studies is shown in Table 3. All studies showed intermediate-to-high relevance with regard to their study population, testing, intervention, and outcome measures.¹⁵⁻²³ The degree to which the enrolled population was representative of patients seen in clinical practice was questionable in 5 studies.^{15-17, 20, 21} The RCT by Pappone et al¹⁷ had low risk of bias because, among other measures, it implemented independent blind assessment of outcomes. All other studies had intermediate overall risk of bias because they had not implemented blind assessment of outcomes.^{15, 16, 18-23}

Discussion

In this systematic review, only a single RCT was found that addressed the best management strategy for patients with asymptomatic pre-excitation. Although data from observational cohorts of asymptomatic patients who did not undergo catheter ablation (n=883) suggest that most of these patients have a benign course, with few clinically significant arrhythmic events during follow-up that ranged from 8 to 96 months, malignant AF (shortest RR \leq 250 ms) developed in up to 9% of patients, and VF developed in up to 2% of patients. These percentages are not trivial, given the potential fatality of these events.¹⁵ Importantly, malignant arrhythmias correlated more with the EP properties of the accessory pathway than with the presence or absence of symptoms.¹⁵ Notably, in the RCT of ablation versus no ablation, the 5-year estimates of the incidence of arrhythmic events were 7% among patients who underwent ablation and 77% among the controls. Therefore, risk stratification with an EP study of patients with asymptomatic pre-excitation may be beneficial, along with consideration of accessory-pathway ablation in those deemed to be at high risk of future arrhythmias. This approach is further supported by the low risk of complications: Complication rates ranged from 0.09% to 1% and included pneumothorax and access site complications in a registry study of EP that included 2169 patients.¹⁵

The question of whether to ablate the accessory pathway(s) in EP study-identified high-risk patients was examined in only 1 RCT, which enrolled 76 patients. In that trial, estimates of the incidence of arrhythmic events were 7% in patients

who underwent ablation versus 77% in patients who did not undergo ablation.¹⁷ The 1 other study that examined patients on the basis of whether an ablation was performed was the largest and longest prospective cohort study by Pappone et al¹⁵. In that study, none of the asymptomatic patients who had undergone ablation of the accessory pathway developed malignant arrhythmia or VF during 8 years of follow-up¹⁵; however, the ablation and no-ablation groups were not matched, and researchers did not adjust for selection bias. Given the small number of patients in the 1 RCT published to date and the observational studies' methodological limitations, including the relatively small sample size of patients included in most of those studies, well-designed and conducted prospective studies, especially RCTs of ablation versus no ablation, are needed.

The decision to ablate the accessory pathway should be informed not only by data on the effectiveness of the procedure, but also by data on the risk of complications. Although 7 of the 9 included studies did not report on complications, 1 study by Pappone et al¹⁵ provided detailed information on complications in 1168 patients who underwent an ablation. The risk of complications ranged from 0.1% (complete heart block) to 0.9% (ablation-induced right bundle-branch block). No ablation-related deaths occurred.

Limitations

This systematic review has several important limitations. First, because of the lack of data from RCTs and controlled prospective studies, the selection bias inherent to observational studies could not be avoided, and the evidence could not be quantitatively synthesized. Second, the inclusion of some patients in >1 study^{15–17,21} made it impossible to examine collective data from all available studies, so the most recent and inclusive study from that group was used.¹⁵ Third, as is generally the case with systematic reviews, this review is limited by the possibility of publication and reporting biases and the inconsistency of outcome definitions across the studies. Fourth, several of the potentially eligible studies had to be excluded because they enrolled asymptomatic and symptomatic patients with pre-excitation and did not report on the characteristics and outcomes of these groups separately. Fifth, allowing studies that included children may have affected the generalizability of the findings to an adult population. Sixth, by limiting the search to studies published since 1970, an important study published in 1968 and conducted in 128 healthy US Air Force men followed for 5 to 28 years was excluded. That study showed that in the absence of cardiac disease and arrhythmias, asymptomatic pre-excitation did not affect the prognosis; although 3 deaths were observed, no known death was attributable to a cardiac cause.²⁴ Given the highly selected study population, however, excluding this study likely did not have a major effect on our findings.

Conclusions

In this systematic review, little evidence was found from RCTs with regard to the best management strategy for patients with asymptomatic pre-excitation. Data from observational studies on 883 patients who did not undergo ablation showed that up to 9% of patients developed malignant arrhythmias, and up to 2% developed VF during follow-up. These observations,

coupled with the very low risk of complications resulting from an EP study, suggest that risk stratification of patients with asymptomatic pre-excitation using an EP study may be beneficial, with consideration of accessory-pathway ablation in those deemed to be at high risk of future arrhythmias. Given the limitations of the existing data, well-designed and well-conducted studies are needed.

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KEY WORDS: AHA Scientific Statements ■ accessory atrioventricular bundle ■ asymptomatic ■ cardiac arrhythmias ■ pre-excitation syndromes ■ risk assessment ■ sudden cardiac death ■ Wolff-Parkinson-White Syndrome

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)*—Risk Stratification for Arrhythmic Events in Patients With Asymptomatic Pre-Excitation: A Systematic Review for the 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia (May 2014)

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Jonathan Hsu	University of California San Diego—Assistant Professor	None	None	None	None	None	None
José A. Joglar, SVT Guideline Vice Chair	UT Southwestern Medical Center—Professor of Internal Medicine; Program Director, Clinical Cardiac Electrophysiology	None	None	None	None	None	None
Richard L. Page, SVT Guideline Chair	University of Wisconsin School of Medicine and Public Health—Chair, Department of Medicine	None	None	None	None	None	None

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*For transparency, the ERC members’ comprehensive disclosure information is available as an online supplement.

ACC indicates American College of Cardiology; AHA, American Heart Association; HRS, Heart Rhythm Society; SVT, supraventricular tachycardia; and UT, University of Texas.

**Risk Stratification for Arrhythmic Events in Patients With Asymptomatic Pre-Excitation:
A Systematic Review for the 2015 ACC/AHA/HRS Guideline for the Management of Adult
Patients With Supraventricular Tachycardia: A Report of the American College of
Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and
the Heart Rhythm Society**

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Richard L. Page (<i>SVT Guideline Chair</i>)	University of Wisconsin School of Medicine and Public Health, Department of Medicine—Chair	None	None	None	None	<ul style="list-style-type: none"> • FDA Systems Medical Device Advisory Board—Chair 	None

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*No financial benefit.

†Significant relationship.

‡Relationship determined not relevant due to a “safe harbor” designation under the following requirements: a) the training is required (by FDA, professional organizations, and/or hospital certification committees) for privileging and/or for patient safety; b) the training is not available from a non-commercial entity; and c) expenses are not paid for by the sponsoring company.

§Dr. Al-Khatib’s relationship with Medtronic was determined not relevant but is included in her comprehensive RWI for transparency. The training event was a self-funded, CME-equivalent presentation with no interaction from Medtronic. The presentation focused on a JAMA article on comparative-effectiveness research of ICDs compared with clinical practice.

ACC indicates American College of Cardiology; AHA, American Heart Association; AHRQ, Agency for Healthcare Research and Quality; CDC, Centers for Disease Control and Prevention; CME, certified medical education; FDA, Food and Drug Administration; HRS, Heart Rhythm Society; JAMA, Journal of the American Medical Association; ICD, implantable cardioverter-defibrillator; NHLBI, National Heart, Lung and Blood Institute; RWI, relationships with industry and other entities; and SVT, supraventricular tachycardia.