**2015 SVT Guideline Data Supplements**

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**Methodology and Evidence Review**

The recommendations listed in this guideline are, whenever possible, evidence based. An extensive evidence review was conducted in April 2014 that included literature published through September 2014. Other selected references published through May 2015 were incorporated by the writing committee. Literature included was derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline. The relevant search terms and data are included in Data Supplement evidence tables. Key search words included but were not limited to the following*: ablation therapy (catheter and radiofrequency; fast and slow pathway), accessory pathway (manifest and concealed), antiarrhythmic drugs, atrial fibrillation, atrial tachycardia, atrioventricular nodal reentrant (reentry, reciprocating) tachycardia, atrioventricular reentrant (reentry, reciprocating) tachycardia, beta blockers, calcium channel blockers, cardiac imaging, cardioversion, cost effectiveness, cryotherapy, echocardiography, elderly (aged and older), focal atrial tachycardia, Holter monitor, inappropriate sinus tachycardia, junctional tachycardia, multifocal atrial tachycardia, paroxysmal supraventricular tachycardia, permanent form of junctional reciprocating tachycardia, pre-excitation, pregnancy, quality of life, sinoatrial node, sinus node reentry, sinus tachycardia, supraventricular tachycardia, supraventricular arrhythmia, tachycardia, tachyarrhythmia, vagal maneuvers (Valsalva maneuver),* and *Wolff-Parkinson-White syndrome*.

**Data Supplement 1. Nonrandomized Trials, Observational Studies, and/or Registries of Clinical Presentation and Differential Diagnosis Based on Symptoms** – Section 2.3.1

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Sganzerla P  1989  (1)  [2702964](http://www.ncbi.nlm.nih.gov/pubmed/2702964) | Prospective, nonrandomized | 16  AVNRT | All AVNRT | Relationship between hemodynamic changes associated w/ artificially induced arrhythmias and the EP properties of the related AV nodal reentry | Group 1 AVNRT w/ short RP  Group 2 AVNRT w/ long RP  No significant difference between the CLs of the two types of SVT (329 and 330-8 ms)  Atypical SVT differed from the typical one by a significantly smaller initial decrease and a more rapid recovery of BP. In group 1, cardiac output and arterial pressure were lower in SVR higher and  PAP equal.  Contraction on a closed valve may be a factor resulting in impaired pulmonary drainage leading to neural factors w/ reduced cardiac output. | The induction of typical SVT (long AH) caused a marked initial fall in systemic BP w/ only a partial recovery, leading to stable hypotension and reduction of cardiac output owing to a decrease in stroke volume. On the contrary, in comparison to sinus rhythm, during the atypical SVT (long HA) a lesser degree of initial hypotension, a complete recovery of BP and no significant change in cardiac output were observed. The different hemodynamic response between the two types of SVT took place w/ the same increase in heart rate indicating that rate is not involved per se in the genesis of these circulatory changes.  Simultaneous contraction more symptomatic for people. |
| Bhandari AK  1992  (2)  [1636582](http://www.ncbi.nlm.nih.gov/pubmed/1636582) | Prospective study | 115 pts who were enrolled in a multicenter clinical trial of flecainide | Pts w/ SVT or AF or both,  49 had SVT | Determine whether sx recorded w/ transtelephonic monitoring correlated w/ SVT or AF | Among 49 pts w/ PSVT, 62.7% of symptomatic calls were associated w/ ECG-documented PSVT as compared w/ 6.6% of asymptomatic calls (p<0.001). | The sensitivity of a symptomatic call was 91% for PSVT |
| Leitch JW  1992  (3)  [1537103](http://www.ncbi.nlm.nih.gov/pubmed?term=(((leitch)%20AND%201992)%20AND%2085)%20AND%201064) | Prospective, nonrandomized | N=22 | 22 pts w/ SVT  AVNRT 13  AVRT 8  AT 1  11 had a h/o syncope | Explore the mechanism of syncope during SVT | Lowest BP found in 1st 10 sec  Compensated BP w/in 60 sec w/ minimal change in CL  shorter and BP lower w/ upright tilt  Comparison of the 7 pts w/ and the 15 pts w/o syncope. The only significant differences occurred in the extent of BP decrease during tachycardia (decrease in mean BP, 70±4 compared w/ 45+5 mm Hg; p=0.01) and in the frequency w/ which syncope occurred during passive tilt testing in sinus rhythm. The CL of tachycardia, in fact, tended to be longer in pts w/ syncope (311±10 compared w/ 290±+11 msec, p=0.27). | Syncope is associated w/ vasodepressor mechanism and is not directly related to the tachycardia CL |
| Lee SH  1995  (4)  [7572623](http://www.ncbi.nlm.nih.gov/pubmed/7572623) | Retrospective review | 207 consecutive pts w/ h/o SVT | 107 pts AP mediated,  100 pts w/ AVNRT | Determine effects of pregnancy on SVT | 3.9% experienced first onset of SVT during pregnancy. Sx were exacerbated in 22% of pts w/ tachycardia in the pregnant and non-pregnant periods. | Pregnancy exacerbates SVT in some but not all pts. |
| Drago F  1996  (5)  [8701888](http://www.ncbi.nlm.nih.gov/pubmed/8701888) | Prospective, nonrandomized | N = 22  children | Ventriculoatrial interval <70 msec in 11 pts and >70 msec in 11 | The aim of this study was to evaluate, by using transesophageal atrial pacing and recording, the clinical and EP features of reciprocating SVT at rest and during exercise and to determine the factors related to syncope during high adrenergic tone. | Group A = SVT, palpitations  Group B = SVT near syncope  Induced SVT via esoph pacing in both groups. | AVRT faster when induced during exercise  Rate of SVT unrelated to sx of pre-syncope |
| Goyal R  1996  (6)  [8831363](http://www.ncbi.nlm.nih.gov/pubmed/8831363)  1996;132:765-7 | Observational | 519  231 AVNRT  288 AVRT | AVNRT or AVRT | Assessment of age of onset | The mean age of sx onset was 32±18 y for AVNRT and 23±14 y for AP-mediated tachycardia. A significantly greater proportion of pts w/ AVNRT had the initial onset of sxs after the age of 20 y (AV nodal reen- trant tachycardia, 67% vs. AP, 41% (p<0.001) | There is a different mean age of sx onset for pts w/ AVNRT and AP-mediated tachycardia. |
| Abe H  1997  (7)  [9392809](http://www.ncbi.nlm.nih.gov/pubmed/?term=Neurohumoral+and+Hemodynamic+Mechanisms+of+Diuresis+During+Atrioventricular+Nodal+Reentrant+Tachycardia) | Prospective study of pts w/ SVT | N=32  13 AVNRT  4 atrial flutter  15 AVRT | 32 consecutive pts w/ PSVT | Hypothesis was that pts w/ AVNRT would have more sx of diuresis because of higher right pressure | Increased diuresis in 12/13 (92%) of pts w/ AVNRT; 2/15 (13%) AVRT; and 1/4 atrial flutter w/ 2:1 AV conduction.  Measured right atrial pressure and plasma ANP in 14 of 32 pts.  RA pressure higher in AVNRT compared to the other tachycardias (16 vs. 5; p<0.01) and ANP levels also higher (215 vs. 63; p<0.001) | Sx of diuresis more common w/ AVNRT. The higher secretion of ANP may be the mechanism because there is a linear relationship between plasma ANP levels and atrial pressure |
| Lessmeier TJ  1997  (8)  [9066458](http://www.ncbi.nlm.nih.gov/pubmed?term=(((unrecognized)%20AND%201997)%20AND%20157)%20AND%20537) | Retrospective survey | 119 consecutive pts | Limited to AVRT, AVNRT | Systematically evaluate the potential for SVT to simulate panic disorder | Criteria for panic disorder per DSM-IV were fulfilled in 67%. SVT unrecognized after initial medical evaluation in 59 (55%) including 41% of 32 w/ preexcitation. Physicians attributed sx to panic, anxiety orstress in 32 of the 59 (54%).  SVT unrecognized a median of 3.3 y  Women more likely to be labeled w/ panic than men (65% vs. 32% p<0.04  SVT diagnosed in 6 (9%) of 64 pts w/ Holters and 8 (47%) of 17 w/ event monitors (p=0.001) | SVT can mimic panic disorders and the diagnosis is often delayed by inappropriate rhythm detection techniques or missed preexcitation. Unrecognized SVT often attributed to psychiatric conditions.  Perhaps misdiagnosis happens in women more often due to miscategorization of “feeling” in survey |
| Kalusche D  1998  (9)  [9812187](http://www.ncbi.nlm.nih.gov/pubmed?term=((kalusche)%20AND%201998)%20AND%20359) | Observational | 395 pt w/ AVNRT  85 were >65 y | Limited to AVNRT | Main objective was to analyze risks and outcomes of ablation, but they also characterized presenting sxs | Elderly patents (mean 70.4 y) more often had syncope or presyncope w/ AVNRT (43.2% vs. 29.8%; P=0.05); had more hospitalizations and emergency department visits because of their sx 56.8 vs. 39.5% p,0.05 even though the CL was longer in the elderly (368 vs. 325 msec; P=0.0001) | Elderly pts have more sxs, ER visits, and hospitalizations despite slower tachycardias. (Outcomes of ablation were no different.) |
| Orejarena LA  1998  (10)  [9426034](http://www.ncbi.nlm.nih.gov/pubmed/9426034) | Population epidemiologic research | Screened 50,000  Identified 1,763 w/ SVT | Limited to PSVT  Standard ECG criteria for PSVT were employed: 1) paroxysmal, 2) normal QRS complex configuration or preexisting bundle branch block, 3) variation in successive RR intervals ≤40 msec, 4) ventricular rate 120 bpm, 5) no evidence of AV dissociation, and 6) no identifiable P waves preceding the QRS complex during tachycardia. | The aim was to determine the epidemiology and clinical significance of PSVT in the general population. | The prevalence was 2.25/1,000 persons and the incidence was 35/100,000 person-ys (95% CI: 23-47).  Those w/ lone PSVT were younger (mean 37 vs. 69 y; p<0.0002), had a faster PSVT heart rate (mean 186 vs. 155 bpm; p<0.0006) and were more likely to have their condition first documented in the emergency room (69% vs. 30%; p<0.0377). The onset of sxs occurred during the childbearing y in 58% of females w/ lone PSVT vs. 9% of females w/ other cardio- vascular disease (p<0.0272).  21 incident pts (64%) had sxsconcordant w/ PSVT before initial ECG documentation.  The probability of recurrence by the end of y 2 of f/u was 0.20 (95% CI: 0.06-0.35). There were no predictors of recurrence. For pts w/ a recurrence, all except one had their first recurrence w/in 12 mo of diagnosis and one had hemodynamic instability. 5 pts died during f/u, none due to PSVT | Approximately 89,000 new cases/y and 570,000 persons w/ PSVT in the United States. |
| Erdogan A  2001  (11)  [11785371](http://www.ncbi.nlm.nih.gov/pubmed?term=(((erdogan)%20AND%2096)%20AND%202001)%20AND%20708) | Cohort survey | 748 pts who underwent ablation responded to a survey | Limited to AVNRT | Analyze the medical h/o pts w/ AVNRT | Interval from onset of sx to ablation was 4.1 +/- 1.5 y. Mean age 55.4 female and 58.7 males. Only 6% had SHD. In females AVNRT appeared after age 50 in 16% and <age 20 in 18%. Women were more symptomatic. Women were more likely to delay ablation (average 7 y) (unknown whether this was due to personal preference or bias due to advice given) | High rate of pt w/ AVNRT begin in an older stage of life |
| Fitzsimmons PJ  2001  (12)  [11526369](http://www.ncbi.nlm.nih.gov/pubmed?term=((fitzsimmons)%20AND%202001)%20AND%20142) | Retrospective review | 238 aviators | Focused on manifest WPW | Report the natural h/o WPW in a nontertiary care population for the development of SCD and SVT | 232 males, 6 women  median age 35 (17-56)  11.7% had sx suggestive of SVT. 1 had syncope and 12 had near syncope.  During f/u SVT occurred in 20.6%. SCD in 1 (0.02%) | Incidence of SVT is 1% per pt y. SCD risk low |
| Hamdan MH  2001  (13)  [11136692](http://www.ncbi.nlm.nih.gov/pubmed?term=((hamdan)%20AND%202001)%20AND%20103) | Prospective analysis | 112 | 112 pts w/ pacemakers | Examine effect of atrial timing during simulated tachycardia on hemodynamic and neural responses. | Decrease in BP greatest w/ simultaneous pacing, less w/ short RP, and least w/ long RP  Increase in CVP followed same trend  SNA% increased w/ all three, but most pronounced w/ simultaneous AV and most w/ short RP  Arterial baroreflex SNA correlated modestly w/ change in CVP | SNA increases during all pacing modes  Decrease in BP and pulse pressure, which is directly related to the tachycardia rate, cardiac function, and AV synchrony. At any given rate, the timing of atrial systole has been shown to alter the hemodynamic response. |
| Razavi M  2005  (14)  [16191112](http://www.ncbi.nlm.nih.gov/pubmed?term=(((Rasavi%20M)%20AND%20Acute)%20AND%201037)%20AND%202005) | Observational | N=17 | AVNRT | Change in BP over time | BP decreased immediately after AVNRT initiation, w/ gradual recovery during the first 30 sec from 71.9±16.5 mm Hg to 86±13.8 mm Hg, p<0.01. When upright, the mean BP time course was similar, but mean BP recovery during AVNRT was slower | A short AV interval is associated w/ a greater mean BP decrease at the onset of tachycardia. These observations may explain clinical sxs immediately after the onset of AVNRT |
| Walfidsson U  2005  (15)  [15733177](http://www.ncbi.nlm.nih.gov/pubmed?term=((walfidsson)%20AND%202005)%20AND%2028) | Survey of pts referred for ablation | 301 pts  226 active drivers | Limited to AVRT and AVNRT | Evaluate the sx in pt w/ SVT and impact on driving | In 226 active drivers, fatigue 77%, dizziness 47%, diaphoresis 52%, near syncope 50%, and syncope14% reported w/ SVT. Women had more sxs for each category.  57% experienced SVT while driving and 42% had to stop because of it (during that episode).  24 pts considered SVT an obstacle to driving. | SVT is frequent while driving and can be associated w/ near syncope or syncope. Women seemed to have worse sxs. Pts w/ near syncope or syncope more likely to consider SVT an obstacle to driving |
| Drago F  2006  (16)  [16835801](http://www.ncbi.nlm.nih.gov/pubmed?term=((drago)%20AND%202006)%20AND%20454) | Observational | 62 children | Limited to AVNRT. | Determine whether severity of sxs was related to EP characteristics | When pts w/ severe sxs were compared to those w/ mild sxs there was no difference in inducibility, CL of AVNRT, or the ERPs of the fast and slow pathways | The severity of sxs was not related to EP characteristics.  -Although this study focused on children, the results are probably applicable to adults |
| Gonzalez-Torrecilla E  2009  (17)  [19539146](http://www.ncbi.nlm.nih.gov/pubmed/19539146) | Prospective analysis | 370 consecutive pts who underwent EP study | AVRNT 262 (23 atypical)  ORT 108  Excluded manifest preexcitation | Assess the independent predictive contribution to the ECG of clinical variables to distinguish major forms of SVT | 370 consecutive pts  ECG interpreted by 2 independent observers  AVNRT more likely to be female, older age of onset (>30)  Correct ECG interpretation more frequent in the AVRT group  Rapid pounding in the neck more common w/ AVNRT (51% vs. 25%) | Age at the onset of sxs, sensation of rapid regular pounding in the neck during tachycardia, and female sex are the only significant clinical variables |
| Laurent G  2009  (18)  [18775049](http://www.ncbi.nlm.nih.gov/pubmed?term=((laurent)%20AND%202009)%20AND%20176) | Mechanism of sx in SVT not understood. They evaluated VA timing | Survey included 152 pts w/ AVNRT and 80 w/ AVRT  Hemodynamic studies on 18 w/ AVRT and AVNRT | 326 pts w/ a variety of clinically documented tachycardias (AVNRT, AVRT, VT, atrial flutter, AF completed a brief self-administered questionnaire regarding the occurrence of 5 sxs: “neck pounding,” chest pounding, palpitations, “shirt flapping,” and dizziness. This paper focuses on AVRT | Measured left atrial pressure during AVRT and simulated AVRT and AVNRT by the timing of pacing the atria and ventricles. | Sx of “shirt flapping” and “neck pounding” occur more frequently in AVNRT. Left atrial contractions during AV valve closure increase left atrial pressure and may explain the differences in sx between AVNRT and AVRT. Other sxs were about the same (chest pounding, palpitations, dizziness)  Arterial pressures were significantly lower and left atrial pressures were significantly higher during native AVRT, simulated AVRT and AVNRT compared w/ sinus rhythm. Simulated AVRT created similar hemodynamic conditions as seen during native AVRT. Simulated AVNRT produced significantly higher left atrial pressure (peak and mean) than simulated AVRT. | The sx of “shirt flapping” appears to be associated w/ pulsatile reversed flow in the pulmonary veins due to left atrial contraction against closed MV and is more common w/ AVNRT |
| Walfridsson U  2009  (19)  [19702600](http://www.ncbi.nlm.nih.gov/pubmed/19702600) | QOL survey | 97 AVNRT  79 AVRT | Focused on pts w/ AVRT and AVNRT | QOL scores | QOL scores were lower for pts w/ AVNRT compared to AVRT. Scores were affected by occurrence more than once a mo, arrhythmia duration, and whether sx occurred not only during exercise but also at rest. | The main conclusion was that QOL scores may direct therapy. |
| Kesek M  2011  (20)  [21077786](http://www.ncbi.nlm.nih.gov/pubmed?term=Symptomatic%20improvement%20after%20catheter%20ablation%20of%20supraventricular%20tachycardia%20measured%20by%20the%20arrhythmia-specific%20questionnaire%20U22) | Assessment of the U22 survey for clinical sxs before and after ablation | 156 pts who underwent ablation of SVT | AVNRT and AVRT | QOL scores | Mean age 43.9 AVNRT vs. 57.1 AVRT  Men 65% AVRT and 38% AVNRT  71% took medications prior to ablation | QOL scores using either the U22 or SF-36 improved after ablation. |
| Cain N  2013  (21)  [23827401](http://www.ncbi.nlm.nih.gov/pubmed/23827401) | Retrospective review | 446 pts | Pts <21 w/ WPW (median age of diagnosis was 7y) | Modes of presentation | Modes of presentation included SVT (38%), palpitations (22%), chest pain (5%), syncope (4%), AF (0.4%), sudden death (0.2%), and incidental findings (26%); data were unavailable in 4% | 64% had sxs at presentation, and an additional 20% developed sxs during f/u. There were 6 sudden deaths (1.3%), w/ an overall incidence of 1.1 per 1,000 pt-y in pts w/ structurally normal hearts and 27 per 1,000 pt-y in pts w/ associated heart disease.  Although this was a pediatric study, it provides historical data that we can expect adults to describe. |
| Maryniak A  2013  (22)  [23129107](http://www.ncbi.nlm.nih.gov/pubmed?term=((maryniak)%20AND%20893)%20AND%202013) | Retrospective analysis | 113 | AVRT or AVNRT pts (9-13 y) | Evaluated cognitive and emotional development in a group of children and adolescents w/ AVRT and AVNRT. | Mean age AVRT 8  Meant age AVNRT 11  32% had hx syncope, more frequently w/ AVRT (37.5% vs. 24%; p=0.16)  Deficiencies in cognitive function were prevalent.  Anxiety levels increase w/ the appearance of sxs. | Both AVRT and AVNRT in childhood and adolescence can have a negative impact on cognitive and emotional development. Pts experiencing AVRT in the first y of life are likely to exhibit particularly severe deficits in cognitive function, including memory. |

AF indicates atrial fibrillation; AP, accessory pathway; ANP, atrial natriuretic peptide; AT, atrial tachycardia; AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; AT, atrial tachycardia; BP, blood pressure; bpm, beats per minute; CL, cycle length; CVP, central venous pressure; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; ECG, echocardiogram; EP, electrophysiological; ERP, effective refractory period; f/u, follow up; h/o, history of; MV, ??; ORT, orthodromic reentrant tachycardia; PAP, pulmonary arterial pressure; PSVT, paroxysmal supraventricular tachycardia; pt, patient; QOL, quality of life; RA, right arterial; SCD, sudden cardiac death; SF-36, Short-Form (36) Healt Survey; SHD, structural heart disease; SNA, sympathetic nerve activity; SVR, systemic valvular resistance; SVT, supraventricular tachycardia; sx, symptom; sx, symptom; U22 questionnaire, Umea 22 Arrhythmia Questions; VA, ventricular arrhythmia; VT, ventricular tachycardia; w/, with; and WPW, Wolff-Parkinson-White syndrome.

Data Supplement 2. Randomized Trials Comparing Principles of Acute and Chronic Therapy – Section 2.4

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Name, Author, Year** | **Aim of Study** | **Study Type (Size, N)** | **Study Intervention Group (n)** | **Study Comparator Group (n)** | **Pt Population** | | **Endpoints** | | | **P Values, OR: HR: RR: & 95% CI:** | **Study Limitations & Adverse Events** |
|  |  |  |  |  | ***Inclusion Criteria*** | ***Exclusion Criteria*** | ***Primary Endpoint (efficacy) and Results*** | ***Safety Endpoint and Results*** | ***Secondary Endpoint and Results*** |  |  |
| Mauritson  1982  (23) [7065555](http://www.ncbi.nlm.nih.gov/pubmed/7065555) | Effectiveness and safety of oral verapamil | 11 | Verapamil 240 mg/d followed by 480 mg/d  (n=11) | Placebo | Symptomatic PSVT, ≥2 episodes/mo, ascertained by ECG  AVNRT  (n=7)  AVRT  (n=2 w/ WPW, n=3 w/ concealed AP) | CHF, severe hypertension, hypotension, VHD or CHD, renal/hepatic failure, SSS, AV block, atrial flutter, AF, AADs | Episodes/d (diary, Holter)  Verapamil 0.1±0.1 ,0.3 ±0.5  Placebo 0.3±0.3 ,0.7 ±0.7  Duration(min) (diary, Holter)  Verapamil 3±3 ,1±2  Placebo 27±5 ,67±111 | Minor AEs in 6 pts on verapamil  5 pts required a total of 35 cardioversions for sustained tachycardia, 2 during verapamil, 33 during placebo (p<0.001)  Programmed electrical stimulation performed at end of study to induce tachycardia. Caused sustained tachycardia in 9 on placebo, 2 on verapamil (p<0.01) | N/A | p<0.05 for primary endpoints | Oral verapamil safe and effective.  Small sample size.  Unclear which pt withdrew, so numbers of AVNRT vs. AVRT may be similar (i.e., 6 vs. 5). |
| Winniford  1984  (24)  [6388299](http://www.ncbi.nlm.nih.gov/pubmed/6388299) | Effect of AV nodal blockers for long-term therapy of PSVT | 11 | One mo of:  Digoxin 0.375 mg/d  Propranolol 240 mg/d  Verapamil 480 mg/d | Direct comparison between all 3, w/ 1 wk of placebo washout | Symptomatic PSVT, ≥2 episodes/mo, ascertained by ECG | ECG evidence of preexcitation | Episodes and duration (ascertained by diary and weekly 24 h Holter), adverse effects, SDCs of each drug  Episodes/wk (diary, Holter)  Digoxin 2.3±3.1, 1.9±2.9  Propranolol 1.5±2.3 ,0.2±0.6  Verapamil 2.9±5.7 ,0.6 ±1.6  Duration(min) (diary, Holter)  Digoxin 75±164, 47±157  Propranolol 60±112 ,1±1  Verapamil 56±148 ,1±1 | Mild side effects in 3/11 pts w/ digoxin and propranolol, and 5/11 w/ verapamil. All SDCs w/in normal reference range. | N/A | p=NS | Only verapamil had been studied in RCT prior to this (above) and given its proven efficacy, authors felt no need for placebo.  Small series of pts.  Unclear mechanism of PSVT (authors speculate all pts w/ AVRNT or oral rehydration therapy w/ concealed conduction. |
| Anderson  1986  (25)  [2868645](http://www.ncbi.nlm.nih.gov/pubmed/?term=2868645) | Efficacy of esmolol in treatment of PSVT | 71  Multicenter, double-blind, partial-crossover study | Esmolol (n=36) | Placebo (n=35) | “SVT” (HR>120)  Note: AVNRT in 18% of subjects | VHD, AV block,  SSS, significant electrolyte  abnormality,  precluding treatment w/ beta blockade, bronchial  asthma, ventricular arrhythmias requiring drug therapy,  cardiogenic shock, CHF (NYHA III-IV), renal or hepatic dysfunction, drug or alcohol abuse,  on other beta-adrenergic blockers or calcium channel  blockers w/in two half-lives of study entry | Therapeutic response: ≥20% reduction in HR, HR<100 bpm, or conversion to NSR.  Therapeutic response to esmolol during the initial treatment period (72%) similar when esmolol was given as a second agent  4 pts (6%) converted to NSR  In the 80% therapeutic response lost w/in 30 min following discontinuation of esmolol infusion | Hypotension which occurred in12% on esmolol, 2% w/ placebo. | N/A | p=NS | Rapid onset and short of  action of esmolol offer safe, effective therapy for acute treatment of pts w/ PSVT. Low numbers of pts w/ AVNRT. |
| Henthorn  1991  (26)  [1898640](http://www.ncbi.nlm.nih.gov/pubmed/1898640) | Flecainide for treatment of symptomatic PSVT (≥2 episodes) | 34  8-wk crossover (after four episodes of PSVT or end of treatment period) | Flecainide  (n=34) | Placebo  (n=34) | PSVT | Syncope, angina, or transient cerebral events during PSVT,  second or third degree AV block or had CHF (NYHA III-IV) | Freedom from symptomatic PSVT at 60 d:  79% events vs. 15%  (p<0.001)  Flecainide slowed symptomatic PSVT HR to 143±12 bpm from 178 ±12 on placebo in 7 pts who had events in the placebo and flecainide treatment phases  (p<0.02) | Significantly more side effects w/ flecainide (p<0.05) | Flecainide vs. placebo:  Recurrence:  8/34 vs. 29/34 (p<0.001).  Median time to first event: 55 vs. 11 d (p<0.001)  Median interval between episodes  >55 vs. 12 d  (p<0.001) | N/A | Despite participation  of 19 medical centers, only 34 pts completed  entire protocol and provided analyzable data.  All pts tolerated flecainide, limiting generalizability.  Transtelephonic monitoring does not permit  assessment of proarrhythmia.  6/34 w/ AVNRT, confirmed by EP study, and 18/34 w/ unknown mechanism. |
| Pritchett1991  (27) [1899432](http://www.ncbi.nlm.nih.gov/pubmed/?term=pritchett+e%2C+datorre+sd%2C+platt+ml) | Dose-response efficacy of flecainide in patents w/ PSVT, PAF, paroxysmal atrial flutter | 42 | Flecainide given in ascending order (25🡪50🡪100🡪150 mg bid)  PSVT  (n=14, Group 1)  PAF or parosysmal atrial flutter  (n=28, Group 2) | Placebo inserted at random (alternating w/ flecainide) at 30 d intervals | PSVT, PAF, or paroxysmal atrial flutter | Syncope, angina, or transient cerebral events during PSVT,  second or third degree AV block or had CHF (NYHA III-IV) . | Among 14 pts in Group 1 (PSVT) who qualified for efficacy analysis, 4 (29%) had no tachycardia while taking placebo.  Number w/ no tachycardia increased w/ progressively larger flecainide doses; w/ the 150 mg twice daily dose, 12 (86%) of 14 pts had no tachycardia (p<0.01 for overall differences among all treatments). | Noncardiac adverse experiences were leading cause of premature study discontinuation during flecainide treatment periods (5 pts in Group 1 and 6 pts in Group 2). | N/A | N/A | Small sample size, short treatment period. |
| Pritchett  1991  (28) [2001087](http://www.ncbi.nlm.nih.gov/pubmed/2001087) | Oral propafenone to prevent symptomatic PSVT  Randomized, double-blind, placebo-controlled, crossover phase, w/ each treatment period lasting up to 60 d. | 23 | Propafenone (n=23) | Placebo  (n=23) | PSVT  (n=14)    PAF  (n=9) | Angina during tachycardia, pulmonary edema, neurologic  sxs.  PAF w/ WPW, on AADs | Compared w/ placebo, propafenone caused an increase in time to first recurrence of arrhythmia (p=0.004)  PSVT:  p=0.03  PAF:  p=0.06  . | Cardiac AEs occurred only in pts w/ PAF (9/11): 2 w/ prolonged episode of AF, 1 w/ atrial flutter w/ a mean ventricular  rate of 263 bpm recorded using the telephone monitor. | HR during recurrences, and not statistically different between propafenone and placebo | N/A | Propafenone efficacious in treating PSVT and PAF.  Major limitation in not knowing how many pts had AVNRT.  . |
| Anderson  1994  (29)  [8074041](http://www.ncbi.nlm.nih.gov/pubmed/?term=anderson+jl%2C+platt+ml%2C+guarnieri) | Long-term efficacy of flecainide (≥6 mo) | 49 | PSVT  (n=21)  PAF  (n=28) | Placebo | Pts enrolled from 3 prior studies evaluating short-term flecainide efficacy | Syncope, angina, or transient cerebral events during PSVT,  second or third degree AV block or had CHF (NYHA III-IV) | -Number of pts w/o attacks  -Time to first attack  -Interval between attacks  -Average frequency of attacks,  -Ventricular rate during attacks.  PSVT pts:  Of 17 efficacy evaluable pts, 14 (82%) had no SVT attacks during the chronic efficacy study compared w/ 4 (24%) w/ no attacks during placebo therapy at baseline (p=0.013).  Time to first arrhythmia attack and time between attacks increased  during chronic therapy w/ flecainide compared w/ placebo treatment (p=0.008 and p=0.012, respectively)  Rates of attack/d not significantly different (p=0.130)  No PSVT pts w/ ventricular arrhythmias | No pt experienced  proarrhythmia, MI, or died during chronic efficacy study. | N/A | N/A | Supports flecainide for chronic therapy of PSVT.  Small numbers of pts w/ PSVT, and PSVT not specifically defined. |
| Chimienti  1995  (30)  [8682031](http://www.ncbi.nlm.nih.gov/pubmed/8682031) | Compare the long-term safety of flecainide and propafenone | 335 | SVT:  flecainide 100 mg (n = 72)  PAF:  flecainide 200 mg (n = 97) | SVT:  propafenone 450 mg (n=63)  PAF: propafenone 450 mg (n=103). | SVT  (n=135)  PAF  (n=200) | LVEF <35%, AV block, QRS >140 msec, SSS, persistent AF (episodes >72 h), VT (episodes >30 sec), NYHA III-IV, ischemic heart disease, hypertrophic cardiomyopathy, hypotension, valvular disease, renal/hepatic insufficiency, thyroid disease, AADs | ITT analysis (probability of 12 mo safe and effective tx)  PSVT:  93% for flecainide and 86% for propafenone (p=0.24)  PAF:  77% for flecainide and 75% for propafenone (p=0.72) | 12 pts on flecainide reported 16 cardiac AEs, of whom 6 discontinued the treatment.  7 propafenone pts had 8 cardiac AEs, of whom 5 discontinued the treatment.  (1 case of VT on propafenone  2 cases of AF w/ rapid ventricular response on flecainide | N/A | N/A | Both flecainide and propafenone were safe in the long-term treatment of pts w/ PSVT.  Only one-third of pts had SVT. |
| UK Propafenone PSVT Study Group  1995  (31) [7586356](http://www.ncbi.nlm.nih.gov/pubmed/7586356) | Efficacy and tolerability of propafenone at 600 mg and 900 mg daily doses (given bid).  2 consecutive crossover periods | 100 | Propafenone 300 mg bid  Propafenone 300 mg tid | Placebo | PSVT  (n=52)  PAF  (n=48)  75 pts in low-dose phase:  45 PSVT, 30 PAF  59 pts advanced to high-dose phase:  34 PSVT, 25 PAF  ≥2 symptomatic episodes by transtelephonic monitoring | PSVT w/ hemodynamic collapse, LVEF ≤25%, recent MI or unstable angina; hepatic/renal failure, SSS, AV block, AADs, female pts of childbearing potential, COPD, myasthenia gravis. | Placebo vs. propafenone:  PSVT, low-dose:  Arrhythmia recurrence or AE  RR: 6.8 (95% CI: 2.2-21.2; p<0.001),  Arrhythmia recurrence  RR: 7.4 (95% CI: 2.3-23.3, p<0.001).  PSVT, high-dose:  Arrhythmia recurrence or AE  RR: 2.2 (95% CI: 0.9-5.3, p=NS);  Arrhythmia recurrence  RR: 15.0 (95: CI: 2.0-113, p=0.009). | More pts experienced more AEs during propafenone (900 mg >600 mg). Most common adverse events during PSVT and PAF groups were related to the gastrointestinal and neuropsychiatric systems. Total numbers of adverse events on propafenone were 46 and 56 in the low-dose and high-dose PSVT group and 67 and 74 in the low-dose and high-dose PAF groups, respectively. | 1 episode of wide-complex tachycardia was documented during propafenone therapy | Propafenone at 600 mg is effective and well tolerated. A larger dose of 900 mg causes more AEs but may be more effective in those who can tolerate it | Sequential design (not randomized after low-dose phase) so population is not generalizable at 900 mg dose.  Not powered for mortality.  Limited in that PSVTs included AVNRT, AT, or AVRT. |
| Dorian  1996  (32)  [8607397](http://www.ncbi.nlm.nih.gov/pubmed/8607397) | Compare oral flecainide to verapamil in preventing PSVT recurrence | 121 pts at 32 sites | Flecainide (n=63) (50 mg bid increased to max of 300 mg/d)  AVNRT(n=17)  AVRT(n=6)  Unspecified (n=40) | Verapamil (n=58) (80 mg tid increased to max of 480 mg/d)  AVNRT(n=10)  AVRT(n=7)  Unspecified (n=41) | PSVT, requiring therapy, majority w/ ≥2 attacks per mo  AVNRT  AVRT  Unspecified PSVT but w/ clinical diagnosis of PSVT | Coexisting PAF, prior MI/UA, NYHA Class III-IV, AV block, preexcitation, AADs | 86% of all flecainide 73% of all verapamil pt-mo occurred w/ 0-1 attack  19 (30%) pts on flecainide vs. 7 (13% of verapamil completed the trial (>270 d) w/o symptomatic attacks (p= 0.026)  f/u 8.1 ±5.1 mo for flecainide and 7.5± 5.4 mo w/ verapamil | 19% of flecainide group vs. 24% verapamil discontinued due to adverse effects (p=NS).  Most common sx: flecainide: dizziness, concentration, sleep, nausea  Verapamil: dyspnea, fatigue, HF sx | N/A | These agents confer potential benefit in pts who are not candidates for RFA | N/A |
| Wanless  1997  (33)  [9124166](http://www.ncbi.nlm.nih.gov/pubmed/?term=wanless+rs%2C+anderson+k) | Sotalol in treatment of PSVT | 126 | Sotalol 80 mg  (n=35)  AVNRT (23%)  Sotalol 160 mg  (n=46)  AVNRT (22%) | Placebo  (n=45)  AVNRT (24%) | Recurrent symptomatic PSVT were eligible for enrollment.  AVNRT  PAF  Paroxysmal atrial flutter  AVRT  Paroxysmal AT | Decompensated CHF, asthma, chronic obstructive airways disease, second degree or third degree AV block, recent MI (<1 mo), recent coronary artery bypass graft surgery (<2 mo), unstable angina pectoris, bradycardia (<50 bpm), SSS, prolonged QTc interval (>0.45 sec), systemic hypertension (diastolic BP >115 mm Hg), electrolyte imbalance, AADs | Time to recurrence of PSVT was less compared w/ placebo when receiving sotalol 80 mg (p=0.04) and sotalol 160 mg (p=0.0009).  On subanalysis, sotalol was shown to be effective in the prophylaxis of both PAF (p=0.03) and paroxysmal reentrant arrhythmias (p=0.0003). | No deaths, cases of ventricular proarrhythmia, CHF. Treatment of pts receiving sotalol were discontinued because of typical beta blocker side effects, including bradycardia, dyspnea, and fatigue. | N/A | N/A | Sotalol efficacious in the prophylaxis of PSVT.  Study limited due to grouping of PSVTs. |
| Lim  1998  (34)  [9437338](http://www.ncbi.nlm.nih.gov/pubmed/?term=(((lim)+AND+1998)+AND+31)+AND+30-1) | Efficacy of VM or CSM to terminate SVT in the ED | N=148  Randomized to VM first (62) or CSM first (86), then crossed-over to other therapy if first not effective | VM (blow into mouthpiece to achieve 40 mm Hg and sustain for at least 30 sec) | CSM (randomized first to left or then right CSM) | 10 y of age or older | ECG w/ obvious atrial flutter, AF or sinus tachycardia, hemodynamically unstable (including poor cerebral perfusion, pulmonary edema or unstable angina). Pts w/ contraindications for CSM (h/o TIA, CVA, carotid bruit) | Conversion to SR | No adverse events directly related to VM or CSM. One pt was diagnosed w/ non-Q wave MI. 4 pts admitted for other medical problems (HF, pneumonia) | N/A | 62 VM first, 19.4% conversion;  86 CSMc first, 10.5% conversion  Crossover: to CSM, 14.0% conversion, and to VM w/ 16.9% conversion  Total conversion rate (VM and CSM, including cross-overs): 27.7%  No difference in efficacy between VM and CSM  VM more effective in men, CSM more effective in older pts  Recurrences w/in 2 h; 3 VM pts, 1 CSM pt | N/A |
| Gupta A  1999  (35)  [10778689](http://www.ncbi.nlm.nih.gov/pubmed/10778689) | Efficacy of IV diltiazem vs. esmolol for terminating PSVT | N=32 (study terminated prematurely due to superiority of diltiazem)  Prospective randomized crossover, open-labeled | Esmolol 0.5 mg/kg twice in 5 min interval | Diltiazem 0.25 mg/kg twice in 5 min interval | SVT  Hemodynamically tolerated in ICU | SHD; AT, AF or atrial flutter excluded | Conversion to SR | N/A | N/A | Diltiazem terminated SVT in all 16 pts where was first drug  Esmolol terminated 4/16 (p<0.001 c/w diltiazem) and other 12 then terminated by diltiazem (total for diltiazem 28/28)  Of the 28 pts responding to diltiazem a second dose was needed in 13.  All 32 pts subsequently underwent EP study; 17 w/ AVNRT, 15 w/ AVRT.  Diltiazem: first bolus converted 5/9 pts w/ AVNRT, and 0/7 w/ AVRT (p<0.0001)  Esmolol: equally ineffective for either tachycardia mechanism | Small trial, terminated early due to superiority of diltiazem. |
| Alboni  2001  (36)  [11216977](http://www.ncbi.nlm.nih.gov/pubmed?term=((alboni)%20AND%202001)%20AND%20548) | Effectiveness of self-administered flecianide or diltiazem/propranolol to terminate SVT | Randomized to placebo, flecainide (3 mg/kg), 120 mg diltiazem/80 mg propranolol on 3 different d for each pt  N=33 (37 enrolled) | Flecainide (3 mg/kg) or 120 mg diltiazem w/ 80 mg propranolol | Placebo | Hemodynamically tolerated and long-lasting SVT confirmed by EP study to be reentrant (AVNRT or AVRT)  Age 18-75, ≤5 episodes/y | Preexcitation, CAD, sinus <50 bpm, LVEF <50% or HF, recent MI, or stroke, need for long term beta blocker, calcium channel blocker, digoxin or AAD or h/o sustained atrial or VT | Conversion w/in 2 h: 52% placebo, 61% flecainide, 94% diltiazem/propranolol (p<0.001). Conversion faster w/ diltiazem/propranolol (p<0.001) | Hypotension, bradycardia | Over 17±12 mo treatment success f/u (SVT terminated in <2 h) in 81% of 26 diltiazem/propanolol pts, 80% of 5 flecainide pts  % pts going to ED was 9% down from 100% of prior y (p<0.0001) | Adverse events: hypotension in 1 placebo, 2 flecainide and 1 diltiazem/propranolol pts; 3 had sinus <50 bpm (3 diltiazem/propranolol, 1 flecainide)  1 diltiazem/propranolol pt had syncope  5 pts ultimately referred for ablation | Unknown if outpt events that pts self-treated were indeed SVT and time to conversion assessed subjectively by pt  Outpt management was not w/ placebo |
| Tendera  2001  (37) [11431663](http://www.ncbi.nlm.nih.gov/pubmed/?term=tendera+m%2C+wnuk-wojnar) | Comparison of dofetilide to propafenone and placebo in the prevention of PSVT | 122 | Dofetilide  (n=40)  Propafenone (n=41) | Placebo (n=41) | 18-75 y w/ ≥1 episode of PSVT w/in 6 wk documented by ECG | Pulmonary disease, myasthenia gravis, bundle branch block, resting bradycardia (<50 bpm), AV block, prolonged QTc, MI, unstable angina, recent sudden death, hematologic /hepatic/renal disease | After 6 mo of treatment, pts taking dofetilide, propafenone, and placebo had a 50%, 54%, and 6% probability, respectively, of remaining free of episodes of PSVT (p<0.001 for both dofetilide and propafenone vs. placebo).  The hazard ratio for dofetilide vs. placebo was 0.33 (95% CI: 0.18-0.61), and the hazard ratio for propafenone vs. placebo was 0.27 (95% CI: 0.14-0.51).  Of 40 pts treated w/ dofetilide and propafenone, 23 (58%) and 25 (61%) had no recurring PSVT, compared w/ 16 (39%) in placebo group. | 19 of 40 pts (48%) treated w/ dofetilide and 21 of 41 (51%) treated w/ propafenone reported no AEs.  No significant differences were noted between 3 groups in incidence of treatment-related adverse events or all-cause adverse events (p=0.73 and p=0.74, respectively). | Total number of episodes occurring during treatment, and type and frequency of sxs during episodes of PSVT before and during treatment  Frequency of episodes lower in pts treated w/ dofetilide or propafenone thancompared to placebo. Active treatment did not alter distribution of sxs during a first episode of PSVT. | N/A | Dofetilide is at least as safe and effective as propafenone as an alternative therapeutic option for the treatment of pts w/ PSVT.  Limited in that PSVTs not specified. |
| Lim  2009  (38)  [19261367](http://www.ncbi.nlm.nih.gov/pubmed?term=(((lim)%20AND%202009)%20AND%2080)%20AND%20523) | Efficacy and safety of slow infusion of calcium channel blockade vs. adenosine in the ED (RCT) | N=206 | Slow infusion of calcium channel blocker: verapamil 1 mg/min to 20 mg total, or diltiazem 2.5 mg/min to 50 mg total  If failed calcium channel blocker then given adenosine | Adenosine (6 mg followed by 12 mg if 6 mg ineffective) vs.  (If adenosine ineffective after 12 mg they received a calcium channel blocker infusion) | 10 y of age or older, SVT not converted by vagal maneuver | Impaired cerebral perfusion, subsequent diagnosis of non-SVT rhythm, pregnancy | Conversion to SR | Hypotension  One pt that received calcium channel blocker became hypotensive | N/A | 102 pts received calcium channel blocker and 98% converted to SR, 104 pts got adenosine, conversion was 86.5% (p=0.002)  BP dropped by -13.0/-8.1 verapamil and -7.0/-9.4 for diltiazem.  Recurrences w/in 2 h: 1 pt w/ diltiazem, 2 from adenosine group  One pt that received calcium channel blocker became hypotensive | Slow infusion of verapamil or diltiazem was effective and well tolerated. Fall in BP transient.  Unclear how many pts were excluded from analysis as a non-SVT rhythm was then identified – how did this cohort fair? |
| Smith  2013  (39)  [23543578](http://www.ncbi.nlm.nih.gov/pubmed/?term=23543578) | Determine effectiveness of VM to terminate SVT | Review of 3 RCTs: 1) Mehta D 1988 (40); 2) Wen ZC 1998 (41); 3) Lim 1998 (34).  Mehta and Wen studies were in a lab setting, Lim in ED setting | N/A | N/A | N/A | N/A | Reversion to SR | Cardiovascular effects of VM (hypotension, bradycardia), mortality from VM, frequency and severity of adverse events from VM | Failure to revert to SR followed by other therapies | Reversion success was 54.3% (19/35) in Mehta, 45.9% (61/133) in Wen and 19.4% in Lim (12/62)  Heterogeneity between studies precluded a meta analysis; adverse effects not reported | Speculated that difference in conversion rates may be due to setting (ED vs. EP lab) |

AAD indicates antiarrhythmic drug; AE, adverse event; AF, atrial fibrillation; AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; bid, two times per day; bpm, beats per minute; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CSM, carotid sinus massage; CVA, cerebral vascular accident; c/w, consistent with; ECG, electrocardiogram; ED, emergency department; EP, electrophysiological; f/u, follow up; HF, heart failure; h/o, history of; HR, heart rate; ICU, intensive care unit; ITT, insulin tolerance test; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; NS, not significant; NSR, normal sinus rhythm; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; pt, patient; RCT, randomized controlled trial; RFA, radiofrequency ablation; RR, relative risk; SDC, serum drug concentration; SHD, structural heart disease; SR, sinus rhythm; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; sx, symptom; TIA, transient ischemic attack; tid, three times per day; tx, treatment; UA, unstable angina; VHD, valvular heart disease; VM, Valsalva maneuver; VT, ventricular tachycardia; w/, with; w/o, without; and WPW, Wolff-Parkinson-White syndrome.

Data Supplement 3. Nonrandomized Trials, Observational Studies, and/or Registries of Principles of Acute and Chronic Therapy – Section 2.4

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| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Waxman  1980  (42)  [7416025](http://www.ncbi.nlm.nih.gov/pubmed/7416025) | Prospective cohort consisting of 33 pts in ED (group A) and 35 pts during EP study (Group B) to assess SVT termination using a protocol of successive vagal interventions until SVT terminated: a) L/R CSP (1-5 sec) b) multiple unilateral CSP c) edrophonium IV followed by CSP d)Valsalva (10 sec) e) edrophonium IV followed by Valsalva f) phenylephrine | N=68  (33 Group A-ED, 38 Group B- EP study) | SVT (AVNRT or AVRT (orthodromic). Overt WPW included. | Termination to SR | In all 68 pts SVT was terminated. 6 pts required phenylephrine.  No complications. Post termination pauses was 1683± 66 ms  In group B (EP study) pts, repeated trials were performed w/ overall 92% success in termination. | Data not broken down by group. However, text describes that 30/33 group A pts terminated SVT by a maneuver up to and including (e). |
| Rankin AC  1989  (43)  [2789911](http://www.ncbi.nlm.nih.gov/pubmed?term=((rankin%5BAuthor%5D)%20AND%201989)%20AND%20195) | Cohort administered adenosine for either spontaneous tachycardia or induced | N=64 of which 54 pts had spontaneous tachycardia and 15 induced by programmed stimulation | Spontaneous and induced tachycardia in 16-79 y old pts | Termination to SR and diagnostic efficacy to identify atrial flutter or AT or VT | Adenosine terminated 46 of 48 episodes of narrow complex tachy  Other tachycardias treated included wide complex (24 pts),  Side effects: dysnea, chest pain, flushing, headache. No adverse hemodynamic effects  High rate of recurrence (1/3) | Adenosine effective for both diagnosis and treatment. Of note administration in wide complex tachycardia was safe. Early recurrences of arrhythmias seen in 35%. |
| Cairns  1991  (44)  [2064090](http://www.ncbi.nlm.nih.gov/pubmed/2064090) | Observational cohort  Adenosine to convert SR in ED setting | N=23 | 16 y or older presenting to ED in an 8 mo study period w/ sustained SVT, rate >140 bpm  Exclusion: severe CHF, unstable angina, acute MI by ECG, hemodynamic compromise. Excluded sinus tachycardia, atrial flutter, AF, QRS >140 ms | Conversion to SR | 2 pts after adenosine identified as not having SVT (a fluter, VT)  24 episodes of SVT in 21 pts of which 96% converted w/ adenosine (mean dose 10±6 mg)  SVT recurred in 57% of episodes and other antiarrhythmic drugs then used to maintain SR.  Adverse effects: 3 pts w/ chest pain, one pt w/ dyspnea but no adverse outcome | Adenosine highly effective in converted SVT but recurrences frequent |
| McCabe  1992  (45)  [1554170](http://www.ncbi.nlm.nih.gov/pubmed?term=(((mccabe)%20AND%201992)%20AND%2021)%20AND%20358) | Prospective cohort  Adenosine 6 mg , then 12 mg if ineffective, and 3rd dose of 12 mg if still ineffective | N=37, prehospital setting | 18 y or older, w/ SVT assessed by paramedic, QRS <120 ms, rate 150-250 bpm  Exclusion: hypersensitivity to adenosine or in extremis | Conversion to SR | 26/37 in SVT (non-SVT rhythms were 5 AF, 4 sinus tach, 2 VT).  23/26 (88%) converted to SR  11 pts hypotensive at presentation in SVT and became stable upon conversion  9 pts had WCT and no hemodynamic compromise w/ adenosine | Small prospective series |
| Gausche  1994  (46)  [8037382](http://www.ncbi.nlm.nih.gov/pubmed?term=(((gausche)%20AND%201994)%20AND%2024)%20AND%20183) | Prospective cohort  Adenosine 12 mg as initial dose, followed in 2 min of another 12 mg if no conversion | N=129, 106 w/ before and after strips  Prehospital setting | 18 y or older, w/ SVT assessed by paramedic. QRS <120 msec, rate >140 bpm.  Exclusion: pregnancy, hypersensitivity to adenosine, sbp <80 mm Hg, or on carbamazepine or dipyridamole | Conversion to SR | 84/106 had SVT (AF in 13, ST in 5, atrial flutter in 2, and VT in 2 cases)  71/84 converted to SR (85%) and 4 needed second 12 mg dose  Adverse effects: chest pain (12), flushing (3), shortness of breath (2), nausea (1), anxiety (1), dizziness (1), headache (1) | Adenosine safe and effective in prehospital setting. |
| Madsen  1995  (47)  [7741343](http://www.ncbi.nlm.nih.gov/pubmed?term=((madsen)%20AND%201995)%20AND%20649) | Nonrandomized, prospective 12 mo chart review of adenosine w/ comparison to historical cohort that received verapamil  Pre-hospital setting (EMS)  Verapamil up to 2 IV doses of 2.5 mg and 5 mg, or up to 2 doses of adenosine , 6 mg and 12 mg | N=73 | Age >14 w/ paramedic assessment of narrow complex tachycardia (QRS <120, rate 160-240 bpm)  3/1990-2/1991 (verapamil) and 3/1991-2/1992 (adenosine)  Pts had to be regarded as stable and first underwent Valsalva prior to administration of verapamil or adenosine by base hospital physician’s order | Conversion to SR  Also incidentally analyzed rate of ECG misinterpretation by EMS and base hospital physician | Verapamil given to 17 pts, of which 6 on subsequent review by cardiologist had AF, attach or sinus tach. 7/11 pts converted to SR (64%). Side effects in 5/17 pts (hypotension, NSVT, PACs)  Adenosine: given to 64 pts, strips available for review in 56 pts. 24 pts on subsequent review by cardiologist had AF, attach, sinus tach, atrial flutter or VT. Of remaining 32 w/ true SVT that got adenosine, 78% converted to SR. Side effects: ventricular ectoic activity, 1st or 2nd degree AV block of <1 min, asystole (2-10 sec), chest pain, flushing, bronchospasm)  Overall misinterpretation of the ECG occurred in 30/73 pts  No difference in conversion rates between verapamil and adenosine | Misinterpretation of the ECG by paramedics and base hospital physician was common.  But serious adverse events unlikely – no reported hemodynamic collapse from intervention.  Conversion to SR by adenosine or verapamil similar (about 70%) |
| Brady  1996  (48)  [8727628](http://www.ncbi.nlm.nih.gov/pubmed?term=((brady)%20AND%201996)%20AND%20574) | Nonrandomized, prospective cohort w/ comparison to historical cohort  Comparison of adenosine (prospective cohort) to verapamil (historical cohort) | N=211 | Inclusion criteria: any age, narrow QRS tachycardia (120-300 bpm), or wide complex (120-300 bpm) who had received 2 doses of lidocaine, palpable pulse, IV in place.  Exclusion: drug sensitivity, cardiac arrest, trauma etiology, for adenosine: prior cardiac transplant, treatment w/ carbamazepine or dipyridamole  Exclusion for verapamil: sbp <90, pulmonary edema, LV dysfunction, age <2 y, WCT | Conversion to SR | Adenosine: 87 of 105 pts received drug, 69% converted to SR  Verapamil: 52 of 106 pts received drug, 88% converted to SR (p=0.1)  Adverse events: adenosine: 4 pts (chest pain, dyspnea, prolonged brady, VT)  Verapamil: 4 pts (hypotension, VT, VF) – 2 pts had received verapamil for WCT and both had hemodynamic collapse  Noted that EMS commonly misinterpreted non-SVT rhythms as SVT (including AF, ST, VT) | Adenosine and verapamil both effective in out of hospital setting to convert SVT.  Rhythms were still commonly misidentified by EMS |
| Luber  2001  (49)  [11146016](http://www.ncbi.nlm.nih.gov/pubmed?term=((luber)%20AND%202001)%20AND%2019) | Observational cohort (retrospective chart review)  Outcomes of pts treated for SVT in ED, including recurrence rates, from 1993-1996 | N=111 | Narrow complex tachycardia (QRS <120 ms), no P waves, rate 120-300 bpm.  1993-1996, single center | Recurrence of SVT  Descriptive percentages of therapies given, pt demographics | Therapies given: adenosine (41%), Valsalva (22%), Calcium channel blocker (14%), beta blockers (4%), cardioversion (1%).  79 pts (71%) discharged from ED, mean age of 49, mean ED stay of 3.8 h, and 3 pts had recurrent SVT w/in 24 h  32 pts (29%) admitted to hospital, mean age 65, 6 pts (19%) had recurrent SVT in the hospital.  SVT recurrence more likely in admitted pts (p<0.05), older pts (p<0.01) or h/o cardiac disease (p<0.01) | Largely a descriptive paper. |
| Roth A  2003  (50)  [12586276](http://www.ncbi.nlm.nih.gov/pubmed/12586276) | Prospective cohort study | 84 | PSVT 77%  AF 23% | Effectiveness of DC cardioversion in pts who did not respond promptly to vagal maneuvers that were tried first and then tried again after intravenously administered medical treatment w/ 1 of the following intravenously administered drugs: adenosine,verapamil, digoxin, and/or procainamide.  All study pts were hemodynamically compromised but did not require cardiopulmonary resuscitation. | DC cardioversion resulted in successful converson to sinus rhythm in all pts after 103 electrical attempts, using 118±69 Joules.  No complications; all but 1 pt (w/ pulmonary edema and cardiogenic shock) discharged alive w/in 7 d of hospitalization. | **Use of DC cardioversion to restore sinus rhythm can be safely and efficaciously applied in the prehospital setting in pts who are hemodynamically compromised but do not require cardiopulmonary resuscitation.** |
| Chronic therapy of SVT (exclude WPW and preexcitation, but include if concealed AP) | | | | | | |
| Neuss H  1988  (51)  [3136637](http://www.ncbi.nlm.nih.gov/pubmed/0003136637) | Open label trial of chronic po flecainide to pts that first given IV dose in EP lab. Pts w/ WPW (concealed or overt) or AVNRT. | 63 pts (47 WPW of which 8 concealed, 36 w/ AVNRT)  Mean f/u 22.8 mo | WPW (overt or concealed) or AVNRT, previously refractory or intolerant to other antiarrhythmic drugs, verapamil or beta blockade)  IV flecainide given during SVT induced at EP study (100 mg over 5 min) | Drug efficacy and tolerance based upon diary  EP study also repeated while on therapy | In AVNRT pts (31) – mean observation of 23 mo, mean flecainide dose 257 mg/d, effective in 20 pts and reduced episodes in 4 other pts. Worsening of attacks seen in 2 pts.  Adverse effects: visual, nervousness, dizziness, taste, hallucinations, vomiting. Therapy discontinued in 3 pts (AVNRT group) | Flecainide effective in reducing subjective episodes – among pts w/ AVNRT was effective in 20/31 pts. |
| Cockrell JL  1991  (52)  [1898629](http://www.ncbi.nlm.nih.gov/pubmed/?term=1898629) | Open-label, uncontrolled trial of long term efficacy of flecainide | 63 pts.  mean f/u 24 mo | All pts w/ AV reentry | Drug efficacy and tolerance | Flecainide prevented or slowed AVRT in 44 pts. who were then followed and 33 (75%) w/ no adverse effects. Isuprel reversed the effects in 11/21 pts. Overall, 33 of 63 pts responded to and tolerated flecainide. 11 pts stopped due to adverse effects. | Flecainide moderately helpful in about 50% of pts over 2 y. |
| Jackman WM  1992  (53)  [1620170](http://www.ncbi.nlm.nih.gov/pubmed/1620170) | Prospective observational cohort | 80 | Symptomatic AVNRT undergoing RFA of slow-pathway | Successful ablation w/ intact AV nodal conduction, guided by atrial slow-path potentials | RFA abolished or modified slow-pathway conduction in 78/80 pts w/o affecting normal AVN conduction. Mean (+/- SD) f/u of 15.5 mo w/o recurrence. | Early report of success of RFA of slow-path conduction guided by atrial slow-path potentials—led to slow-pathway ablation being preferred method. Provided evidence that atrial insertions of fast and slow path are anatomically distinct. |
| Gambhir DS  1996  (54)  [8682552](http://www.ncbi.nlm.nih.gov/pubmed/8682552) | Prospective cohort study | 9 | All pts w/ symptomatic AVNRT, recurrent palpitations for 2-12 y EP study performed, IV amiodarone then oral therapy subsequently EP study repeated 1.5-3 mo later | No pts reported sxs of tachycardia during mean f/u of 65 d on oral amiodarone  IV amiodarone terminated AVNRT in 7/9 pts (retrograde FP in 4/7 and anterograde SP in 3/7)  Not inducible on PES after oral therapy, largely to due to prolonging refractoriness in atrium and ventricle, and depressing conduction through FP | No pts reported sxs of tachycardia during mean f/u of 65 d on oral amiodarone  IV amiodarone terminated AVNRT in 7/9 pts (retrograde FP in 4/7 and anterograde SP in 3/7)  Not inducible on PES after oral therapy, largely to due to prolonging refractoriness in atrium and ventricle, and depressing conduction through FP | Small series of pts, but all w/ AVNRT  Oral therapy w/ amiodarone is effective in suppressing AVNRT.  IV amiodarone is effective in acute therapy.  EP study efficacy. |
| Spector P  2009  (55)  [19699343](http://www.ncbi.nlm.nih.gov/pubmed/19699343) | Systematic review and meta-analysis to evaluate the safety and efficacy of RFA of AVNRT, AP-mediated, and atrial flutter. | For AVNRT and AP-mediated: 39 primary studies w/ 49 treatment arms in 7,693 pts. | Previous reviews or meta-analyses; animal or in vitro studies; subjects aged <18 y or mixed populations of which >15% were pediatric pts; f/u of <7 d; not studies of RFA; alternative energy sources used for ablation; AV junction ablation w/ pacemaker implantation; <40 pts per arrhythmia or ablation technique; published only in abstract form; published before 1990; and published in languages other than English, Spanish, French, Italian, German, and Portuguese. | SVT (AVNRT and AP-mediated)  Single- and multiple-procedure success, arrhythmia recurrence, repeat ablation, adverse events, and death | Single-procedure success: 93.2%  (95% CI 90.8-95.5%).  Multiple-procedure success: 94.6%  (95% CI 92.4- 96.9).  Post-ablation arrhythmia: 5.6%  (95% CI 4.1-7.2%).  Repeat ablation: 6.5% (95% CI 4.7-8.3%)  All-cause mortality: 0.1%  Adverse events: 2.9% | First meta-analysis of RFA for AVNRT, AVRT (AP-mediated).  Demonstrates high efficacy rates and low rates of complications. |
| Bohnen M  2011  (56)  [21699857](http://www.ncbi.nlm.nih.gov/pubmed/21699857?dopt=Citation) | Prospective observational cohort, single center  Incidence and predictors for major complications of catheter ablation | 1676 procedures | All pts undergoing ablation in a 2 y period (2009-2011) at a high volume center for variety of arrhythmias (SVT, AF, VT due to SHD or idiopathic) | Complications assessed over 30 d post-procedure. | 524 SVT ablations performed of which major complications (total 0.8%) included perforation (n=1), pseudoaneurysm (groin, n=2), pulmonary edema (1). No instances of conduction system damage | Total major complication rate for SVT ablation below 1% in this contemporary prospective study. |
| Outcomes (Registry Data) | | | | | | |
| Hindricks G  1993  (57)  [8131762](http://www.ncbi.nlm.nih.gov/pubmed/?term=8131762) | Prospective cohort | 4398 | AT/atrial flutter (n=141, 3.2%)  AVJ (n=900, 20.5%)  AVNRT (n=815, 18.5%)  AVRT: (n = 2222, 50.5%)  VT (n=320, 7.3%). | Incidence of complications | Complications occurred in 223 pts (5.1%) overall  AT/atrial flutter: 5.0%  AVJ: 3.2%  AVNRT: 8.0%  AVRT: 4.4%  VT: 7.5%  Complications more in AVNRT RFA compared to AVJ or AP ablation (p<0.001)  Complications more in VT compared to AVJ (p<0.002) or AP (p<0.02) | Early report showing high incidence of complications after AVNRT ablation. |
| Hindricks G  1996  (58)  [8682135](http://www.ncbi.nlm.nih.gov/pubmed/8682135) | Prospective cohort | 4463 | AVNRT (n=880) | Incidence of AV block | AV block (4/ 880, 4.7%).  AV block higher in fast pathway ablation (19/361, 5.3%, p<0.05)  6.3% in centers w/ limited experience in RFA (≤30 pts treated, p<0.05), and higher in these low-volume centers for both slow and fast pathway ablation (p<0.05) | Early report showing 5% incidence of AV block after RFA for AVNRT, and higher w/ fast pathway ablation. |
| Calkins H  1999  (59)  [9892593](http://www.ncbi.nlm.nih.gov/pubmed/9892593) | Prospective cohort | 1050  (previously enrolled in RFA clinical trial) | RFA of AVNRT, AP, or AVJ  AVNRT (n=373)  AP (n=500)  AVJ (n=121) | Efficacy and safety of RFA w/ long-term f/u. | Overall success:  95%  Overall recurrence  6%  Success:  AVNRT: 97%  AP: 93%  AVJ: 100%  Recurrence:  AVNRT: 5%  AP: 8%  AVJ: 2%  Predictors of success:  -AVNRT  OR: 3.94 (95%CI: 1.93-8.04; p=0.0002)  -Left free wall AP  OR: 3.09 (95% CI: 1.46-6.53; p=0.0003)  -Experience of ablation center (>39 pts)  OR: 2.39 (95% CI: 1.21- 4.71; p=0.012)  Joint predictors of mortality:  -EF (p=0.003)  -SHD (p=0.016)  -AVJ ablation (p=0.048) | Shows RFA is a favorable option w/ low risk of complications and recurrence, and identifies pts who are at risk. Per-protocol analysis |
| Cheng  2000  (60)  [11103056](http://www.ncbi.nlm.nih.gov/pubmed/11103056) | Comparison of cost effectiveness of RFA w/ medical management of PSVT | Symptomatic pts w/ 4.6 unscheduled visits/y for arrhythmia while on long-term drug therapy | RFA:  Estimated population:  AVNRT: 65%  AVRT w/ concealed AP: 30%  Efficacy estimates:  AVNRT: 97%  AVRT w/ concealed AP: 93%  Recurrence estimates:  AVNRT: 5%  AVRT w/ concealed AP: 8%  Drug efficacy: 60% | Perspective: societal  Outcomes: costs (office visit, annual drug rx, EP study, RFA, PPM, PPM replacement)  QALY  Life-years  Marginal cost-effectiveness ratios | W/ monthly episodes of PSVT, RFA most effective and least expensive option  RFA reduced lifetime medical expenditures by $27,940 compared w/ long-term pharmacologic therapy  Lifetime costs:  RFA:  $61,880  Long-term drug rx:  $89,820  Episodic drug rx:  $143,530  RFA improved quality-adjusted life expectancy by 3.10 QALYs. | RDA improves quality of life and reduces costs when treating highly symptomatic pts.  Effects in less symptomatic not studies |
| Scheinman MM  2000  (61)  [10879389](http://www.ncbi.nlm.nih.gov/pubmed/10879389) | Prospective cohort study  (NASPE registry) | 3,357 | Ablation of AVNRT, AP, AVJ, atrial flutter, AT, IST, VT, idiopathic VT  AVNRT (n=1,197 [35.6%)  AVJ (n=646)  AP (n=654)  AT (n=216)  Atrial flutter (n=447)  IST (n=40) | Efficacy and safety of RFA w/ long-term f/u. | AVNRT  Success: 96.1%  Complications: 2%  AVJ:  Success: 96%  Complications: 25 pts  Recurrence:3.5%  AP:  Success: 94-96%  Complications: 31 pts total  Recurrence: 4.6%  AT:  Success: 51-79%  Complications:5 total  Recurrence:15.2%  Atrial flutter:  Success: 86%  Complications:12 pts  Recurrence:14.7%  IST:  Success: 71%  Complications:2 pts  Recurrence:10% | Large series reporting success of RFA, and stratification by age group confirms safety and efficacy in elderly pts, as well as by type of facility (teaching vs. community). |

AF, atrial fibrillation; AT, atrial tachycardia; AP, accessory pathway; AV, atrioventricular; AVJ, atrioventricular junction; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; bpm, beats per minute; CHF, congestive heart failure; CI, confidence interval; CSP, carotid sinus pressure; DC, direct current; ECG, electrocardiogram; ED, emergency department; EF, ejection fraction; EMS, emergency medical services; EP, electrophysiological; FP, fast pathway; f/u, follow up; h/o, history of; IST, inappropriate sinus tachycardia; IV, intravenous; LV, left ventricular; MI, myocardial infarction; NASPE, North American Society of Pacing and Electrophysiology; NSVT, non-sustained ventricular tachycardia; OR, odds ratio; PAC, premature atrial complex; PES, programmed electrical stimulation; PPM, prosthesis-patient mismatch; PSVT, paroxysmal supraventricular tachycardia; pt, patient; QALY, quality-adjusted life year; RFA, radiofrequency ablation; rx, prescription; sbp, systolic blood pressure; SD, standard deviation; SHD, structural heart disease; SP, slow pathway; SR, sinus rhythm; ST, sinus tachycardia; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; WCT, wide complex tachycardia; w/, with; and WPW, Wolff-Parkinson-White syndrome.

Data Supplement 4. Randomized Trials Comparing Sinus Tachyarrhythmias – Section 3

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| **Study Name, Author, Year** | **Aim of Study** | **Study Type (Size, N)** | **Study Intervention Group (n)** | **Study Comparator Group (n)** | **Pt Population** | | **Endpoints** | | | **P Values, OR: HR: RR: & 95% CI:** | **Study Limitations & Adverse Events** |
|  |  |  |  |  | ***Inclusion Criteria*** | ***Exclusion Criteria*** | ***Primary Endpoint (efficacy) and Results*** | ***Safety Endpoint and Results*** | ***Secondary Endpoint and Results*** |  |  |
| BEAUTIFUL  2008 (62)  [18757088](http://www.ncbi.nlm.nih.gov/pubmed?term=(((fox%5BAuthor%5D)%20AND%202008)%20AND%20372)%20AND%20807) | To determine if HR lowering w/ ivabradine reduces cardiovascular death and morbidity in pts w/ coronary disease and LV systolic dysfunction | Randomized, double blind placebo controlled, parallel group. Multicenter  10,917 pts enrolled. Intention to treat analysis | Ivabradine 5 mg increased to 7.5 mg bid | Placebo | Coronary artery disease, LVEF <40%  Age ≥55, or ≥18 if diabetic  Sinus rhythm, HR≥60 bpm  Angina and HF sxs stable over 3 mo prior to enrollment on stable doses of at least 1 mo of conventional medical therapy | MI or coronary revascularization w/in prior 6 mo  Stroke/TIA in prior 3 mo  Pacemaker or ICD  VHD needing surgery w/in 3 y  Sick sinus syndrome, long QT, complete heart block, uncontrolled HTN, NYHA IV  Other medications w/ strong CYP P450 3A4 inhibition | Composite of cardiovascular death, hospital admission for acute MI, hospital admission for new onset or worsening HF | N/A | Mortality  Cardiac death (MI, HF, due to cardiac procedure  Cardiovascular death  Hospital admit for acute MI or unstable angina  Coronary revascularization  Hospital admit for HF  Hospital admit for acute MI | Median f/u 19 mo. Baseline mean HR 71.6±9.9 bpm, lowered at 12 mo by 6 bpm and by 5 bpm at 24 mo corrected for placebo  Primary endpoint unchanged by ivabradine  For pts w/ HR of 70 bpm or higher, ivabradine reduced admit to hospital for fatal and non fatal MI and coronary revascularization (secondary endpoints)  87% were on beta blockers  No difference in serious adverse events between pts treated w/ ivabradine or placebo | Heart rate reduction not a specified endpoint of the trial, though is reported.  Not an IST population but trial does demonstrate safety of ivabradine in a high risk population in a large, randomized, placebo controlled trial  Heart rate reduction modest but baseline heart rates are lower compared to an IST population. |
| SHIFT  2010  (63)  [20801500](http://www.ncbi.nlm.nih.gov/pubmed?term=(((swedberg%5BAuthor%5D)%20AND%202010)%20AND%20376)%20AND%20875) | To determine if HR lowering w/ ivabradine improves outcomes in HF | Randomized, double-blind, placebo-controlled, parallel-group. Multicenter trial that enrolled 6558 pts. | Ivabradine 5-7.5 mg bid | Placebo | Age ≥18 in sinus w/ resting HR of ≥70  Stable HF sxs over prior 4 wk  Prior hospital admit for HF in previous 12 mo  LVEF ≤35%  On optimum, stable medical therapy over prior 4 wk | CHD  Primary severe valvular disease  Recent MI (<2 mo)  Pacing for ≥40%/d  AF/atrial flutter  Symptomatic hypotension  Pts not allowed to receive non-dihydropyridine calcium channel blocker, class I anti-arrhythmic or strong inhibitor of CYP3A4 | Composite of cardiovascular death or hospital admission for worsening HF. Intention to treat analysis | N/A | Composite cardiovascular death or hospital admit for worsening HF in pts receiving at least 50% of target daily dose of beta blocker (metoprolol target dose = 150 mg/d)  All cause death  Any CV death  Hospital admit (any)  CV hospital admit  Death from HF  Composite of CV death, hospital admit for worsening HF, hospital admit for non-fatal MI | Median f/u 22.9 mo.  HR at 28 d decreased by 15.4±10.7 bpm in ivabradine c/w baseline and by 10.9 (CI 10.4-11.4) bpm c/w placebo. At 1 y, HR reduction was 9.1 (CI 8.5-9.7) bpm c/w placebo, and at study end 8.1 (CI 7.5-8.7) bpm c/w placebo  Primary endpoint reached in 24% of ivabradine group and 29% of placebo (p<0.0001), driven by difference in hospital admission for HF and death due to HF.  Fewer serious adverse events in ivabradine group (p=0.025). 5% of ibabradine pts w/ symptomatic bradycardia compared to 1% of placebo (p<0.0001). Visual side effects (phosphenes) in 3% of ivabradine group vs. 1% of placebo (p<0.0001) | Heart rate reduction not a specified endpoint of the trial, though is reported.  Not an IST population but trial does demonstrate safety of ivabradine in a high risk population in a large, randomized, placebo controlled trial  HR reduction modest but baseline heart rates are lower compared to an IST population. |
| Cappato R  2012  (64)  [22981555](http://www.ncbi.nlm.nih.gov/pubmed?term=(((cappato%5BAuthor%5D)%20AND%202012)%20AND%2060)%20AND%201323) | To determine the effectiveness of ivabradine to reduce sxs due to IST | Double blind, randomized, placebo controlled crossover  (N = 21) | Ivabradine (2.5-7.5 mg twice daily) for 6 wk then 7 d washout then crossover to placebo for 6 wk (n = 10) | Placebo for 6 wk then 7 d washout then crossover to ivabradine for 6 wk (n = 9) | Mean resting dtime HR >95 on Holter or >25 bpm symptomatic rise in HR from supine to standing or in response to stress | Underlying SHD (excluded by echocardiogram), SVT, orthostatic hypotension, compensatory sinus tachycardia, on antiarrhythmic therapy, renal or hepatic insufficiency, on inhibitor of CYP3A4 | Sx resolution from 7 sx indicators | N/A | HR measurements (rest, exercise), exercise capacity | Ivabradine: >70% sx elimination (RR: 0.25; 95% CI: 0.18-0.34; p<0.001), resting heart rate reduced (p=0.011), and during exertion (p=0.001) and increased exercise performance | Duration of therapy short (6 wk), some pts did not improve in sxs despite heart rate reductions. Long term effectiveness and safety not studied. |

AF indicates atrial fibrillation; bid, two times per day; bpm indicates beats per min; CI, confidence interval; CPY3A4, cytochrome p450 3A4; CV, cardiovascular; c/w, consistent with; f/u, follow up; HF, heart failure; HR, heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; IAST, inappropriate sinus tachycardia; N/A, not available; pt, patient; RR, relative risk; SHD, structural heart disease; sx, symptom; TIA, transient ischemic attack; and w/, with.

Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of Sinus Tachyarrhythmias – Section 3

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| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Lee RJ  1995  (65)  [7586260](http://www.ncbi.nlm.nih.gov/pubmed/7586260) | Prospective observational | 16 pts (12 w/ SAN modification and 4 w/ SAN ablation) | Symptomatic, medically refractory pts w/ IST undergoing RFA enrolled  Procedure:  - Activation mapping (point-by-point)  - Mapping guided by fluoroscopy or  ICE (to visualize crista)  - Isoproterenol  F/u tests:  - Autonomic blockade (intrinsic HR) w/ propranolol + atropine before and after ablation  - ETT  - Holter | Procedural success:  SAN modification: at least 25% reduction in sinus HR under same conditions of catecholamine infusion w/ either retention of normal P wave axis or low atrial escape  Total SAN ablation: reduction in HR >50% of tachycardia HR w/ junctional escape | Mean f/u = 20.5±0.4 mo  SAN modification:  - Procedural success 12/12 (100%) pts  - 2 recurrences during F/U 7.1±1.7 mo  Total SAN ablation:  - Procedural success 4/4 (100%) pts  - No recurrences at F/U  Complications:  - 2 pts PPM (both had total SAN ablation)  - 1 pt transient right diaphragmatic paralysis  - 1 pt transient SVC syndrome | - SAN modification is feasible and should be considered as alternative to complete AV junction ablation in pts w/ disabling sxs of IST that is refractory to medical therapy.  -SAN modification may be aided by ICE. |
| Rakovec P  2009  (66)  [19998013](http://www.ncbi.nlm.nih.gov/pubmed/19998013) | Consecutively treated cohort | 13 | Resting HR on ECG >100 bpm  Normal thyroid function, SHD excluded by echocardiogram | Evaluation at baseline (ECG, Holter) and after 2 wk on ivabradine 15 mg/d (repeat Holter) | 11 women, 2 men, mean age 42±8 y  7/13 were pretreated w/ beta blockers.  Mean HR decreased from 94±10 to 74.6±5.2 bpm w/ ivabradine (12 pts whose prior therapy could be discontinued or did not have prior therapy drug therapy). In 10 pts where min and max HR could be determined, the max HR decreased from 150.3±13.4 bpm to 120.6± 9.8 bpm and min HR decreased from 66.7±9.6 to 54.8±6.9.  P<0.001 for all HR comparisons (paired t tests).  One pt on metoprolol 300 mg/d switched to 15 mg of ivabradine and decrease of 4 bpm noted. | Limitation – small cohort, no meaningful comparisons to beta blockade could be made. |
| Calo L  2010  (67)  [20621618](http://www.ncbi.nlm.nih.gov/pubmed/20621618) | Prospective, nonrandomized consecutively enrolled cohort | 18 | Inclusion: Symptomatic IST,  Exclusion: secondary causes of tachycardia, SHD (echocardiogram performed)  Beta blockers and non-dihydropyridine calcium channel blockers interrupted before study | Stress test ECG for evaluation of sxs, maximal load, basal HR, maximal HR. Evaluation of stress ECG and 24-h Holter made at baseline, 3 mo, 6 mo  Pts treated w/ ivabradine 5 mg-7.5 mg twice daily | Mean and maximal HR on Holter reduced compared to baseline at 3 or 6 mo (p<0.001) and at 6 mo compared to 3 mo (p=0.02)  Resting and Maximal HR on stress test reduced and increased achieved maximal load | Ivabradine lowers HR and improves sxs over 3 to 6 mo.  Limitation – non-randomized, small cohort |
| Kaplinsky E  2010  (68)  [20544616](http://www.ncbi.nlm.nih.gov/pubmed/20544616) | Prospective, observational cohort | 4 | Resting HR ≥100, mean HR ≥90 on 24-h Holter  Also noted: not previously treated w/ beta blocker or verapamil. SHD and secondary causes of tachycardia excluded | Evaluation at baseline, wk 1, 2, 3 and 4 and 2nd and 3rd mo. At 3 mo, Holter, ETT and QOL questionnaire performed.  Ivabradine initiated at 5 mg bid, increased to 7.5 mg bid after first wk. | Ivabradine decreased resting HR from mean of 106.5±3 at baseline to 88.5 ±2 at wk 1 and 77 ±3 by wk 2 and 73.7 ±13 at mo 3. Holter monitor determined mean, max and minimum HR also reduced by 15-24% compared to baseline, exercise time increased, QOL improved. | Limitation- small cohort |
| Zellerhoff S  2010  (69)  [20859616](http://www.ncbi.nlm.nih.gov/pubmed/20859616) | Prospective observational cohort | 10 | Pts had failed or refused conventional therapy (beta blocker, calcium channel blocker, class IC AAD).  Blood count, electrolytes and TSH normal. SHD excluded.  EP study performed in 3 pts to exclude SVT.  One pt w/ prior ablation of sinus node and pacemaker and another pt w/ prior ablation. | Ivabradine 5 mg-7.5 mg bid, w/ additional beta blocker therapy in 3 pts and monotherapy in 7 pts.  72-h Holter at baseline and during therapy. Sx assessment performed by telephone at mean f/u of 16±9 mo | Ivabradine reduced max and mean HR (baseline, max heart = 176±45, mean 84±11. On ivabradine max HR was 137 ±36 and mean 74±8 bpm, p<0.05. Min HR not significantly changed  Of 8 pts contacted on followup at 16±9 mo, sxs improved in 3 pts and completely resolved in 5 pts. | Limitation – small cohort |
| Benezet-Mazuecos J  2013  (70)  [23510001](http://www.ncbi.nlm.nih.gov/pubmed/23510001) | Non randomized prospectively enrolled cohort | 24 | Inclusion: symptomatic pts diagnosed w/ IST at single institution (2009-2012) IST defined as resting dtime HR >100; excessive increase in HR w/ activity. Two Holters to confirm IST  Exclusion: secondary cause of tachycardia | Comparison of baseline to 6 mo of mean, minimal, and maximal HR on Holter, and sxs assessed by SF-36 Health Survey  (Secondary – assessment at 1 y and asked to stop treatment and reevaluate by Holter after 1 mo washout)  Pts treated w/ ivabradine 5 mg-7.5 mg bid | At 6 mo, maximal HR, mean HR, and minimal HR reduced (p<0.05). SF-36 mean score improved on ivabradine (p<0.001)  At 1 y 10 pts accepted to stop ivabradine w/ 2 pts continued to have IST criteria | At 6 mo ivabradine improved HR indices and sxs. Stopping ivabradine at 1 y showed HR continued to be in normal range in 8/10 pts.  Limitation – non randomized, small cohort. Unclear given that pts that stopped the drug at 1 y no longer met criteria for IST that cohort itself may have consisted of pts w/ milder forms of IST or did not truly have IST. |
| Ptaszynski P  2013  (71)  [22772053](http://www.ncbi.nlm.nih.gov/pubmed/22772053) | Prospective,  nonrandomized cohort | 20  (pts treated first w/ metoprolol for 4 wk, then ivabradine for 4 wk) | resting HR>100, or mean HR >90 bpm during 24-h Holter  Antiarrhythmic therapy discontinued at least 4 wk prior  Secondary causes for tachycardia and SHD were excluded | Aim: Evaluate safety and efficacy of ivabradine compared to metoprolol | Mean and resting HR lower w/ both metoprolol and ivabradine compared to baseline (p<0.001)  Exercise capacity (METS) on ETT improved w/ both metoprolol and ivabradine compared to baseline (p<0.001)  Sxs reduced more w/ ivabradine compared to metoprolol (p<0.05)  70% treated w/ ivabradine were free of sxs related to IST  Side effects: Metoprolol – hypotension in 30%, asymptomatic sinus bradycardia (40-50 bpm) in 25% | Ivabradine and metoprolol both reduced HR. Ivabradine better tolerated and improved sxs to greater extent  Limitation – short term (4 wk therapy per treatment), small sample size, nonrandomized w/o crossover; no washout period between drugs |
| Ptaszynski P  2013  (72)  [23078130](http://www.ncbi.nlm.nih.gov/pubmed?term=((ptaszynski%5BAuthor%5D)%20AND%202013)%20AND%2042) | Prospective, nonrandomized cohort | 14 | Inclusion: IST w/ resting HR ±100 bpm in sitting position and average HR ±90 bpm in 24-h Holter, following successful slow pathway ablation for AVNRT. Pts had also received at least 3 mo of beta blocker therapy  Exclusion: secondary cause of tachycardia and SHD | Evaluation at baseline, 1 mo and 2 mo of therapy w/ ivabradine (5 mg -7.5 mg bid). Resting ECG, 24-h Holter to determine resting, mean, maximum HR, and evaluation of rhythm from Holter corresponding to sxs.  ETT performed at baseline, 4 wk and 8 wk  Questionnaire to assess sxs before and after 30 and 60 d – EHRA score | Mean resting HR at 30 and 60 d reduced compared to baseline (p<0.001)  24-h Holter w/ reduced mean and mean HR during daily activity (p<0.001).  Improved exercise capacity w/ ivabradine (p<0.001)  Reduced sxs w/ no severe sxs in any pts by 2 mo | At 2 mo severe sxs were eliminated in all pts.  Limitation – No long term data for efficacy or if IST resolved |
| Ptaszynski P  2013  (73)  [23426376](http://www.ncbi.nlm.nih.gov/pubmed?term=(((ptaszynski%5BAuthor%5D)%20AND%202013)%20AND%2018)%20AND%20338) | Prospective, observational cohort | 20 | Inclusion: IST w/ resting HR ≥100 bpm in sitting position and average HR ≥90 bpm in 24-h Holter. Pts previously treated w/ beta blockers or verapamil w/o effect or poorly tolerated  Exclusion: secondary cause of tachycardia and SHD; postural orthostatic tachycardia or h/o orthostatic intolerance | Received metoprolol succinate 47.5 mg - 95 mg daily for first 4 wk, then ivabradine added 5 mg- 7.5 mg twice daily for additional 4 wk (combination therapy)  Holter and ETT performed baseline, 4 wk, and 8 wk.  Sxs assessed by questionnaire (EHRA score) | Resting HR: baseline 114.4±7.5, at 4 wk 97.3 ±14.4 and 8 wk 90.5 ±13.3 bpm, P<0.001.    Mean and maximal HR on Holter monitor also lower in combination therapy compared to either baseline or monotherapy w/ beta blockade (P<0.001).  Exercise capacity also increased.  After 1 mo of combined therapy no pts reported IST related sxs | Limitation – no long term data |
| Kang KT  2014  (74)  [25015944](http://www.ncbi.nlm.nih.gov/pubmed/25015944) | Retrospective chart review (10 pediatric centers) | 249 pts | Pediatric patient with focal AT (median age at diagnosis: 7.2 y), diagnosed based on ECG, 24-h Holter, or event monitor data consistent w/ EP criteria.  168 pts received antiarrhythmic medications (44 different medication combinations), including 154 pts as initial therapy and 14 pts after initial management with catheter ablation. Median duration of first-line therapy was 89 d. | Characterization of current management strategies for focal AT in children | Resolution of focal AT in 89% (including spontaneous resolution w/o catheter ablation in 34%).  -antiarrhythmic medications used for initial therapy with control of focal AT in 72% (BB were most common, 53%, and most effective, 42%). 34% of the 154 pts w/ first-line therapy along achieved complete suppression or rate control of focal AT. 9 pts had serious AE while on antiarrhythmic medications.  -catheter ablation successful in 109 of 134 pts (81%).  -53 of 72 pts (74%) presenting at age <3 y had spontaneous resolution (including 50 pts aged <1 y). Spontaneous resolution observed in 18 of 129 pts >5 y.  -Cardiomyopathy observed in 28%. 80% of pts with cardiomyopathy had focal AT resolution at last f/u.  Lower recurrence rates when electroanatomic mapping techniques are used vs. conventional mapping techniques (16% vs. 35%; p=0.02). | Focal AT is managed successfully in most children. Many pts control focal AT with medications, but catheter ablation is used for most pts and successful for all ages.Spontaeous resolution is common, emphasizing delayed ablation in this group.  Limitations:  -retrospective study, variable f/u duration (median 2.1 y) and available data. |
| Case series | | | | | | |
| Callans DJ  1999  (75)  [10334440](http://www.ncbi.nlm.nih.gov/pubmed/10334440) | Case series | 10 pts  (13 procedures) | Symptomatic, drug refractory pts referred for RFA of IST  Procedure:  - Primarily anatomic-based using ICE guidance, but also activation mapping for confirmation (point-by-point or electroanatomic w/ Carto)  - Isoproterenol infusion | Procedural success: - - Abrupt decrease (≥30 bpm) in sinus rate during RF lesion delivery  - Sudden appearance of superiorly directed p wave morphology (negative P in lead III)  - Persistence of these features despite isoproterenol up to 4 mcg/min for at least 30 min following final RF lesion | 11/13 (85%) procedures successful  Local circumferential swelling w/ reduction in diameter of SVC-RA junction to 12.6±3.3 mm (24% reduction, p=0.0001)  Complications – “none”  - Reduction in diameter of SVC-RA junction by ≥30% compared w/ baseline observed in 5 pts; no pts had clinical signs for SVC syndrome.  - Small adherent thrombi in 4 pts  - 1 pt ppm (after complete SN ablation) | Conclusions:  - RFA for IST can cause considerable swelling and narrowing of SVC-RA junction.  - ICE might be useful in preventing excessive tissue swelling that could lead to complications. |
| Man KC  2000  (76)  [10676693](http://www.ncbi.nlm.nih.gov/pubmed/10676693) | Case series | 29 pts | Consecutive, drug refractory, symptomatic pts who underwent RFA of IST  Procedure:  - Activation mapping (point-by-point)  - Isoproterenol infusion 1-2 mcg/min | Procedural success: Reduction of baseline sinus rate to <90 bpm, and a 20% or greater reduction in sinus rate during infusion of isoproterenol. | Procedural success 22/29 (76%) pts  Sxs due to IST recurred in 6/22 (27%) at mean f/u 4.4±3 mo  Additional procedures in 3 pts  Overall success 19/29 (66%) pts over long-term  Complications in 2/29 (7%) pts  - Sinus pauses/near-syncope (ppm)  - Paralysis of right hemidiaphragm | RFA is at best only modestly effective for managing pts w/ IST. |
| Marrouche NF  2002  (77)  [11897449](http://www.ncbi.nlm.nih.gov/pubmed?term=(((marrouche%5BAuthor%5D)%20AND%202002)%20AND%2039)%20AND%201046) | Case series | 39 pts | Inclusions:  “Debilitating” IST (no prior drugs in 6 pts)  Exclusions:  - Prior sinoatrial node ablation at other center  - F/u <2 y  - POTS  Procedure:  - Mapping at baseline and after isoproterenol (or aminophylline)  - Earliest site of activation by 3D electroanatomic mapping targeted  - Autonomic testing (10 pts w/ resting HR >100) - tested response to esmolol before ablation  - ETT before and after ablation  - ICE to verify crista | Procedural success:  HR drop below 120 bmp during isoproterenol 2 mcg/min alone or in combination w/ aminophylline  (Look for SN acceleration during RFA delivery)  When endpoint achieved, then recreated 3D map of RA  Observe for recovery of HR for 45 to 60 min after last ablation | Sinoatrial node successfully modified in all pts (100%)  Drop in mean HR from 99 ±14 bpm to 72±8 bpm, p<0.01  Shift in caudal activation along crista terminalis on 3D map was more pronounced after RFA than during esmolol (23 ±11 mm vs. 7±5 mm, p<0.05)  No pt underwent ppm after mean f/u 32±9 mo.  21% of pts experienced recurrence of IST and were successfully re-ablated  Complications:  SVC syndrome (1 pt), requiring dilation | 3D mapping provides an effective tool to monitor and guide RFA for IST. (Seems to eliminate excessive destruction of SN and reduce or eliminate risk of complete SN ablation.)  Difference in caudal shift seen after esmolol and following sinoatrial node modification suggests that adrenergic hypersensitivity is not the only mechanism responsible for IST. |
| Lin D  2007  (78)  [17338721](http://www.ncbi.nlm.nih.gov/pubmed/17338721) | Case series | 7 pts | Medically refractory IST referred for ablation  Procedure:  - Non-contact mapping (Endocardial Solutions, Ensite array, 4 mm Chilli Cooled Ablation system)  - Isoproterenol 1-10 mcg/min  - Intrinsic HR evaluated w/ BB and atropine | Endpoint: Decrease in HR of ≥25% off isoproterenol and associated change in P wave morphology in III and AVF from positive to a flat or negative defection c/w more inferior origin | Procedural success: 100%  Complications: 1 pt ppm (symptomatic junctional bradycardia requiring ppm 2 wk after procedure) – but also had prior RFA | Non-contact mapping in conjunction w/ saline-cooled ablation for SN modification may provide effective HR control for treatment of IST. |
| Frankel DS  2012  (79)  [22471900](http://www.ncbi.nlm.nih.gov/pubmed/22471900) | Case series | 33 pts | Consecutive, drug refractory, symptomatic  Procedure:  - Evolved from anatomic approach using ICE to EP approach using multi-electrode mapping (St. Jude Ensite or Biosense Webster)  - Isoproterenol | Procedural endpoint:  - Decrease of >25% in resting HR, w/ blunted HR response to isoproterenol and shift of P wave morphology from positive to flat or negative in leads III and AVF  - Cranial to caudal shift in site of earliest RA activation pre and post SAN modification was measured using mapping system (later y) | F/u 2.0±1.5 y  - 18% recurrent IST  - 27% developed non-IST tachyarrhythmia (42% had non-IST arrhythmia prior to SAN modification)  2 deaths (unrelated) during long-term f/u:  - 1 mechanical fall  - 1 pulseless electrical activity (end-stage cardiomyopathy)  Complications (long-term):  12% required ppm for SAN dysfunction | Non-IST tachyarrhythmias are common in pts w/ IST before and after SAN modification, and are often responsible for sxs during f/u. |
| Takemoto M  2012  (80)  [22333369](http://www.ncbi.nlm.nih.gov/pubmed?term=(((takemoto%5BAuthor%5D)%20AND%202012)%20AND%2051)%20AND%20357) | Case series | 6 pts | Consecutive, drug refractory, “debilitating”  Procedure:  - Non-contact mapping (St. Jude Ensite)  - Break-out sites also identified as earliest sites that showed rS pattern w/ sudden increase in peak negative potential on noncontact unipolar electrogram  - Isoproterenol 2-5 mcg/min | Procedural endpoint:  When break-out sites observed at heart rate >100 bpm moved from the tall P wave zone to the normal P wave zone, w/ and w/o IV isoproterenol | F/U 29±2 mo  Procedural success 6/6 (100%)  1 y F/U: 0 recurrences  1 ½ y: 1/6 pts had recurrence of IST and underwent repeat RFA w/ success  Also showed improvement of HR on Holter, BNP, NYHA functional class, exercise tolerance, and time to achieve HR of 130 bpm on ETT post-ablation  Complications: none | Non-contact mapping can be used to safely and effectively treat IST. |
| Huang HD  2013  (81)  [23313383](http://www.ncbi.nlm.nih.gov/pubmed/23313383) | Case report using stellate ganglion block | 1 | 34 y old woman previously treated w/ verapamil, beta blockers, clonidine  Baseline mean HR (Holter) 104 bpm. Tilt table hr increased from 86 to 104 bpm at 2 min (70 deg)  Stellate ganglion block performed (transient Horner syndrome) (right, then left 2 d later) | Following bilateral stellate ganglion block, Holter w/ mean HR of 73 bpm.  Last f/u at 4 mo w/ resting HR of 87 bpm. | Following bilateral stellate ganglion block, Holter w/ mean HR of 73 bpm.  Last f/u at 4 mo w/ resting HR of 87 bpm. | Mechanisms for lasting effect unclear as anesthetic agent used has half-life of 4-5 h |

AAD indicates antiarrhythmic drug; AVNRT, atrioventricular nodal reentrant tachycardia; bid, two times per day; BNP, B-type natriuretic peptide; bpm indicates beats per min; c/w, consistent with; ECG, electrocardiogram; EHRA, European Heart Rhythm Association; EP, electrophysiological; ETT, exercise tolerance test; f/u, follow up; h/o, history of; HR, heart rate; ICE, intracardiac echocardiography; IST, inappropriate sinus tachycardia; IV, intravenous; METS, metabolic equivalents; NYHA, New York Heart Association; POTS, postural orthostatic tachycardia syndrome; PPM, prosthesis-patient mismatch; pt, patient; QOL, quality of life; RF, radiofrequency; RFA, radiofrequency ablation; SF, short form; SHD, structural heart disease; SN, sinus node; SVC, superior vena cava; SVC-RA, superior vena cava-right atrial; SVT, supraventricular tachycardia; sx, symptom; w/, with; and w/o, without.

Data Supplement 6. Nonrandomized Trials, Observational Studies, and/or Registries of Focal Atrial Tachycardia – Section 4.1

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| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Gillette PC  1977  (82)  [902384](http://www.ncbi.nlm.nih.gov/pubmed/?term=((gillette%5BAuthor%5D)+AND+1977)+AND+571) | Observational | 7 children (6 wks to 9 y of age) | Sustained automatic AT taken to EP lab | Programmed stimulation and drug testing | 1 responded to digoxin, 3 responded to propranolol and digoxin; diphenylhydantoin in one and reserpine in1 | Newborn and pediatric population |
| Creamer JE  1985  (83)  [3966957](http://www.ncbi.nlm.nih.gov/pubmed?term=((creamer%5BAuthor%5D)%20AND%201985)%20AND%20164) | Case report | 3 (23, 33 and 57 y of age, all man) | Symptomatic persistent AT | Acute (IV) and long term (oral) response to flecainide | All responded acutely and on long term f/u from 3 mo to 3 y | Case report demonstrating flecainide is effective in focal AT in selected pts. |
| Kunze KP  1986  (84)  [3082957](http://www.ncbi.nlm.nih.gov/pubmed/3082957) | Observational | 5 pts (mean age 37) | Chronic symptomatic ectopic AT failed 4 other antiarrhythmic drugs including amiodarone and verapamil | Assess acute and long term outcomes w/ encainide and flecainide therapy | 4/5 pts had complete suppression of AT by encainide and 1/5 had significant reduction at a mean f/u of 8 mo. 3/5 pts did not tolerate encainide. These pts responded to flecainide w/o any side effects | One of the more comprehensive mechanism-based investigation in human subjects. Differentiation of mechanisms is based on best established criteria although overlaps between reentry and trigger are present; drug response was not specific. It is not apparent whether these were micro- or macro-reentry circuits. Ablation targeted the earliest activation, suggesting micro-reentry. |
| Lucet V  1987  (85)  [3122689](http://www.ncbi.nlm.nih.gov/pubmed/?term=3122689) | Observational | 30 children, age 3 mo to 20 y | All pts treated w/ propafenone for a mean period of 14 mo | Clinical outcomes on propafenone therapy | Study cohorts: chronic AT (8), junctional arrhythmia (9), ventricular arrhythmia (13). Propafeone was “more effective” than amiodarone in 3 pts w/ chronic AT and as effective as amiodarone in 2. Side effects were present in 27%, although “generally well tolerated”. | There is significant limitation of the study due to the observational nature of the study design and mix of different arrhythmias. |
| Mehta AV  1988  (86) [3339178](http://www.ncbi.nlm.nih.gov/pubmed?term=(((mehta%5BAuthor%5D)%20AND%201988)%20AND%20379)%20AND%2085) | Observational | 10 infants and children; median age 6 mo, range from new born to 7.5 y | Met ECG critieria for ectopic AT | Acute and long term response to a sequence of drug testing. One pt underwent surgical ablation; one pt underwent catheter ablation | Digoxin did not suppress any AT but did slow the ventricular rate by 5-20% in 8 pts. IV propranolol was effective in AT suppression in 3/5 pts; oral propranolol was effective in 2/5. Class Ia and Ib antiarrhythmic agents were not effective in AT suppression and worsened the ventricular rate. IV amiodarone was effective in 3 /4 pts and oral amiodarone was effective in one pt. During f/u (10-28 mo), AT resolved in 4 pts and was well controlled in 4 pts. Surgical and catheter ablation was each performed in one pts | This small study was conducted in new born and very young children |
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| Colloridi V  1992  (87)  [1729843](http://www.ncbi.nlm.nih.gov/pubmed?term=((Colloridi%5BAuthor%5D)%20AND%201992)%20AND%20123) | Case study | 5 pediatric pts | Ectopic AT was met by ECG criteria | Pts failed a mean of three drugs | Sotalol was added to digoxin; AT was suppressed in all 5 pts | A small case series study showing effect of sotalol on AT in pediatric pts |
| von Bernuth G  1992  (88)  [1396817](http://www.ncbi.nlm.nih.gov/pubmed/1396817) | Observational | 21 infants and children | Automatic AT was documented by Holter and ECG; 12 were incessant, 7 were repetitive, 2 were undefined; 16/21 were symptomatic | All pts were treated w/ 1-8 antiarrhythmic drugs (median 3) | Amiodarone was most effective followed by class Ic drugs: flecainide and propafenone. During a median f/u of 2.5 y (range from 4 mo to 21 y), 12 were in sinus rhythm, 5 were w/o any drugs. Nine pts were still on antiarrhythmic drugs; all were intermittent except one | Small observational study in the pediatric population |
| Chen SA  1994  (89)  [8087935](http://www.ncbi.nlm.nih.gov/pubmed/8087935) | Observational | 36 (57+/-13 y of age) | Sustained AT referred to the EP lab for ablation | Programmed stimulation, drug testing, Valsalva, monophasic AP recording and ablation to assess AT mechanisms | 20/36 had reentrant AT,  9/36 triggered (DAD)  7/36 automatic  Immediate success 40/41 (98%)  Recurrence 2/40 (5%) in 18 mons f/u  2 failed RF, both were triggered | One of the earlier more comprehensive mechanism-based investigation in human subjects. Differentiation of mechanisms is based on best established criteria although overlaps between reentry and trigger are present; drug response was not specific. It is not apparent whether these were micro- or macro-reentry circuits. Ablation targeted the earliest activation, suggesting micro-reentry. |
| Engelstein ED  1994  (90)  [8205677](http://www.ncbi.nlm.nih.gov/pubmed/8205677?dopt=Citation) | Observational | 27 pts  Automatic (7 pts, age 34+/- 18); sinus node reentry (6 pts, age 58+/- 16); atrial flutter (8 pts, age 62+/- 8); intra-atrial reentry (5 pts, age 70 +/- 8 ); triggered tachycardia (1 pt, age 79) | Pts were referred for electrophysiology study (25 pts; 17 for symptomatic SVT, 7 for VT, 1 for syncope) or cardioversion (2 pts w/ atrial flutter) | Mechanism of tachycardia was confirmed during electrophysiology study. Response to adenosine was assessed according to EP study determined mechanisms | Adenosine terminated all sinus node reentry tachycardia (6/6), triggered tachycardia (1/1). Adenosine transiently suppressed automatic AT (7/7); it had not effect on reentry tachycardia (13/13) | These earlier observations established our current understanding of potential mechanisms of AT and drug effects as predicted by underlying mechanisms. |
| Heusch A  1994  (91)  [7527342](http://www.ncbi.nlm.nih.gov/pubmed/?term=7527342) | Observational | 72 children, mean age was 34 mo (range 0-192) | All pts were treated w/ propafenone | AT or junctional tachycardia were in 10/72 pts (14%). Other arrhythmias including AV reentrant tachycardia (32 pts, 44%), atrial flutter (16 pts, 22%), atrial reentry tachycardia (3 pts, 4%) and ventricular arrhythmias (11 pts, 16%). | Propafenone was effective in controlling atrial or junctional ectopic tachycardia in 83%. Of the entire study cohorts, better outcomes were observed in pts w/ normal hearts and in whom onset of arrhythmias was pre-natal. | A mix of many different arrhythmias renders interpretation of results difficult. The study population is young children, many w/ congenital heart conditions |
| Janousek J  1998  (92)  [9605053](http://www.ncbi.nlm.nih.gov/pubmed/?term=9605053) | European, retrospective and multicenter study | 722 infants and children from 27 European centers coordinated by the Working Group on Pediatric Arrhythmias and Electrophysiology of the Association of European Pediatric Cardiologist | All pts were treated w/ oral propafenone | Safety outcomes | Ectopic AT was in 66/722 study cohort. Other arrhythmias included reentrant SVT (388), junctional ectopic tachycardia (39), atrial flutter (21), ventricular premature complexes (140), VT (78) and other (39). 249/722 had SHD. Adverse events included sinus node dysfunction (4), complete heart block (2), SVT proarrhythmia (2), accelerated ventricular rate during atrial flutter (1), ventricular arrhythmias (5), unexplained syncope (1). Cardiac arrest occurred in 6 (0.6%, 2 had WPW, 3 had SHD) | A large retrospective multicenter study on the safety of propafenone in the pediatric population. |
| Kalman JM  1998  (93)  [9462592](http://www.ncbi.nlm.nih.gov/pubmed?term=((kalman%5BAuthor%5D)%20AND%201998)%20AND%20451) | Observational | 23 pts, 27 RA tachycardia | 17 female, age 41 +/- 14 y; h/o AT suspected from RA; point to point mapping w/ 5 mm tip steerable catheter | ICE localization of AT origin; outcomes of RFA | 23/27 localized to RA; 4 were from right superior pulmonary vein; other sites include posterior septum, coronary sinus os, RAA; 18/27 (67%) were on the CT; 26/27 successful ablation (96%); all visualized by ICE | Visual confirmation by ICE of ablation site; high prevalence of AT originating from cristae terminalis |
| Markowitz SM  1999  (94)  [10355690](http://www.ncbi.nlm.nih.gov/pubmed/10355690?dopt=Citation) | Observational | 30 pts (age 55 +/- 18 y) | Referred to EP study for evaluation and treatment of tachycardia | Assess response to adenosine according to EP study determined mechanisms | Adenosine terminated 14/17 focal AT and transiently suppressed the other 3 pts. Only 1/13 macrorenetrant tachycardia was terminated by adenosine. The termination occurred in the slow of conduction w/ decrementing properties. Verapamil terminated all of the focal ATs when tested | This study highlighted the challenges remain in differentiating automatic vs. triggered focal AT. The proportion of focal AT terminated by adenosine (presumably due to triggered activity) is significantly different from the report from Englestein 1994, from the same lab. |
| Morton JB  2001  (95)  [1140539](http://www.ncbi.nlm.nih.gov/pubmed/11405398)8 | Observational | 9 pts from 64 consecutive pts underwent RFA for RA AT | 6 male, 50 +/- 20 y; AT from CT; point to point steerable catheter | Mapping and localization of AT to CT | 34/67 (51%) from CT; 8 (12%) from CS; 10 (15%) para-Hisian; 9 (13%) from TA. 8/9 were successfully ablated; 1 was not inducible | AT originating from CT is common |
| Kistler PM  2003  (96)  [12821250](http://www.ncbi.nlm.nih.gov/pubmed?term=((kistler%5BAuthor%5D)%20AND%202003)%20AND%202212) | Observational | 7 pts/ 172 consecutive pts w/ focal AT | AT from mitral annulus  Point to point mapping | Mapping and ablation need to make note how they figured out where it was coming from | All mapped to left fibrous trigone and mitral-aortic continuity; P wave low amplitude in precordial leads, biphasic, negative followed by positive; 100% success rate | Mitral annular origin is less common |
| Kistler PM  2003  (97)  [14557361](http://www.ncbi.nlm.nih.gov/pubmed?term=((kistler%5BAuthor%5D)%20AND%202003)%20AND%201968) | Observational | 27 pts w/ 28 ATs | AT from pulmonary veins; 39 +/- 16 y; point to point mapping w/ or w/o Lasso | Mapping and ablation | Right superior pumonlary vein 11, left superior pulmonary vein 11, left inferior pulmonary vein 5, right inferior pulmonary vein 1; 26/28 were ostia; 100% successful; 4 recurrence; 25/28 were focal; 3/28 segmental | 28/172 consecutive focal ATs (16%) from pulmonary vein; high success rate; majority at ostia |
| Gonzalez MD  2004  (98)  [15533857](http://www.ncbi.nlm.nih.gov/pubmed?term=((gonzalez%5BAuthor%5D)%20AND%202004)%20AND%203187) | Observational | 10 pts/35 consecutive pts (28%) | AT from mitral-aortic continuity | Mapping and ablation | Tachycardia CL 340 msec +/- 56; local e-P – 44 msec +/- 14; 100% successful | Provided a brief discussion on mouse embryo and the specialized conduction system in near the mitral-aortic continuity region |
| Kistler PM  2005  (99)  [15862424](http://www.ncbi.nlm.nih.gov/pubmed?term=((kistler%5BAuthor%5D)%20AND%202005)%20AND%201488) | Observational | 13 pts (of 193 w/ focal AT) | 7 female; 41 +/- 6 y; AT from tricuspid annulus (TA); point to point mapping | Mapping and localization of AT to TA | Negative p wave in all inferior leads; negative or isoelectric in V1, positive in avL; 11/13 successfully ablated; 2 noninducible; no recurrence in 25 mo | 13/ 193 (6.7%) of all AT are from coronary sinus os. |
| Eidher U  2006  (100)  [16650262](http://www.ncbi.nlm.nih.gov/pubmed?term=((eidher%5BAuthor%5D)%20AND%202006)%20AND%20358) | Observational | 38 pts, 49 episodes of AT | “monomorphic” AT, excluded typical atrial flutter and AF; likely included macro-reentry atypical flutter | Ibutilide conversion to SR in the acute setting | 19/49 (38.8%) conversion | Inclusion does not differentiate focal AT from macro-reentry AT; conversion rate appear to be lower than atrial flutter and AF. |
| Ouyang F  2006  (101)  [16814658](http://www.ncbi.nlm.nih.gov/pubmed/16814658) | Observational | 9 pts; 6 failed previous “para-Hisian” ablation; 6 female | NCC AT | Location and ablation | Local egram preceded His local A by 12 msec; no H on the ablation catheter; all ablation was successful w/o recurrence  Age 54 +/- 12, range 32-66 | One of the earlier observational studies reported AT localized to NCC and successfully ablated; highlights mapping NCC early if AT appears para-Hisian |
| Roberts-Thomson KC  2007  (102)  [17286568](http://www.ncbi.nlm.nih.gov/pubmed?term=(((roberts%5BAuthor%5D)%20AND%202007)%20AND%2018)%20AND%20367) | Observational | 10 pts (of 261 w/ focal AT) | 9 male, 39 =+/- 20 y; AT from RAA; point to point mapping w/ 4 mm tip deflectable catheter | Mapping and localization to RAA | P wave negative in V1; low amplitude or positive in inferior leads; acute success rate in 100%, no recurrence | RAA AT is less common 10/261 (3.8%) |
| Medi C  2009  (103)  [19422986](http://www.ncbi.nlm.nih.gov/pubmed?term=((medi%5BAuthor%5D)%20AND%202009)%20AND%201791) | Case control | 30 pts w/ cardriomyopathy vs. 301 w/o cardiomyopathy | AT induced cardiomyopathy | Outcome assessment | AT induced caridomyopathy 10% ( 30/301); incessant, younger (39 +/- 22 vs. 51 +/- 17, 60% males vs. 38%), longer tachycardia CL (502 msec vs. 402 msec); LVEF was restored in 97% pts | Prevalence of AT induced cardiomyopathy 10% in all AT pts; RFA is highly successful in restore LVEF |
| Liu X  2010  (104)  [20797494](http://www.ncbi.nlm.nih.gov/pubmed/20797494) | Case control | 13 study pts  15 PAF/PVI  25 PAF | AT origination from NCC | Local e-gram, activation sequence, electroanatomical mapping, histology, and P-wave morphology | Wide initial activation patter in the right atrium (RA), left atrium (LA) from the parahistian area; earliest activation in the NCC; no atrial myocardium in the NCC; NCC was adjacent to the atrial para-septal tissue | Presence of “para-Hisian AT” should raise awareness of close anatomical relationship to atrial –paraseptal tissue and NCC  Early mapping and ablation in the NCC may increase ablation success and reduce complications  P wave morphology may not differentiate NCC-AT from left atrial or RA paraseptal AT |
| Biviano AB  2012  (105)  [21967474](http://www.ncbi.nlm.nih.gov/pubmed/21967474) | Observational | 24, 14 female, age 48+/- 18 | Focal left atrial AT; no prior h/o AF | Location and short term ablation outcome | CL 347 msec (190-510 msec); CS, septum (5), free wall, MVA, roof, LAA, ligament of Marshall and PV (6)  Immediate success 19/22 ATs | A good observational study on the distribution of left atrial AT location; contemporary techniques; no major complications; success rate is consistent w/ the literature |
| de Loma-Osorio A  2013 (106)  [24774111](http://www.ncbi.nlm.nih.gov/pubmed/24774111) | Spanish registry from 74 centers, voluntary | 333 of 11042 procedures (3%) | Registry included all ablation procedures from 2012 | Ablation outcomes | Acute success rate 284/333 (85.3%); RA 61%, 36% in LA; complications 7/333 (2.1%), 1 permanent pacemaker, 2 vascular, 4 pericardial effusion | One of the few national registries |
| Mano H  2013  (107)  [23595943](http://www.ncbi.nlm.nih.gov/pubmed/?term=23595943) | Case control | 6 study cohorts, 12 controls | Anatomical substrate for NCC-AT vs. AVNRT | Comparing P wave duration, PQ, intracardiac intervals and local anatomy between NCC-AT and AVNRT | P wave duration, PQ and AH intervals were longer in NCC-AT than AVNRT; AS (aortic roof to IVS angle) angle was steeper and IVS was thicker | Interesting details, but not sure how useful for clinical practice |

AF indicates atrial fibrillation; AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; CL, cycle length; CT, crista terminalis; DAD, delayed afterdepolarizations; ECG, electrocardiogram; EP, electrophysiological; f/u, follow up; h/o, history of; ICE, intracardiac echocardiography; IV, intravenous; IVS, intraventricular septum; LA, left atrial; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; MVA, mitral valve area; NCC, non-coronary cusp; pt, patient; PV, pulmonary vein; RA, right atrial; RF, radiofrequency; RFA, radiofrequency ablation; SHD, structural heart disease; SR, sinus rhythm; SVT, supraventricular tachycardia; VT, ventricular tachycardia; w/, with; w/o, without; and WPW, Wolff-Parkinson-White syndrome.

Data Supplement 7. Randomized Trials Comparing Multifocal Atrial Tachycardia – Section 4.2

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Name, Author, Year** | **Aim of Study** | **Study Type (Size, N)** | **Study Intervention Group (n)** | **Study Comparator Group (n)** | **Pt Population** | | **Endpoints** | | | **P Values, OR: HR: RR: & 95% CI:** | **Study Limitations & Adverse Events** |
|  |  |  |  |  | ***Inclusion Criteria*** | ***Exclusion Criteria*** | ***Primary Endpoint (efficacy) and Results*** | ***Safety Endpoint and Results*** | ***Secondary Endpoint and Results*** |  |  |
| Arsura E  1989  (108)  [3052051](http://www.ncbi.nlm.nih.gov/pubmed/3052051) | To determine efficacy of verapamil, metoprolol or placebo in MAT | Randomized, double-blind, placebo-controlled study of verapamil and metoprolol in treatment of MAT; 13 pts (4 male, 9 female) | 9 pts verapamil, 9 pts metoprolol | 10 pts given placebo (2 pts given placebo on both days) | MAT diagnosed via ECG. | Reversible precipitants of MAT (hypoxia, electrolyte abnormalities, anemia, acidosis, and serum digoxin or theophylline levels outside therapeutic range) – if corrected and pt continued to have MAT, able to participate.  CHF; SBP <100 mm Hg; bronchospasm; h/o greater than first-degree heart block; bifascicular block; altered sinus node function; hypersensitivity to either age; estimated survival time <72 h; use of either study agent w/in preceding 72 h | Conversion to sinus rhythm, a decline in the ventricular rate of ≥15%, or decline in ventricular rate to <100 bpm | N/A | Repeat physical exam and arterial blood gas values. | 2/10 (20%); 4/9 (44%); 8/9 (89%) showed a response to placebo, verapamil, or metoprolol, respectively  Mean slowing of ventricular rate was 3.4, 7.3, and 24.5% for placebo, verapamil, and metoprolol, respectively (p<0.01 for metoprolol vs. placebo).  Five pts who had a response to metoprolol had failed to have a response to verapamil. | Metoprolol appears more effective than verapamil in treating MAT. Caution must be exercised in selecting pts |
| McCord JK  1998  (109)  [9462615](http://www.ncbi.nlm.nih.gov/pubmed/9462615) | To assess the use of IV Mg for MAT in pts w/ COPD | Randomized; 14 pts | 9 pts received 2 grams over 5 min and 10 g over 5 h | 5 pts received Placebo | Pts w/ COPD and MAT | Cr ≥2.0 mg/dL,  intolerance to IV infusion | Rhythm assessment at 5 h  Pts treated w/ magnesium had a slowing of heart rate from 130 to 99 beats per min  Placebo- no effect on HR.  NSR at end of infusion in 7/9 treated w/ Mg vs. 1/5 w/ placebo. | N/A | N/A | N/A | Caregivers not blinded. Small sample size with no control group. |

BP indicates blood pressure; CI, confidence interval; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; Cr, creatinine; ECG, electrocardiogram; HR, heart rate; IV, intravenous; MAT, multifocal atrial tachycardia; N/A, not applicable; OR, odds ratio; pt, patient; RR, relative risk; and SBP, systolic blood pressure.

Data Supplement 8. Nonrandomized Trials, Observational Studies, and/or Registries of Multifocal Atrial Tachycardia – Section 4.2

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| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Iseri LT  1985  (110)  [4050650](http://www.ncbi.nlm.nih.gov/pubmed/4050650) | Observational | 8 | 8 pts w/ MAT received 7-12 Gm IV mag over 5 h | NSR | N/A | MAT was successfully converted to sinus rhythm or sinus tachycardia in seven pts. MAT rhythm (at slow rate) persisted in one pt. |
| Hazard PB  1987  (111)  [3792010](http://www.uptodate.com/contents/multifocal-atrial-tachycardia/abstract-text/3792010/pubmed) | Observational, active treatment w/ metoprolol | 25 | 25 pts w/ MAT that was complicating severe cardiopulmonary illness | Observed its effect on heart rate and rhythm, BP, and arterial blood gase | All pts showed slowing of heart rate, averaging 54.0±4.0 bpm (p<0.001)  pH and PaCO2 were unaltered; mean PaO2 increased by 12.2 +/- 5.8 torr (p<0.05) | Metoprolol is effective in the management of MAT. |

B indicates blood pressure; bpm, beats per minute; MAT, multifocal atrial tachycardia; N/A, not applicable; NSR, normal sinus rhythm; PaCO2, partial pressure of carbon dioxide; pt, patient; and w/, with.

Data Supplement 9. Randomized Trials Comparing Atrioventricular Nodal Re-Entrant Tachycardia – Section 5

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Name, Author, Year** | **Aim of Study** | **Study Type (Size, N)** | **Study Intervention Group (n)** | **Study Comparator Group (n)** | **Pt Population** | | **Endpoints** | | | **P Values, OR: HR: RR: & 95% CI:** | **Study Limitations & Adverse Events** |
|  |  |  |  |  | ***Inclusion Criteria*** | ***Exclusion Criteria*** | ***Primary Endpoint (efficacy) and Results*** | ***Safety Endpoint and Results*** | ***Secondary Endpoint and Results*** |  |  |
| Pharmacological Therapy | | | | | | | | | | | |
| Waxman HL  1981 (112)  [7447203](http://www.ncbi.nlm.nih.gov/pubmed/7447203) | Effectiveness of IV verapamil | 50 | Group 1 (n=20) w/ AF or flutter  Group 2 (n=30)  PSVT (AVNRT in 8 pts), | N/A | PSVT w/ AF, atrial flutter, PSVT | N/A | Control of ventricular response in group 1, restoration of sinus rhythm in group 2  In Group 1 low-dose verapamil (0.075 mg/kg body weight) decreased the mean ventricular rate from 146 to 114 bpm (p<0.01) compared to a decrease of 145 to 132 bpm (p<0.01) after placebo.  In Group 2, 14/29 pts converted to sinus rhythm after low-dose verapamil, 9/15 after high-dose verapamil (0.15 mg/kg), and 1/24 after placebo (p<0.01). | N/A | N/A | N/A | Verapamil results in a clinically significant slowing of the ventricular response in AF or atrial flutter and is superior to placebo for conversion of PSVT to sinus rhythm |
| Mauritson DR  1982  (23)  [7065555](http://www.ncbi.nlm.nih.gov/pubmed/7065555) | Effectiveness and safety of oral verapamil | 11 | Verapamil 240 mg/d followed by 480 mg/d  (n=11) | Placebo | Symptomatic PSVT, ≥2 episodes/mo, ascertained by ECG  AVNRT  (n=7)  AVRT  (n=2 w/ WPW, n=3 w/ concealed AP) | CHF, severe hypertension, hypotension, VHD or CHD, renal/hepatic failure, SSS, AV block, atrial flutter, AF, AADs | Episodes/wk (diary, Holter)  Verapamil 0.1±0.1 ,0.3 ±0.5  Placebo 0.3±0.3 ,0.7 ±0.7  Duration (min) (diary, Holter)  Verapamil 3±3 ,1±2  Placebo 27±5 ,67±111 | Minor AEs in 6 pts on verapamil  5 pts required a total of 35 cardioversions for sustained tachycardia, 2 during verapamil, 33 during placebo (p<0.001)  PES performed at end of study to induce tachycardia. Caused sustained tachycardia in 9 on placebo, 2 on verapamil (p<0.01) | N/A | p<0.05 for primary endpoint | Oral verapamil safe and effective.  Small sample size.  Unclear which pt withdrew, so numbers of AVNRT vs. AVRT may be similar (i.e., 6 vs. 5). |
| Winniford MD  1984  (24)  [6388299](http://www.ncbi.nlm.nih.gov/pubmed/6388299) | Effect of AV nodal blockers for long-term therapy of PSVT | 11 | One mo of:  Digoxin 0.375 mg/d  Propranolol 240 mg/d  Verapamil 480 mg/d | Direct comparison between all 3, w/ one wk of placebo washout | Symptomatic PSVT, ≥2 episodes/mo, ascertained by ECG | ECG evidence of preexcitation | Episodes and duration (ascertained by diary and weekly 24-h Holter), adverse effects, SDCs of each drug  Episodes/wk (diary, Holter)  Digoxin 2.3±3.1, 1.9±2.9  Propranolol 1.5±2.3, 0.2±0.6  Verapamil 2.9±5.7, 0.6±1.6  Duration (min) (diary, Holter)  Digoxin 75±164, 47±157  Propranolol 60±112, 1±1  Verapamil 56±148, 1±1 | Mild side effects in 3/11 pts w/ digoxin and propranolol, and 5/11 w/ verapamil. All SDCs w/in normal reference range. | N/A | p=NS | Only verapamil had been studied in RCT prior to this (above), and given its proven efficacy, authors felt no need for placebo.  Small series of pts.  Unclear mechanism of PSVT (authors speculate all pts w/ AVRNT or ORT w/ concealed conduction. |
| Yeh SJ  1984  (113) [3964710](http://www.ncbi.nlm.nih.gov/pubmed/?term=yeh+sj%2C+lin+fc+%2C+chou+yy) | Effect of diltiazem and propranolol as pill-in-the-pocket | 15 | Combination diltiazem 120 mg/propranolol 160 mg vs. placebos | Direct comparison on 2 consecutive d | Inducible PSVT  AVRT (n=13)  AVNRT (n=2) | N/A | W/ placebo PSVT lasted 164±89 min; 4 pts had spontaneous conversion.  W/ diltiazem and propranolol PSVT lasted 39±49 min (p<.001). 14 pts had spontaneous conversion in an average of 27 ±15 min.  None of the 14 pts had electrical reinduction of sustained PSVT after conversion.  Outpatient f/u w/ 50/51 conversion of PSVT w/in 21±16 min, f/u of 5.6 mo. | The heart rate was 87±16 bpm before and  59±10 bpm at 90 min after diltiazem and propranolol  (p<0.001).  The systolic and diastolic pressures  were, respectively, 111±11 and 77±10 mm  Hg before and 88 + 9 and 66 + 9 mm Hg after diltiazem and propranolol (p<0.001) | N/A | N/A | Single dose of diltiazem/propranolol terminated acute PSVT  Limited due to EP study efficacy and low numbers of AVNRT pts. Not placebo controlled. |
| Anderson S  1986 (25)  [2868645](http://www.ncbi.nlm.nih.gov/pubmed/?term=2868645) | Efficacy of esmolol in treatment of PSVT | 71  Multicenter, double-blind, partial-crossover study | Esmolol (n=36) | Placebo (n=35) | “SVT” (HR>120)  Note: AVNRT in 18% of subjects | VHD, AV block,  SSS, significant electrolyte  abnormality,  precluding treatment w/ beta blockade, bronchial  asthma, ventricular arrhythmias requiring drug therapy,  cardiogenic shock, CHF (NYHA III-IV), renal or hepatic dysfunction, drug or alcohol abuse,  on other beta-adrenergic blockers or calcium channel  blockers w/in two half-lives of study entry | Therapeutic response: ≥20% reduction in HR, HR<100 bpm, or conversion to NSR.  Therapeutic response to esmolol during the initial treatment period (72%) similar when esmolol was given as a second agent  4 pts (6%) converted to NSR  In the 80% therapeutic response lost w/in 30 min following discontinuation of esmolol infusion | Hypotension which occurred in12% on esmolol, 2% w/ placebo. | N/A | p=NS | Rapid onset and short of  action of esmolol offer safe, effective therapy for acute treatment of pts w/ PSVT. Low numbers of pts w/ AVNRT. |
| \*DiMarco JP  1990 (114)  [2193560](http://www.ncbi.nlm.nih.gov/pubmed/2193560) | Evaluate dose responses of adenosine in terminating PSVT | 359 total in both protocols  (n=201) | Sequential IV bolus doses of adenosine (3, 6, 9, 12 mg)  (n=137) | Saline placebo  (n=64) | PSVT | Severe CHF, unstable angina, recent MI, severe valvular regurgitation, intracardiac shunts, sleep apnea, current methylxanthine or dipyridamole use | Adenosine terminated  acute episodes of PSVT, vs. placebo:  3 mg: 35.2% vs. 8.9%  6 mg 62.3% vs. 10.7%  9 mg: 80.2% vs. 14.3%  12 mg: 91.4% vs. 16.1% | Adenosine caused mild, transient side effects in 36% of pts (flushing, chest pain/pressure, hypotension, dyspnea) | N/A | p<0.0001 | Overall efficacy of adenosine high, especially w/ increasing doses |
| \*DiMarco JP  1990 (114)  [2193560](http://www.ncbi.nlm.nih.gov/pubmed/2193560) | Compare adenosine to verapamil in terminating PSVT | 359 total in both protocols  (n=158) | 6-12 mg adenosine  (n=77) | 5-7.5 mg of verapamil.  (n=81) | PSVT | Severe CHF, unstable angina, recent MI, severe valvular regurgitation, intracardiac shunts, sleep apnea, current methylxanthine or dipyridamole use | Cumulative response rates  Adenosine:  6 mg: 57.4  12 mg: 93.4%  Verapamil:  5 mg: 81.3%  7.5 mg: 91.4% | Adenosine caused mild, transient side effects in 36% of pts | N/A | N/A | Overall efficacy of adenosine is similar to verapamil, but onset of action is more rapid. |
| Henthorn RW  1991 (26)  [1898640](http://www.ncbi.nlm.nih.gov/pubmed/1898640) | Flecainide for treatment of symptomatic PSVT (≥2 episodes) | 34  8-wk crossover (after four episodes of PSVT or end of treatment period) | Flecainide  (n=34) | Placebo  (n=34) | PSVT | Syncope, angina, or transient cerebral events during PSVT,  second or third degree AV block or had CHF (NYHA III-IV) | Freedom from symptomatic PSVT at 60 d:  79% events vs. 15%  (p<0.001)  Flecainide slowed symptomatic PSVT HR to 143±12 bpm from 178 ±12 on placebo in 7 pts who had events in the placebo and flecainide treatment phases  (p<0.02) | Significantly more side effects w/ flecainide (p<0.05) | Flecainide vs. placebo:  Recurrence:  8/34 vs. 29/34 (p<0.001).  Median time to first event: 55 vs. 11 d (p<0.001)  Median interval between episodes  >55 vs. 12  (p<0.001) | N/A | Despite participation  of 19 medical centers, only 34 pts completed  entire protocol and provided analyzable data.  All pts tolerated flecainide, limiting generalizability.  Transtelephonic monitoring does not permit assessment of proarrhythmia  6/34 w/ AVNRT, confirmed by EP study, and 18/34 w/ unknown mechanism. |
| Pritchett EL  1991  (27)  [1899432](http://www.ncbi.nlm.nih.gov/pubmed/?term=pritchett+e%2C+datorre+sd%2C+platt+ml) | Dose-response efficacy of flecainide in patents w/ PSVT, PAF, paroxysmal atrial flutter | 42 | Flecainide given in ascending order (25🡪50🡪100🡪1150 mg twice daily)  PSVT  (n=14, Group 1)  PAF or parosysmal atrial flutter  (n=28, Group 2) | Placebo inserted at random (alternating w/ flecainide) at 30 d intervals | PSVT, PAF, or paroxysmal atrial flutter | Syncope, angina, or transient cerebral events during PSVT,  second or third degree AV block or had CHF (NYHA III-IV) . | Among 14 pts in Group 1 who qualified for efficacy analysis, 4 (29%) had no tachycardia while taking placebo.  Number w/ no tachycardia increased w/ progressively larger flecainide doses; w/ the 150 mg twice daily dose, 12 (86%) of 14 pts had no tachycardia (p<0.01 for overall differences among all treatments). | Noncardiac adverse experiences were leading cause of premature study discontinuation during flecainide treatment periods (5 pts in Group 1 and 6 pts in Group 2). | N/A | N/A | Small sample size, short treatment period. |
| Pritchett EL  1991  (28)  [2001087](http://www.ncbi.nlm.nih.gov/pubmed/2001087) | Oral propafenone to prevent symptomatic PSVT  Randomized, double-blind, placebo-controlled, crossover phase, w/ each treatment period lasting up to 60 d. | 23 | Propafenone (n=23) | Placebo  (n=23) | PSVT  (n=14)    PAF  (n=9) | Angina during tachycardia, pulmonary edema, neurologic  sxs.  PAF w/ WPW syndrome, on AADs | Compared w/ placebo, propafenone caused an increase in time to first recurrence of arrhythmia (p=0.004)  PSVT:  p=0.03  PAF:  p=0.06  . | Cardiac AEs occurred only in pts w/ PAF (9/11): 2 w/ prolonged episode of AF, 1 w/ atrial flutter w/ a mean ventricular  rate of 263 bpm recorded using the telephone monitor. | N/A | N/A | Propafenone efficacious in treating PSVT and PAF.  Major limitation in not knowing how many pts had AVNRT.  . |
| Dougherty AH  1992 (115)  [1510006](http://www.ncbi.nlm.nih.gov.offcampus.lib.washington.edu/pubmed/1510006) | Efficacy and safety of IV diltiazem | 87  AVNRT (n=25)  AVRT (n=60)  AT (n=2) | Diltiazem | Placebo | Induction of PSVT w/ PES, required  to have a rate of 120 bpm and to persist for 115 min. | Pts w/ severe congestive heart  failure, sinus node dysfunction, pregnancy, myocardial  infarction w/in 2 wk of study, or hypotension (SBP <90 mm Hg) | Conversion to sinus rhythm occurred in 4 of 14 pts (29%) w/ 0.05 mg/kg of diltiazem, 16 of 19 (84%) w/ 0.15 mg/kg, 13 of 13 (100%) w/ 0.25 mg/kg, and 14 of 17 (82%) w/ 0.45 mg/kg compared w/ 6 of 24 (25%) treated w/ placebo.  Conversion rates in groups receiving doses of 0.15 to 0.45 mg/kg of diltiazem were superior to that in the placebo group (p<0.001).  Time to conversion was 3.0±2.6 min in responding diltiazem pts compared w/ 5.9±6.1 min in responding control pts. | N/A | Most frequent adverse response to diltiazem was hypotension (7 of 63 pts); however, only 4 pts had sxs related to hypotension. | N/A | IV diltiazem in doses of 0.15, 0.25 and 0.45 mg/kg is effective and safe for acute management of PSVT. |
| Anderson JL  1994 (29)  [8074041](http://www.ncbi.nlm.nih.gov/pubmed/?term=anderson+jl%2C+platt+ml%2C+guarnieri) | Long-term efficacy of flecainide (≥6 mo) | 49  PSVT  (n=21)  PAF  (n=28) | Flecainide | Placebo | Pts enrolled from 3 prior studies evaluating short-term flecainide efficacy (2 above, Pritchett and Henthorn—one [Anderson, 1989]) not tabulated above due to PAF-only population) | Syncope, angina, or transient cerebral events during PSVT,  second or third degree AV block or had CHF (NYHA III-IV) | -Number of pts w/o attacks  -Time to first attack  -Interval between attacks  -Average frequency of attacks,  -Ventricular rate during attacks.  PSVT pts:  Of 17 efficacy evaluable pts, 14 (82%) had no SVT attacks during the chronic efficacy study compared w/ 4 (24%) w/ no attacks during placebo therapy at baseline (p=0.013).  Time to first arrhythmia attack and time between attacks increased  during chronic therapy w/ flecainide compared w/ placebo treatment (p=0.008 and p=0.012, respectively)  Rates of attack/d not significantly different (p=0.130)  No PSVT pts w/ ventricular arrhythmias | No pt experienced  proarrhythmia, MI, or died during chronic efficacy study. | N/A | N/A | Supports flecainide for chronic therapy of PSVT.  Small numbers of pts w/ PSVT, and PSVT not specifically defined. |
| Chimienti M  1995 (30)  [8682031](http://www.ncbi.nlm.nih.gov/pubmed/8682031) | Compare the long-term safety of flecainide and propafenone | 335 | AVNRT:  flecainide 100 mg (n = 72)  PAF:  flecainide 200 mg (n = 97) | AVNRT:  propafenone 450 mg (n=63)  PAF: propafenone 450 mg (n=103). | PAF  (n-200)  AVNRT  (n=135) | LVEF <35%, AV block, QRS >140 msec, SSS, persistent AF (episodes >72 h), VT (episodes >30 sec), NYHA III-IV, ischemic heart disease, hypertrophic cardiomyopathy, hypotension, valvular disease, renal/hepatic insufficiency, thyroid disease, AADs | ITT analysis  PSVT:  93% for flecainide and 86% for propafenone (p=0.24)  PAF:  77% for flecainide and 75% for propafenone (p=0.72) | 12 pts on flecainide reported 16 cardiac AEs, of whom six discontinued the treatment.  7 propafenone pts had 8 cardiac AEs, of whom 5 discontinued the treatment.  (1 case of VT on propafenone  2 cases of AF w/ rapid ventricular response on flecainide | N/A | N/A | Both flecainide and propafenone were safe in the long-term treatment of pts w/ PSVT.  Limited in that only one-third of pts w/ AVNRT. |
| UK Propafenone PSVT Study Group  1995  (31)  [7586356](http://www.ncbi.nlm.nih.gov/pubmed/7586356) | Efficacy and tolerability of propafenone at 600 and 900 mg daily doses (given twice daily).  2 consecutive crossover periods | 100 | Propafenone 300 mg bid  Propafenone 300 mg tid | Placebo | PSVT  (n=52)  PAF  (n=48)  75 pts in low-dose phase:  45 PSVT, 30 PAF  59 pts advanced to high-dose phase:  34 PSVT, 25 PAF  ≥2 symptomatic episodes by transtelephonic monitoring | PSVT w/ hemodynamic collapse, LVEF ≤25%, recent MI or unstable angina; hepatic/renal failure, SSS, AV block, AADs, female pts of childbearing potential, COPD, myasthenia gravis. | Placebo vs. propafenone:  Relative risks, PSVT, low-dose:  Arrhythmia recurrence or AE  6.8 (95% CI: 2.2-21.2; p<0.001)  Arrhythmia recurrence  7.4 (95% CI: 2.3-23.3; p<0.001)  Relative risks, PSVT, high-dose:  Arrhythmia recurrence or AE  2.2 (95% CI: 0.9-5.3; p=NS)  Arrhythmia recurrence  15.0 (95% CI: 2.0-113; p=0.009) | More pts experienced more adverse events during propafenone (900 mg>600 mg). Most common adverse events during PSVT and PAF groups were related to the gastrointestinal and neuropsychiatric systems. Total numbers of adverse events on propafenone were 46 and 56 in the low-dose and high-dose PSVT group and 67 and 74 in the low-dose and high-dose PAF groups, respectively. | 1 episode of wide-complex tachycardia was documented during propafenone therapy | N/A | Propafenone at 600 mg is effective and well tolerated. A larger dose of 900 mg causes more adverse effects but may be more effective in those who can tolerate it.  Sequential design (not randomized after low-dose phase) so population is not generalizable at 900 mg dose.  Not powered for mortality.  Limited in that PSVTs included AVNRT, AT, or AVRT. |
| Wanless RS  1997 (33)  [9124166](http://www.ncbi.nlm.nih.gov/pubmed/?term=wanless+rs%2C+anderson+k) | Sotalol in treatment of PSVT | 126 | Sotalol 80 mg  (n=35)  AVNRT (23%)  Sotalol 160 mg  (n=46)  AVNRT (22%) | Placebo  (n=45)  AVNRT (24%) | Recurrent symptomatic PSVT were eligible for enrollment.  AVNRT  PAF  Paroxysmal atrial flutter  AVRT  Paroxysmal AT | Decompensated CHF, asthma, chronic obstructive airways disease, second degree or third degree AV block, recent myocardial infarction (<1 mo), recent coronary artery bypass graft surgery (<2 mo), unstable angina pectoris, bradycardia (<50 bpm), SSS, prolonged QTc interval (>0.45 sec), systemic hypertension (diastolic pressure >115 mm Hg), electrolyte imbalance, AADs | Time to recurrence of PSVT was less compared w/ placebo when receiving sotalol 80 mg (p=0.04) and sotalol 160 mg (p=0.0009).  On subanalysis, sotalol was shown to be effective in the prophylaxis of both PAF (p=0.03) and paroxysmal reentrant arrhythmias (p=0.0003). | No deaths, cases of ventricular proarrhythmia, CHF. Treatment of pts receiving sotalol were discontinued because of typical BB side effects, including bradycardia, dyspnea, and fatigue. | N/A | N/A | Sotalol efficacious in the prophylaxis of PSVT.  Study limited due to grouping of PSVTs. |
| Gupta A  1999  (35)  [10778689](http://www.ncbi.nlm.nih.gov/pubmed/10778689) | IV diltiazem and esmolol in acute therapy of PSVT | 32 (initially 50 enrolled, but trial stopped early) | Hemodynamically tolerated PSVT | N/A | Two sequential doses w/ a 5 min interval of either drug were administered before crossover. Diltiazem was given in a dose of 0.25 mg/kg while the esmolol dose was 0.5 mg/kg. | N/A | Diltiazem terminated PSVT in all the 16 pts in whom it was given as the first drug. The 12 pts who did not respond to esmolol were also effectively treated w/ diltiazem.  28/28 pts responded to diltiazem while only 4/16 pts responded to esmolol (p<0.001)  Of the 28 pts who responded to diltiazem, in 13 pts the second bolus of diltiazem worked after the first one had failed. | No significant adverse effects were seen. | N/A | N/A | IV diltiazem is highly effective and safe for terminating PSVT. When the first bolus is ineffective, the second bolus given after 5 min usually succeeds. Esmolol in the dose of 0.5 mg/kg has poor efficacy for terminating PSVT, even when 2 boluses are administered. |
| Alboni P  2001 (36)  [11216977](http://www.ncbi.nlm.nih.gov/pubmed/11216977) | Pill-in-the-pocket approach to management of PSVT, well-tolerated | 33 | Flecainide (n=33)  Diltiazem/ propranolol (n=33) | Placebo (n=33) | AVNRT and AVRT confirmed by EP study  Well-tolerated (no sxs of dyspnea, syncope, presyncope, no interference w/ normal activities  Infrequent (≤5 episodes/y) w/ ≥1 ED visit/y  PSVT documented by ECG | Preexcitation, CAD, resting bradycardia <50 bpm, LVEF <50%, h/o HF, severe “general diseases,” recent MI or CVA, acute illness, need for AADs, h/o sustained atrial/ventricular tachyarrhythmias | Conversion to sinus rhythm occurred w/in 2 h in 52%, 61%, and 94% of pts on placebo, flecainide and diltiazem/ propranolol, respectively (p<0.001)  The conversion time was shorter after diltiazem/ propranolol (32±22 min) than after placebo (77±42 min, p<0.001) or flecainide (74± 37 min, p<0.001).  26 pts discharged on diltiazem/ propranolol and 5 on flecainide. During 17±12 mo f/u, treatment successful in 81% of diltiazem/ propranolol pts and in 80% of flecainide pts (all the arrhythmic episodes were interrupted out-of-hospital w/in 2 h). In remaining pts, a failure occurred during ≥1 episodes because of drug ineffectiveness or drug unavailability.  During f/u, the percentage of pts calling for emergency room assistance was significantly reduced as compared to the y before enrollment (9% vs. 100%, p<0.0001). | Four pts (1 placebo, 1 diltiazem/ propranolol, and 2 flecainide) had hypotension and four (3 diltiazem/ propranolol and 1 flecainide) a sinus rate <50 bpm following SVT interruption | N/A | N/A | Use of these agents is efficacious in acute therapy, both w/ in-hospital and outpt therapy. However, only 4/5 pts discharged on flecainide. Complications not trivial and all pts pre-tested w/ EP study. |
| Tendera M  2001  (37)  [11431663](http://www.ncbi.nlm.nih.gov/pubmed/?term=tendera+m%2C+wnuk-wojnar) | Comparison of dofetilide to propafenone and placebo in the prevention of PSVT | 122 | Dofetilide  (n=40)  Propafenone (n=41) | Placebo (n=41) | 18-75 y w/ ≥1 episode of PSVT w/in 6 wk documented by ECG | Pulmonary disease, myasthenia gravis, BBB, resting bradycardia (<50 bpm), AV block, prolonged QTc, MI, unstable angina, recent sudden death, hematologic /hepatic/renal disease | After 6 mo of treatment, pts taking dofetilide, propafenone, and placebo had a 50%, 54%, and 6% probability, respectively, of remaining free of episodes of PSVT (p<.001 for both dofetilide and propafenone vs. placebo).  The hazard ratio for dofetilide vs. placebo was 0.33 (95% CI: 0.18-0.61), and the hazard ratio for propafenone vs. placebo was 0.27 (95% CI: 0.14-0.51).  Of 40 pts treated w/ dofetilide and propafenone, 23 (58%) and 25 (61%) had no recurring PSVT, compared w/ 16 (39%) in placebo group. | 19 of 40 pts (48%) treated w/ dofetilide and 21 of 41 (51%) treated w/ propafenone reported no adverse events.  No significant differences were noted between 3 groups in incidence of treatment-related adverse events or all-cause adverse events (p=0.73 and p=0.74, respectively). | N/A | N/A | Dofetilide is at least as safe and effective as propafenone as an alternative therapeutic option for the treatment of pts w/ PSVT.  Limited in that PSVTs not specified. |
| Catheter Therapy (including cyroablation vs. RFA studies) | | | | | | | | | | | |
| Langberg JJ  1993  (116)  [8491010](http://www.ncbi.nlm.nih.gov/pubmed/8491010) | Slow vs. fast path ablation for AVNRT | 50 | Anterior (n=22)  Up to 1 h or 10 RF applications before alternative technique | Posterior (n=28)  Up to 1 h or 10 RF applications before alternative technique | AVNRT | None stated | Primary success rates, anterior vs. posterior  (55% vs. 68%, p=NS)  All pts who failed initial approach were successfully treated by alternative technique w/o developing high-grade AV block | One pt w/ RBBB during an anterior lesion  One pt w/ complete AV block complete during posterior lesion | N/A | N/A | Posterior (slow path) approach to RF modification of AV node is as effective as the anterior (fast path) approach, and both techniques associated w/ a low risk of complications.  Limiting to 1 h or 10 attempts may underestimate success rates. |
| Kalbfleisch SJ  1994  (117)  [8113557](http://www.ncbi.nlm.nih.gov/pubmed/8113557) | Comparison of anatomic vs. EGM mapping for AVNRT ablation (slow path) | 50 | Anatomic (n=25)  sequential RF energy applications (up to 12) delivered along tricuspid annulus from level of the coronary sinus ostium to His bundle | EGM mapping (n= 25)  Target sites along posteromedial tricuspid annulus near coronary sinus ostium | AVNRT | None stated | Anatomic vs. mapping:  Effective in 84 vs. 100%  (p=0.1)  4 w/ an ineffective anatomic approach had a successful outcome w/ mapping approach | N/A | ITT analysis  Mapping vs. anatomic:  Time required for ablation: (28±21 vs. 31±31 min, p=0.7)  Duration of fluoroscopy:  (27±20 vs. 27±18 min, p=0.9)  Mean number of RF applications:  (6.3±3.9 vs. 7.2±8.0, p=0.6) | N/A | The anatomic and mapping approaches for ablation of the slow AV nodal pathway are comparable in efficacy and duration.  Generalizability limited, and applicable only to technique described (e.g., authors cite not applicable for expanded anatomic approach or an EGM mapping approach that required the presence of a slow pathway potential).  Small sample; probability of detecting a 20% difference in efficacy between two techniques only 0.67. |
| Kopelman HA  2003  (118)  [12633642](http://www.ncbi.nlm.nih.gov/pubmed/?term=kopelman+ha%2C+prater+sp) | Efficiency of conventional fluoroscopic and electroanatomic mapping (CARTO) in guiding catheter ablation of AVNRT | 20 | Electroanatomic mapping  (n=10) | Fluoroscopic mapping  (n=10) | AVNRT | None stated | Electroanatomic vs. fluoroscopy:  Fluoroscopic duration:  12.6±6.8 vs. 35.9±18.3 min, p<0.001  Fluoroscopic exposure (0.7±0.5 vs. 9.6±5.0 min; p<0.001  Total procedure time:  83.6±23.6 vs. 114±19.3 min, p=0.008  Total fluoroscopic exposure:  4.2±1.4 vs. 15.9±-6.4 min, p<0.001  Number of RF applications:  2.7±1.6 vs. 5±2.8, p=0.018,  Duration of RF:  165.3±181.6 vs. 341±177.7 sec, p=0.013  Total energy delivery:  24.3±3.1 vs. 28.7±4.5 watts, p=0.042 | No acute or long-term 8.9±2.2 mo) complications or arrhythmia recurrence in either group | N/A | N/A | Electroanatomic mapping  offers significantly shorter procedure and fluoroscopy times, improving the efficiency of the procedure and reducing X-ray exposure.  Small sample size, curious lack of side effects.  Cost higher w/ electroanatomical mapping catheter, but likely  offset by potential for improved efficiency, pt  throughput and X-ray exposure from reductions in procedure and fluoroscopy times. |
| Kimman GP  2004  (119)  [15589641](http://www.ncbi.nlm.nih.gov/pubmed/15589641) | CA vs. RFA | 63 | CA (n=30) | RFA (n=33) | AVNRT | None stated | Procedural success achieved in 91% RFA and 93% CA | N/A | Median number of CA applications lower than RFA (p<0.005)  Both fluoroscopy and procedural times were comparable | N/A | CA useful for treatment of tachyarrhythmias near the compact AV node.  Questionable whether lack of junctional rhythm is seen w/ CA makes this approach safer than RFA, as authors remark. |
| Zrenner B  2004  (120)  [15589640](http://www.ncbi.nlm.nih.gov/pubmed/15589640) | CA vs. RFA for AVNRT | 200 | CA (n=100) | RFA (n=100) | AVNRT | N/A | Cumulative incidence of primary endpoint (a combination of procedural failure, permanent complete AV block and AVNRT recurrence) higher in the CA group, p=0.03 | Transient AV block was encountered in  18% pts in the CA group and in 8%  in RF group (p<0.04)  21 episodes of transient AV block occurring during cryomapping (n = 4) or CA (n = 17) and 8 episodes during RF applications. The duration of transient AV block ranged from 2-420 s in CA group and from 2-180 s in RF group | Procedural success defined as elimination of slow pathway or noninducibility of AVNRT  CA vs. RFA  97% vs. 98% | N/A | Early pilot study (first prospective randomized investigation comparing  CA w/ RFA of AVNRT) showing CA associated w/ a comparable acute success rate but a higher recurrence rate as compared w/ RFA in pts w/ AVNRT. |
| Kardos A  2007  (121)  [18214124](http://www.ncbi.nlm.nih.gov/pubmed/18214124) | Test the feasibility of cryomapping during AVNRT and AVRT  Note: ablation performed only if cryomapping terminated the tachycardia w/o prolongation of AV conduction | 30  AVNRT n=17  AVRT  n=13  Randomized after dx of AVRT or AVNRT made  9 APS in CA, 4 in RF | CA (n=13 ) | RFA (n=17) | AVNRT or AVRT w/ anteroseptal pathway | AVRT w/ a posteroseptal, left-sided, or right free wall AP | CA vs. RFA  Overall acute success rate:  85 vs. 82.4%, p=0.43 | CA: in one pt, ablation not attempted because of AV prolongation  RFA: two pts w/ temporary second-degree AV block | CA vs. RFA  Long-term success rate (12 mo f/u) similar between the two groups  Fluoroscopy and the procedure time similar (p=0.37 and p=0.14, respectively).  Mean number of applications:  2 (1-6) vs. 7 (1-41), p=0.002 | N/A | First study to assess ICE mapping guided ablation in a prospective randomized method.  Cryomapping a feasible method to determine exact location of APs and of slow pathway during tachycardia.  Cryomapping performed during tachycardia causes less ablation lesions w/o increasing procedure and fluoroscopy times.  Pediatric pts eligible and pts in CA group younger (median age 20 vs. 44).  No control, and arguably 2 groups not comparable because RF not safe during tachycardia when substrate located near AV node.  LocaLisa system used in CA and RF groups, thus improving performance c/w “conventional” RFA. |
| CRYANO Study  2010  (122)  [21098435](http://www.ncbi.nlm.nih.gov/pubmed/21098435) | CA vs. RFA for AVNRT | 509 | CA (n=251) | RFA (n=258) | AVNRT | Prior AVNRT ablation CHD, prior pacemaker implantation, pregnancy, and inability to follow study protocol | Immediate ablation failure, permanent AV block, and AVNRT recurrence during a 6-mo f/u  CA vs. RFA  12.6% vs. 6.3%, p=0.018)  Immediate ablation success: 96.8% vs. 98.4%, p=NS  Permanent AV block:  0% vs. 0.4%, p=NS  AVNRT recurrence:  9.4% vs. 4.4%; P=0.029 | N/A (AV block in primary endpoint) | CA vs. RFA.  Procedure duration  (138±54 vs. 123±48 min, p=0.0012)  Device problems:  13 vs. 2 pts, p=0.033)  Pain perception lower in the cryoablation group. p<0.001 | N/A | CA for AVNRT is as effective as RFA over short term but associated w/ higher recurrence rate at 6-mo f/u.  Risk of permanent AV block does not differ significantly between CA and RFA.  Potential benefits of CA relative to ablation safety and pain perception offset by longer procedure times, more device problems, and a high recurrence rate. |
| Rodriguez-Entem FJ  2013 (123)  [23080326](http://www.ncbi.nlm.nih.gov/pubmed/23080326) | Efficacy of CA vs. RFA | 119 | CA (n=60) | RFA (n=59) | AVNRT | N/A | Acute procedural success achieved in 98% CA group and 59 100% in RFA group | One pt in RFA group underwent complete AV block and pacemaker implantation | CA vs. RFA  Over a mean f/u period of 256.6 d, there was a significant difference in AVNRT recurrence (15 vs. 3.4%, p=0.03). | N/A | CA of AVNRT is a clinically effective alternative to RF ablation, w/ excellent acute success rate.  Despite a slightly higher rate of recurrence during long-term f/u, CA may be considered first-line approach, especially in younger people. |

**\***Two protocols tested in same study.

AAD indicates antiarrhythmic drug; AE, adverse effect; AF, atrial fibrillation; AP, accessory pathway; APS, acute procedureal success; AT, atrial tachycardia; AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; BBB, bundle branch block; bid, two times per day; bpm indicates beats per min; CA, cryoablation; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; c/w, consistent with; ECG, electrocardiogram; ED, emergency department; EGM, electrogram; EP, electrophysiological; f/u, follow up; HF, heart failure; h/o, history of; HR, heart rate; ICE, intracardiac echocardiography; ITT, intention to treat; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; NS, not significant; NSR, normal sinus rhythm; NYHA, New York Heart Association; ORT, orthodromic reciprocating tachycardia; PAF, paroxysmal atrial fibrillation; PES, programmed electrical stimulation; PSVT, paroxysmal supraventricular tachycardia; pt, patient; RBBB, right bundle branch block; RCT, randomized controlled trial; RF, radiofrequency; RFA, radiofrequency ablation; sbp, systolic blood pressure; SDC, serum drug concentration; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; sx, symptom; tid, three times per day; VHD, valvular heart disease; VT, ventricular tachycardia; w/, with; w/o, without; and WPW, Wolff-Parkinson-White syndrome.

Data Supplement 10. Nonrandomized Trials, Observational Studies, and/or Registries of Atrioventricular Nodal Re-Entrant Tachycardia – Section 5

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| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Vagal Maneuvers/Cardioversion | | | | | | |
| Mehta D  1988  (40)  [2897005](http://www.ncbi.nlm.nih.gov/pubmed/?term=mehta+d%2C+wafa+s%2C+ward+de) | Prospective cohort study comparing 4 vagal maneuvers: right CSM, left CSM, face immersion in water, Valsalva maneuver | 35 | AVNRT (n=11)  AVRT (n=24)  EP study to induce SVT by PES  Excluded AADs taken 72 h prior to admission (amiodarone stopped prior to 3 mo), no AADs during admission | Termination of at least 2 of 3 episodes of induced SVT | Vagal maneuvers terminated tachycardia in 22 (63%)  pts.  Valsalva maneuvers  in supine position in 19 pts (54%), right CSM in 6 (17%), left CSM in 2 (5%), and face immersion in 6 (17%). (p<0.001 for difference).  Vagal maneuvers more effective in pts w/ AVRT than AVNRT (79% vs. 27%, p<0.01)  Pts w/ AVRT  terminated by a vagal maneuver were significantly  younger (p<0.001) than those w/ AVRT who did not respond to vagal maneuver; no such age difference seen w/ AVNRT | Valsalva most effective vagal maneuver for terminating PSVT.  Limited in that study conducted during EP study. |
| Wen ZC  1998  (41)  [9851958](http://www.ncbi.nlm.nih.gov/pubmed/9851958) | Prospective cohort study | 133 | AVRT (n=85)  AVNRT (n=48)  EP study to induce PSVT by PES  Excluded atrial flutter, AF organic heart disease or other systemic diseases involving the autonomic function (e.g., diabetes), those who could not blow into an aneroid manometer to maintain a pressure of 35 mm Hg for 20 sec, and those w/ unstable hemodynamics during tachycardia. | Termination of PSVT | Vagal maneuvers more effective in terminating AVRT than AVNRT (53 vs. 33%, p<0.05).  AVNRT: vagal maneuvers terminated tachycardia in antegrade slow pathway (14%) or in retrograde fast pathway (19%).  Baroreflex sensitivity was poorer but isoproterenol sensitivity test better in pts w/ AVNRT. | Vagal maneuvers effective, more so for AVRT.  Limited in that study conducted during EP study. |
| Roth A  2003  (50)  [12586276](http://www.ncbi.nlm.nih.gov/pubmed/12586276) | Prospective cohort study | 84 | PSVT 77%  AF 23% | Effectiveness of DC cardioversion in pts who did not respond promptly to vagal maneuvers that were tried first and then tried again after intravenously administered medical treatment w/ 1 of the following intraveneously administered drugs: adenosine, verapamil, digoxin, and/or procainamide.  All study pts were hemodynamically compromised but did not require cardiopulmonary resuscitation. | DC cardioversion resulted in successful converson to sinus rhythm in all pts after 103 electrical attempts, using 118±69 Joules.  No complications; all but one pt (w/ pulmonary edema and cardiogenic shock) discharged alive w/in 7 d of hospitalization. | **Use of DC cardioversion to restore sinus rhythm can be safely and efficaciously applied in the prehospital setting in pts who are hemodynamically compromised but do not require cardiopulmonary resuscitation.** |
| Pharmacological Therapy | | | | | | |
| Rinkenberger RL  1980  (124)  [7418184](http://www.ncbi.nlm.nih.gov/pubmed/7418184) | Prospective cohort study | 28 | AVNRT (n=6)  AVRT (n=6)  AF/atrial flutter (15)  AT(n=3) | Effect of IV and oral verapamil | IV verapamil terminated AVNRT in all 6 pts  Oral verapamil given to 19/28 pts, 7 reported improvement in sxs after 19 mo f/u (shorter frequency and shorter duration) | IV verapamil effective in acute termination, while oral verapamil has selective efficacy. |
| Das G  1988  (125)  [2905710](http://www.ncbi.nlm.nih.gov/pubmed/?term=das+g%2C+Tschida) | Prospective cohort study | 113 | Pts w/ PSVT (HR >100). | Efficacy and safety of esmolol. Also investigated feasibility of transferring pts from esmolol to alternate oral AADs w/o loss of therapeutic response. | 95 (84%) achieved therapeutic response (reduction in heart rate of 15% or more or conversion to sinus rhythm). 93% achieved therapeutic response at esmolol doses of 200 micrograms/kg/min or lower.  (88%) pts successfully transferred to oral AADs.  Most frequent adverse effect observed during the study was hypotension, which resolved quickly (16±14 min) | Esmolol effective in HR reduction or convertion to NSR, and majority of pts successfully treated w/ esmolol can be safely and effectively transferred to oral AADs. |
| Rankin AC  1989  (43)  [2789911](http://www.ncbi.nlm.nih.gov/pubmed/2789911) | Cohort study | 64 | 94 episodes of sustained, regular tachycardia; 40 pts w/ 64 episodes of narrow complex tachycardia (9 induced at EP study) | Efficacy of IV adenosine | Adenosine restored sinus rhythm in 25 pts 46/48 pts) w/ “junctional tachycardia,” found to be due to AVRT or AVNRT | Not specific for AVNRT (defined AVRT and AVNRT as “junctional tachycardia” |
| Amsterdam EA  1991  (126)  [1880230](http://www.ncbi.nlm.nih.gov.offcampus.lib.washington.edu/pubmed/?term=amsterdam+ea%2C+kulcyski) | Prospective cohort study | 16 | AF (n=11)  Atrial flutter (n=2)  PSVT (n=2)  MAT (n=1) | In 13 responders (81%), mean ventricular rate decreased from 134±6 to 106±7 bpm 10 min after metoprolol administration and controlled for 40-320 min w/o further therapy.  Metoprolol reduced ventricular rate by >15% in 11 (69%) of 16 pts, including 9 (82%) of 11 pts w/ AF. In one w/ AF and one w/ PSVT, ventricular rate was reduced by >12% | Hypotension, occurring in five pts, was the most frequent side effect but was transient and readily managed. | Metoprolol was rapidly effective in controlling ventricular rate in a majority of pts w/ supraventricular tachyarrhythmias. Limited data for AVNRT. |
| Cairns CB  1991  (44)  [2064090](http://www.ncbi.nlm.nih.gov/pubmed/2064090) | Observational cohort | 23 | Conversion to SR  16 y or older presenting to ED in an 8 mo study period w/ sustained SVT, rate >140 bpm  Exclusion: severe CHF, unstable angina, acute MI by ECG, hemodynamic compromise. Excluded sinus tachycardia, atrial flutter, AF, QRS >140 ms | Adenosine to convert SR in ED setting | 2 pts after adenosine identified as not having SVT (atrial flutter, VT)  24 episodes of SVT in 21 pts of which 96% converted w/ adenosine (mean dose 10±6 mg)  SVT recurred in 57% of episodes and other antiarrhythmic drugs then used to maintain SR.  Adverse effects: 3 pts w/ chest pain, one pt w/ dyspnea but no adverse outcome | Adenosine highly effective in converted SVT but recurrences frequent |
| Musto B  1992  (127)  [1615792](http://www.ncbi.nlm.nih.gov/pubmed/1615792) | Prospective cohort study | 35  9 pts w/ AVNRT (Age 10-23) | Recurrent PSVT documented by ECG; no h/o VT or AF, well-tolerated PSVT not induced by stress  9 total pts w/ AVNRT, remainder w/ AVRT | Termination of PSVT by flecainide. | PSVT terminated in 6/9. | Pts prescreened w/ EP study. Non-randomized study, and limited number of pts w/ AVNRT. |
| Gambhir DS  1995  (128)  [7558090](http://www.ncbi.nlm.nih.gov/pubmed/7558090) | Prospective cohort study | 26 | All pts w/ symptomatic PSVT, recurrent palpitations for 1-13 y  EP study performed, IV flecainide given and then EP study repeated 20-30 min later w/ IV flecainide | Effective in terminating all pts w/ AVNRT, 11/12 w/ AVRT  Time to termination both similar (146±70 vs. 149±29 sec, AVNRT vs. AVRT)  AVNRT reinducible in one pt w/ AVNRT, 4 pts w/ AVRT  Selective depression of retrograde limb | N/A | IV flecainide effective and safe for acute episodes of AVNRT and AVRT  Oral therapy presumed to be effective given effects in preventing reinducibility.  EP study efficacy. |
| Gambhir DS  1996  (54)  [8682552](http://www.ncbi.nlm.nih.gov/pubmed/8682552) | Prospective cohort study | 9 | All pts w/ symptomatic AVNRT, recurrent palpitations for 2-12 y EP study performed, IV amiodarone then oral therapy subsequently EP study repeated 1.5-3 mo later | No pts reported sxs of tachycardia during mean f/u of 65 d on oral amiodarone  IV amiodarone terminated AVNRT in 7/9 pts (retrograde FP in 4/7 and anterograde SP in 3/7)  Not inducible on PES after oral therapy, largely to due to prolonging refractoriness in atrium and ventricle, and depressing conduction through FP | N/A | Small series of pts, but all w/ AVNRT  Oral therapy w/ amiodarone is effective in suppressing AVNRT.  IV amiodarone is effective in acute therapy.  EP study efficacy. |
| Glatter KA  1999  (129)  [10051297](http://www.ncbi.nlm.nih.gov/pubmed/?term=glatter+ka%2C+cheng+jie) | Retrospective cohort study | 229 | PSVT during EP study  AVRT (n=59)  Typical AVNRT (n=82)  Artypical AVNRT (n=13)  PJRT (n=12)  AT (n=53)  IST (n=10) | Determining the mechanism of PSVT w/ adenosine response | Adenosine of limited value in determining mechanism of PSVT  100% of pts w/ AVNRT, AVRT, atypical AVNRT, and PJRT terminated w/ adenosine | N/A |
| Ablation | | | | | | |
| Jackman WM  1992  (53)  [1620170](http://www.ncbi.nlm.nih.gov/pubmed/1620170) | Prospective observational cohort | 80 | Symptomatic AVNRT undergoing RFA of slow-pathway | Successful ablation w/ intact AV nodal conduction, guided by atrial slow-path potentials | RFA abolished or modified slow-pathway conduction in 78/80 pts w/o affecting normal AVN conduction. Mean (±SD) f/u of 15.5 mo w/o recurrence. | Early report of success of RFA of slow-path conduction guided by atrial slow-path potentials—led to slow-pathway ablation being preferred method. Provided evidence that atrial insertions of fast and slow path are anatomically distinct. |
| Kay GN  1992  (130)  [1572026](http://www.ncbi.nlm.nih.gov/pubmed/1572026) | Prospective observational cohort | 34 | Slow pathway ablation (n=30)  Fast pathway ablation (n=4) | Antegrade conduction over the fast pathway remained intact in all 30 pts after successful selective slow pathway ablation  There was no statistically significant change in the atrio-His interval (68.5±21.8 msec before and 69.6±23.9 msec after ablation) or AV Wenckebach rate (167±27 beats per min before and 178±50 beats per min after ablation) after slow path ablation | 3 complications in two pts, including an episode of pulmonary edema and the development of spontaneous AV Wenckebach block during sleep in one pt after slow pathway ablation and the late development of complete AV block in another pt after fast pathway ablation. Over a mean f/u period of 322±73 d, AVNRT recurred in three pts, all of whom were successfully treated w/ a second ablation. | Early report suggesting benefits of slow pathway ablation over fast pathway ablation. |
| Bogun F  1996  (131)  [8837581](http://www.ncbi.nlm.nih.gov/pubmed/8837581) | Prospective observational cohort | 7 w/ noninducible AVNRT compared w/ 34 w/ inducible AVNRT | Spontaneous but noninducible AVNRT (w/ evidence of dual AV nodal physiology at EP study) | All evidence of dual AV node pathways was eliminated in six pts, and dual AV node physiology remained present in one pt.  During a mean f/u period of 15±10 mo (range 8 to 27), no pt had a recurrence of symptomatic tachycardia (success rate 95%). | N/A | Slow pathway ablation may be clinically useful in pts w/ documented but noninducible PSVT who have evidence of dual AV node pathways  First recommendation that slow pathway ablation be indicated in pts w/ spontaneous PSVT w/ dual AV node physiology but noninducible PSVT in EP study.  Small sample size. |
| D’Este D  2005  (132)  [16814416](http://www.ncbi.nlm.nih.gov/pubmed/16814416) | Prospective cohort study | 93 | Pts w/ AVNRT prospectively followed for mean 13.2 y, compare outcomes of ablation (n=18) vs. AADs (n=24) vs. no therapy (n=38)  AADs: flecainide, propafenone, verapamil, sotalol, atenolol, diltiazem | At f/u, asymptomatic for 3 y:  Ablation: 100%  AADs: 60.8%  No therapy: 44.7%  Untreated pts who became asymptomatic had a shorter duration of sxs before enrolment (3.7±1.5 vs. 7.1±3.6 y, p<0.05) and a shorter mean length of tachycardia episodes (3.8±2.4 vs. 42.6±17.8 min, p<0.02) than pts from same group who remained symptomatic | 3 pts died, 10 lost to f/u | During a long-term f/u a considerable number of untreated pts w/ AVNRT become asymptomatic.  Suggests that pts w/ infrequent and minor sxs may be able to be treated conservatively (i.e., no ablation or AADs.  Study directly evaluates AVNRT and suggests efficacy of ablation over AADs.  Limitations that the results are sx based. |
| Spector P  2009  (55)  [19699343](http://www.ncbi.nlm.nih.gov/pubmed/19699343) | Systematic review and meta-analysis to evaluate the safety and efficacy of RFA of AVNRT, AP-mediated, and atrial flutter. | For AVNRT and AP-mediated: 39 primary studies w/ 49 treatment arms in 7,693 pts | Previous reviews or meta-analyses; animal or in vitro studies; subjects aged <18 y or mixed populations of which >15% were pediatric pts; f/u of <7 d; not studies of RFA; alternative energy sources used for ablation; AV junction ablation w/ pacemaker implantation; <40 pts per arrhythmia or ablation technique; published only in abstract form; published before 1990; and published in languages other than English, Spanish, French, Italian, German, and Portuguese. | SVT (AVNRT and AP-mediated)  Single- and multiple-procedure success, arrhythmia recurrence, repeat ablation, adverse events, and death | Single-procedure success: 93.2%  (95% CI: 90.8-95.5%).  Multiple-procedure success: 94.6%  (95% CI: 92.4- 96.9).  Post-ablation arrhythmia: 5.6%  (95% CI: 4.1-7.2%).  Repeat ablation: 6.5% (95% C:I 4.7-8.3%)  All-cause mortality: 0.1%  Adverse events: 2.9% | First meta-analysis of RFA for AVNRT, AVRT (AP-mediated).  Demonstrates high efficacy rates and low rates of complications. |
| Outcomes (Registry Data) | | | | | | |
| Hindricks G  1993  (57)  [8131762](http://www.ncbi.nlm.nih.gov/pubmed/?term=8131762) | Prospective cohort | 4398 | AT/atrial flutter (n=141, 3.2%)  AVJ (n=900, 20.5%)  AVNRT (n=815, 18.5%)  AVRT: (n = 2222, 50.5%)  VT (n=320, 7.3%). | Incidence of complications | Complications occurred in 223 pts (5.1%) overall  AT/atrial flutter: 5.0%  AVJ: 3.2%  AVNRT: 8.0%  AVRT: 4.4%  VT: 7.5%  Complications more in AVNRT RFA compared to AVJ or AP ablation (p<0.001)  Complications more in VT compared to AVJ (p<0.002) or AP (p<0.02) | Early report showing high incidence of complications after AVNRT ablation. |
| Hindricks G  1996  (58)  [8682135](http://www.ncbi.nlm.nih.gov/pubmed/8682135) | Prospective cohort | 4463 | AVNRT (n=880) | Incidence of AV block | AV block (4/ 880, 4.7%).  AV block higher in fast pathway ablation (19/361, 5.3%, p<0.05)  6.3% in centers w/ limited experience in RFA (≤30 pts treated, p<0.05), and higher in these low-volume centers for both slow and fast pathway ablation (p<0.05) | Early report showing 5% incidence of AV block after RFA for AVNRT, and higher w/ fast pathway ablation. |
| Calkins H  1999  (59)  [9892593](http://www.ncbi.nlm.nih.gov/pubmed/9892593) | Prospective cohort | 1050  (previously enrolled in RFA clinical trial) | RFA of AVNRT, AP, or AVJ  AVNRT (n=373)  AP (n=500)  AVJ (n=121) | Efficacy and safety of RFA w/ long-term f/u. | Overall success:  95%  Overall recurrence  6%  Success:  AVNRT: 97%  AP: 93%  AVJ: 100%  Recurrence:  AVNRT: 5%  AP: 8%  AVJ: 2%  Predictors of success:  -AVNRT  OR: 3.94 (95% CI: 1.93-8.04; p=0.0002)  -Left free wall AP  OR: 3.09 (95% CI: 1.46-6.53; p=0.0003)  -Experience of ablation center (>39 pts)  OR: 2.39 (95% CI: 1.21-4.71; p=0.012)  Joint predictors of mortality:  -EF (p=0.003)  -SHD (p=0.016)  -AVJ ablation (p=0.048) | Shows RFA is a favorable option w/ low risk of complications and recurrence, and identifies pts who are at risk. Per-protocol analysis |
| Scheinman MM  2000  (61)  [10879389](http://www.ncbi.nlm.nih.gov/pubmed/10879389) | Prospective cohort study  (NASPE registry) | 3,357 | Ablation of AVNRT, AP, AVJ, atrial flutter, AT, IST, VT, idiopathic VT  AVNRT (n=1,197 [35.6%)  AVJ (n=646)  AP (n=654)  AT (n=216)  Atrial flutter (n=447)  IST (n=40) | Efficacy and safety of RFA w/ long-term f/u. | AVNRT  Success: 96.1%  Complications: 2%  AVJ:  Success: 96%  Complications: 25 pts  Recurrence: 3.5%  AP:  Success: 94-96%  Complications: 31 pts total  Recurrence: 4.6%  AT:  Success: 51-79%  Complications: 5 total  Recurrence: 15.2%  Atrial flutter:  Success: 86%  Complications: 12 pts  Recurrence: 14.7%  IST:  Success: 71%  Complications: 2 pts  Recurrence: 10% | Large series reporting success of RFA, and stratification by age group confirms safety and efficacy in elderly pts, as well as by type of facility (teaching vs. community). |
| Special Ablation Techniques | | | | | | |
| Friedman PL  2004  (133)  [15851143](http://www.ncbi.nlm.nih.gov/pubmed/?term=friedman+pl%2C+dubuc+m%2C+green+ms) | Multicenter prospective study | 157  (166 initially enrolled) | AVNRT (n=101)  AVRT (n=44) AF (n=12) | Efficacy of cryomapping/ablation | Acute success overall 83%  Success in AVNRT 91%, 69% AVRT and 67% AVJ (p<0.001)  Per-protocol:  Success in AVNRT 93%, 77% for AVRT and 67% for AVJ  Long-term success after 6 mo 91% overall, 94% for AVNRT  Cryomapping successfully identified ablation targets in 64% of pts, effects completely reversible w/in minutes in 94% of attempts | Acute success lower for CA compared to studies in RFA, but w/ no difference in long-term outcomes or arrhythmia recurrence.  Later reports show improved success. |
| de Sisti A  2011  (134)  [22017562](http://www.ncbi.nlm.nih.gov/pubmed/22017562) | Systematic review | 22 studies w/ 2,654 pts | Cryoablation for AVNRT compared to RFA | Overall success 95% (95% CI: 85-99%), but recurrence rate 11% (95% CI: 2-20%). RFA recurrence rate reported at 3-5%. | N/A | Cryoablation effective and safe, but lower long-term clinical efficacy compared to RFA. |
| Hanninen M  2013  (135)  [24016223](http://www.ncbi.nlm.nih.gov/pubmed/?term=hanninen+m%2C+yeung) | Systematic review and meta-analysis | 14 studies (5 RCTs), 5,617 pts (1990-2012). 3 studies pediatric | Pts w/ AVNRT treated w/ cryoablation vs. RFA (81%) | AVNRT recurrence (>2 mo post procedure; acute procedural failure and AV block requiring pacing | Acute failure w/ cryoablation was nonsignificantly slightly higher than w/ RFA (RR: 1.44; p=0.12).  Long-term recurrence higher w/ cryoablation (RR: 3.66; p=0.0002)  RFA associated w/ permanent AV block in 0.75% of pts, none w/ cryoablation (p=0.01). | Although late-recurrence more common w/ cryoablation than w/ RFA, avoidance of permanent AV block is advantageous |
| Santangeli P  2014  (136)  [24293174](http://www.ncbi.nlm.nih.gov/pubmed/24293174) | Systematic review and meta-analysis | 14 studies (9 observational) w/ 2,340 pts (1980-2013) | Pts w/ AVNRT treated w/ CA (54%) vs. RFA (46%) | Successful ablation, procedural time, fluoroscopy time, complications | Acute success in 88% w/ RFA, vs. 83% treated w/ CA (OR: 0.72; p=0.16)  RFA associated w/ shorter total procedure time (p=0.004), but slightly longer fluoroscopy time (p=0.002).  Permanent AV block occurred in 0.9% RF case, none in CA cases (OR: 3.60; p=0.035).  Freedom from recurrent AVNRT (10.5 mo median f/u) 97% in RF group vs. 90.9% in the CA group (OR: 0.40; p< 0.001). | RF significantly reduces the risk of long-term arrhythmia recurrence compared to cryoablation, but is associated w/ a higher risk of permanent AV block. No significant difference in acute success. |

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; AVJ, atrioventricular junction; AVN, atrioventricular node; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; bpm, beats per min; CA, cryoablation; CHF, congestive heart failure; CSM, carotid sinus massage; DC, direct current; ECG, electrocardiogram; ED, emergency department; EF, ejection fraction; EP, electrophysiological; FP, fast pathway; f/u, follow up; HR, heart rate; IST, inappropriate sinus tachycardia; IV, intravenous; MAT, multifocal atrial tachycardia; N/A, not applicable; NASPE, North American Society of Pacing and Electrophysiology; OR, odds ratio; PES, programmed electrical stimulation; PJRT, permanent junctional reciprocating tachycardia; PSVT, paroxysmal supraventricular tachycardia; pt, patient; RFA, radiofrequency ablation; RR, relative risk; SD, standard deviation; SHD, structural heart disease; SP, slow pathway; SR, sinus rhythm; SVT, supraventricular tachycardia; sx, symptom; VT, ventricular tachycardia; w/, with; and w/o, without.

Data Supplement 11. Randomized Trials Comparing Manifest and Concealed Accessory Pathways – Section 6.1

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Name, Author, Year** | **Aim of Study** | **Study Type (Size, N)** | **Study Intervention Group (n)** | **Study Comparator Group (n)** | **Pt Population** | | **Endpoints** | | | **P Values, OR: HR: RR: & 95% CI:** | **Study Limitations & Adverse Events** |
|  |  |  |  |  | ***Inclusion Criteria*** | ***Exclusion Criteria*** | ***Primary Endpoint (efficacy) and Results*** | ***Safety Endpoint and Results*** | ***Secondary Endpoint and Results*** |  |  |
| Henthorn RW 1991  (26)  [1898640](http://www.ncbi.nlm.nih.gov/pubmed/?term=1898640) | Double blind placebo controlled crossover trial of flecainide | 34 pts | 8 wk on flecainide | 8 wk on placebo | 13 w/ AVRT  7 w/ AVNRT  3 w/ AT  28 unknown | Syncopy, angina, and/or neurological sxs during tachycardia. Second or third degree AV block. NYHA CHF class III, IV | Flecainide superior to placebo. Flecainide associated w/ 79% freedom from PSVT and placebo 15% p<0.001. Median time to 1st PSVT 11 d in placebo group and 55 d in flecainide group. Flecainide slowed PSVT to 143±12 bpm from 178±12 bpm on placebo. | Side effects: flec 63% and placebo 36%. All not significant. | Flecainide was well tolerated. | Flecainide associated w/ 79% freedom from PSVT and placebo 15% p<0.001. Median time to 1st PSVT 11 d in placebo group and 55 d in flecainide group. Flecainide slowed PSVT to 143±12 bpm from 178±12 bpm on placebo. Side effects on flec 63% and placebo 36%. All not significant. | Study period was brief |
| Pritchett EL  1991  (28)  [2001087](http://www.ncbi.nlm.nih.gov/pubmed/?term=2001087) | Double blind placebo controlled crossover trial of propafenone | 33 pts | 60 d on propafenone | 60 d on propafenone | 16 pts w/ PSVT and 17 w/ PAF. Not clear number of AP | NYHA class III or IV HF. Second or third degree AV block. Sxs of syncope, angina, neurological events during tachycardia. | Well-designed study showing propafenone superior to placebo. Propafenone prolonged the recurrence rate of arrhythmia and was 20% the recurrence rate of placebo. | No serious side effects | N/A | Time to first recurrence prolonged for the propafenone group, p=0.004. | The study was brief and not clear how many AP pts studied. |
| UK Propafenone Study Group 1995  (31)  [7586356](http://www.ncbi.nlm.nih.gov/pubmed/?term=7586356) | Double blind, placebo controlled study of propafenone | 100 pts | Propafenone | Placebo | PSVT 52 pts  AF 48 pts  Unclear if any AP pts | Documented second or third degree AV block. Class III or IV HF. Sxs of syncope, angina, during tachycardia | Arrhythmia recurrence. Relative risk of treatment failure for placebo compared to propafenone was 6.8 (95% CI: 2.2-21.2; p<0.001; n=45) for PSVT and 6.0 (95% CI: 1.8-20.0; p=0.004) for AF. | One episode of wide QRS tachy. | Not applicable | Relative risk of treatment failure for placebo compared to propafenone was 6.8 (95% CI: 2.2-21.2; p<0.001; n=45) for PSVT and 6.0 (95% CI: 1.8-20.0; p=0.004) for AF. | Unusual study design. |
| Dorian P  1996  (32)  [8607397](http://www.ncbi.nlm.nih.gov/pubmed/8607397?dopt=Citation) | Randomized multicenter study of verapamil vs. flecainide for treatment of PSVT | 121 pts | Verapamil | Flecainide | 63 pts on flecainide and 58 verapamil.  Followed for 8.1±5.1 and 7.5±5.4 mo, respectively. | Prior AF, atrial flutter, myocardial infarction, unstable angina. NYHA Class III or IV CHF. Second or third degree AV block. | 86% of flecainide pt-mo and 73% of verapamil pt-mos w/ 0 or 1 episode of PSVT. | N/A | N/A | 30% on flecainide and 13% on verapamil were free of PSVT (p=0.026) | Flecainide and verapamil were moderately effective for the prevention of PSVT. |

AF indicates atrial fibrillation; AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; bpm, beats per min; CHF, congestive heart failure; CI, confidence interval; HF, heart failure; N/A, not applicable; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; pt, patient; sx, symptom; and w/, with.

Data Supplement 12. Nonrandomized Trials, Observations Studies, and/or Registires of Manifest and Concealed Accessory Pathways – Section 6.1

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Risk Stratification of Symptomatic Patients with Manifest Pathways | | | | | | |
| Klein GJ  1979  (137)  [492252](http://www.ncbi.nlm.nih.gov/pubmed/?term=492252) | Observational study of pts w/ WPW and VF | 25 | 25 WPW pts w/ VF compared to 73 pts w/o | Comparing EP findings | Pts w/ WPW and VF had higher prevalence of AVRT (14/25 vs. 18/73, p=0.004) and multiple APs (5/25 vs. 4/73; p=0.012). The shortest preexcited RR was less in VF pts (mean RR 180 vs. 240 msec; p<0.0001) as was the mean RR (mean 269 vs. 340 msec; p<0.0001). | WPW pts w/ h/o VF had more rapid AF (mean RR 180 msec) and increased prevalence of AVRT and multiple APs compared to control. |
| Rinne E  1987  (138)  [3630940](http://www.ncbi.nlm.nih.gov/pubmed/?term=3630940) | Observational study of clinical vs. induced rhythms | 126 | WPW pts w/ clinical AVRT and AF | Relation between clinical and induced arrhythmias | The shortest RR of clinical AF compared w/ the induced AF (r=0.72; p<0.00001). AVRT CL was similar (r=0.79; p<0.00001). 41% of pts w/ clinical AVRT had AF induced w/ shortest RR <250 msec. | There was good reproducibility between clinical and induced AF and AVRT. Clinical AVRT pts were at high risk for rapid AF at EP study. |
| Sharma AD  1987  (139)  [3598007](http://www.ncbi.nlm.nih.gov/pubmed/?term=3598007) | Observational study comparing noninvasive and EP study | 67 | WPW pts w/ noninvasive and EP testing | Comparing findings of noninvasive tests and EP tests. | EP study (AF w/ shortest RR<250 msec) identified 7/9 pts w/ clinical VF. Continuous preexcitation during exercise testing had a sensitivity of 80%, specificity of 28.6% and predictive accuracy of 11.8%. | EP testing was more accurate than stress testing in predicting WPW pts at risk for VF. Stess testing had high sensitivity. |
| Gaita F  1989  (140)  [2773792](http://www.ncbi.nlm.nih.gov/pubmed/?term=2773792) | Observational study of accuracy of noninvasive tests | 65 | Consecutive WPW pts studied w/ procainamide, stress testing and EP. 15 pts were asymptomatic; 50 had sxs. | Comparison of noninvasive tests to EP findings. | 24 pts had high risk AF (shortest RR <250 msec, AP ERP<250 msec). Persistence of the delta wave during stress testing has a sens of 96%, spec of 17% to identify high-risk pts (PPV 40% and NPV 88%). | Stress tests and IV procainamide tests had good sensitivity and NPV but low specificity and PPV for identifying high risk WPW pts |
| Beckman KJ  1990  (141)  [2303633](http://www.ncbi.nlm.nih.gov/pubmed/?term=2303633) | Observational study of ability of EP study to predict arrhythmic events | 42 | WPW pts w/ no sxs up to clinical AVRT/AF. | Assessing if EP findings predicted clinical events | During a f/u of 7.5±4.9 y, showed the only variables that correlated w/ subsequent arrhythmia were h/o documented arrhythmias before EP study (p<0.01) and inducible AVRT at EP study (p<0.05). | H/o arrhythmia and inducible arrhythmia predict subsequent events. |
| Pappone C  2012  (142)  [22215859](http://www.ncbi.nlm.nih.gov/pubmed/?term=22215859) | Observational study identifying risk factors in symptomatic WPW pts | 369 | WPW pts followed to assess predictive factors from EP study | Evaluate the predictors of malignant rhythms | Mean f/u 42.1±10 mo. 29 pts w/ malignant arrhythmias, 168 asymptomatic on f/u, 172 w/ AVRT/AF. Malignant arrhythmia pts had shorter AP ERP (p<0.001), AVRT triggering AF (p<0.001), and multiple APs. | Short AP ERP, AVRT triggering AF, were independent predictors of malignant arrhythmias. |
| Spar DS  2012  (143)  [22221954](http://www.ncbi.nlm.nih.gov/pubmed/?term=22221954) | Observational study of the utility of exercise testing | 76 pediatric pts <22 y. | WPW pts w/ exercise and EP testing | Exercise test results compared to EP findings | 11 pts w/ sudden loss of delta, 18 gradual, and 47 no loss during exercise. Of pts w/ 1:1 AP conduction <270 msec, none in sudden loss group and 18 in no loss group. Pts in gradual loss group more likely to have a left sided AP. | Pts w/ sudden loss of preexcitation during exercise had longer 1:1 conduction when the AP blocked and none had 1:1 over the AP <270 msec. |
| Wackel P  2012  (144)  [22978820](http://www.ncbi.nlm.nih.gov/pubmed/?term=22978820) | Observational study of long term f/u of noninvasive tests | 24 pediatric pts <22 y | WPW pts w/ Holter, stress test, ECG and EP | Noninvasive test results compared to EP findings | 24 pts w/ at least one noninvasive test showing loss of preexcitation. 2 of the 24 had rapid AP conduction (1:1 over AP <260 msec). The noninvasive tests had a PPV of 92% and a NPV of 31%. 16 of 24 had loss of delta during stress test and none of those had rapid conduction at EP. | Small study showed loss of preexcitation during noninvasive testing had a high PPV and specificity for slow AP conduction during EP. |
| Pappone C  2014  (145)  [25052405](http://www.ncbi.nlm.nih.gov/pubmed/?term=25052405) | Prospective single center registry of WPW pts | 2169 pts | All pts w/ a manifest AP underwent EP study±RF. Followed 8 y | Both asymptomatic and symptomatic pts studied at EP to identify risk factors for VF | 1001 pts (550 asymptomatic) did not undergo RF and 1168 (550 asymptomatic) underwent RF. F/u of 8 y. VF occurred in 1.5% of the no-RF group (mean age 11 y) and no VF occurred in the RF treated group (p<0.001). VF was associated w/ a short ERP of the AP w/ an optimal cut-off of 240 msec (p<0.001) and AVRT initiating AF (p<0.001). | Large single center registry showing that EP findings identified pts w/ a manifest AP at high risk for VF and the risk was eliminated w/ ablation. |
| Acute Treatment | | | | | | |
| Sellers TD  1977  (146)  [872319](http://www.ncbi.nlm.nih.gov/pubmed/872319) | Acute EP study of IV digitalis effects on AF in WPW | 21 pts | WPW pts w/ AF induced during EP study and given IV digitalis | Safety for AF in WPW | Digitalis shortened the CL of the shortest preexcited RR in 6/21 pts increased the CL in 7/21 pts and had no effect in 5/21. Digitalis directly related to onset of AF degenerating to VF in 9/21 pts. Each of these 9 had a shortest RR <230 msec during AF baseline. | This study is old but highlights the risk of digitalis in WPW pts w/ AF |
| Sellers TD  1977  (147)  [830205](http://www.ncbi.nlm.nih.gov/pubmed/?term=830205) | Single center study of IV procainamide and quinidine in WPS pts w/ induced | 33 pts | All pts w/ a manifest AP and induced AF | IV procainamide studied to assess effects on conduction during AF | IV procainamide prolonged the shortest RR between preexcited complexes during AF by 20-70 msec in 15 of 21 pts and no change in 6 pts. | IV procainamide prolonged the shortest RR between preexcited complexes in induced AF |
| Hamer A  1981  (148)  [7223599](http://www.ncbi.nlm.nih.gov/pubmed/?term=7223599) | Single center study of IV verapamil in pts w/ AVRT | 19 pts | All pts had AVRT: 12 w/ a manifest and 7 w/ a concealed AP | lV verapamil to assess EP changes and effects on AVRT | IV verapamil prolonged refractoriness and delayed conduction in the AV node but no effect on the AP. Sustained AVRT initiated in 15 pts and terminated by verapamil in 13 pts. | IV verapamil was effective in terminating AVRT |
| Hombach V  1981  (149)  [7206601](http://www.ncbi.nlm.nih.gov/pubmed/?term=7206601) | Acute EP study of IV atenolol for treatment of induced PSVT | 18 pts | Mixed group: 5 w/ AVRT, 2 w/ AVNRT, 6 w/ atrial flutter, 6 w/ AT, 1 w/ VT | IV atenolol given for treatment of induced PSVT | Atenolol was effective in preventing pacing induced AVRT in 3 of 5 pts w/ WPW. | Small study published in Klin Wochenschr showing IV atenolol prevented reinduction of AVRT in 3 of 5 pts. |
| Scheinman BD  1982  (150)  [6812745](http://www.ncbi.nlm.nih.gov/pubmed/?term=6812745) | Case report | 1 pt | WPW pt w/ AF | IV amiodarone given to treat AF | The ventricular rate during AF increased from 170 to 230 bpm | IV amiodarone accelerated the rate of AF in a pt w/ WPW |
| Morady F, et al., 1987  (151)  [2439997](http://www.ncbi.nlm.nih.gov/pubmed/?term=2439997) | Observational study of IV propranolol administered during AF | 10 pts | All pts w/ preexcited AF. | The effects of IV propranolol during preexcited AF were assessed. | AF terminated in 3 of the 10 pts. The mean ventricular rate during preexcited AF was slowed by 15-56 bpm in 6 pts; no effect in 3 pts; and increased from 203 to 267 bpm in 1 pt. | The authors concluded that IV propranolol should not be used in pts w/ preexcited AF if most QRS complexes are preexcited. |
| Schutzenberger W, et al., 1987  (152)  [3610399](http://www.ncbi.nlm.nih.gov/pubmed/?term=3610399) | Case report | 1 pt | WPW pt w/ AF | IV amiodarone given to treat AF | IV amiodarone accelerated the rate of preexcited AF | IV amiodarone accelerated the rate of AF in a pt w/ WPW |
| Huycke EC  1989  (153)  [2918157](http://www.ncbi.nlm.nih.gov/pubmed/0002918157) | IV Diltiazem vs. placebo for the termination of PSVT | 54 pts | 20 pts AVNRT  34 pts AVRT (19 pts w/ manifest and 15 w/ concealed APs) | Safety and efficacy for termination of AVNRT and AVRT | PSVT terminated in 90% of pts w/ diltiazem and 19% w/ placebo. 100% of AVNRT pts converted and 81% of AVRT pts converted.  Side effects: adverse effects in 6%. | IV diltiazem is safe and effective for treatment of AVRT |
| DiMarco JP  1990  (114)  [2193560](http://www.ncbi.nlm.nih.gov/pubmed/?term=2193560) | Placebo controlled study of the acute treatment of PSVT w/ adenosine and IV verapamil | 359 pts | PSVT pts given adenosine, placebo, or verapamil for termination. 36% had AVNRT and 64% had AVRT. 22% of pts had manifest APs. | Safety and efficacy of adenosine for PSVT | Dose ranging study. IV adenosine doses of 6, 9, 12 mg converted 62.3%, 80.2%, and 91.4% of PSVT. Placebo converted 10.7%, 14.3%, and 16.1% w/ 4-dose sequence.  In trial 2, adenosine 6 mg followed by 12 mg had success of 57.4% and 93.4% (average time to termination 30 sec). AVNRT success 92% and AVRT success 97%. 61 total pts received adenosine.  IV verapamil 5 mg followed by 7.5 mg if necessary was successful in 81.3% and 91.4%. 95% pts w/ AVNRT and 96% pts w/ AVRT were successfully converted w/ verapamil. 64 total pts received verapamil; manifest pts not excluded.  Side effects: 36% w/ adverse effects lasting <1 min. Severe side effects in 2.3% including flushing, chest pain, and dyspnea. | Both IV adenosine and IV verapamil effective for acute treatment of AVNRT and AVRT. |
| Furlong R  1995  (154)  [7605518](http://www.ncbi.nlm.nih.gov/pubmed/?term=7605518) | Acute prospective case series study of adenosine for termination of PSVT | 31 pts | PSVT of undocumented mechanism | Adenosine given prehospital for management of PSVT | 31 pts w/ PSVT, 28 (90%) converted to sinus after the first (16) or second or third (13) dose. No significant complications reported | Adenosine was effective for treating PSVT (unclear how many pts had AVRT) |
| Boriani G  1996  (155)  [8644602](http://www.ncbi.nlm.nih.gov/pubmed/?term=8644602) | Case report | 1 pt | WPW pt w/ AF | IV amiodarone given to treat AF | IV amiodarone given to treat WPW w/ preexcited AF resulted in VF | IV amiodarone resulted in ventricular fibrillation |
| Wen ZC  1998  (41)  [9851958](http://www.ncbi.nlm.nih.gov/pubmed/?term=9851958) | Acute study of vagal maneuvers for termination of PSVT | 133 pts | Mixed group w/ PSVT: 85 w/ AVRT | Effects of vagal maneuvers on PSVT termination | Of 85 pts w/ AVRT, vagal maneuvers terminated 53% | Vagal maneuvers terminate 53% of pts w/ AVRT |
| Glatter KA  2001  (156)  [11602497](http://www.ncbi.nlm.nih.gov/pubmed/11602497) | Acute study of IV ibutilide in pts w/ WPW + AF | 22 pts | WPW pts w/ AF at time of EP study | EP properties, safety and AF termination | Ibutilide terminated AF in 95%. In 18 additional pts ibutilide prolonged the AP ERP from 275±40 to 320±60 msec p<0.01. No placebo arm. | Ibutilide sass safe and effective terminating AF is WPW. |
| Shiraishi H  2002  (157)  [12135176](http://www.ncbi.nlm.nih.gov/pubmed/?term=12135176) | Case report | 1 pt | Pt w/ a concealed pathway and AVRT | IV verapamil given to treat AVRT | IV verapamil terminated AVRT the pt developed non-sustained polymorphic VT. Authers did EP study and mechanism unknown. | IV verapamil terminated AVRT in pt w/ concealed pathway but non-sustained polymorphic VT then developed |
| Neumar RW, et al., 2010  (158)  [20956224](http://www.ncbi.nlm.nih.gov/pubmed/?term=20956224) | AHA ACLS Guidelines | N/A | Acute treatment of pts w/ bradycardia and tachycardia | Expert developed guidelines | Reviews role of direct current electrical cardioversion, vagal maneuvers and antiarrhythmic drug therapy for the treatment of supraventridular tachycardia in the emergency department including WPW w/ AF and SVT | Electrical cardioversion recommended for the treatment of WPW w/ AF or SVT and hemodynamic instability |
| Delaney B  2011  (159)  [20926952](http://www.ncbi.nlm.nih.gov/pubmed/?term=20926952) | Meta-analysis of the efficacy of adenosine vs. verapamil for treatment of stable PSVT | 692 pts/events | PSVT of undocumented mechanism | 8 trials included that compared verapamil and adenosine | Adenosine converted 90.8% and verapamil 89.9%. More minor side effects w/ adenosine. More hypotension w/ verapamil (3.7% vs. 0.6%). | Both adenosine and verapamil were effective for termination of PSVT. Verapamil had more associated hypotension. |
| Smith GD, et al., 2013  (39)  [23543578](http://www.ncbi.nlm.nih.gov/pubmed/23543578?dopt=Citation) | Cochrane Database review of randomized trials of Valsalva | 316 pts i | All pts w/ SVT. Number of pts w/ AVRT was not specified. | Valsalva compared to “other” vagal maneuvers | The reversion of SVT to sinus rhythm following Valsalva in the 3 studies was 19.4%, 45.9%, and 54.3% | Valsalva was effective in converting SVT to sinus rhythm. |
| Long-Term Pharmacological Treatment | | | | | | |
| Sellers TD  1977  (146)  [872319](http://www.ncbi.nlm.nih.gov/pubmed/872319) | Acute EP study of IV digitalis effects on AF in WPW | 21 pts | WPW pts w/ AF induced during EP study and given IV digitalis | Safety for AF in WPW | Digitalis shortened the CL of the shortest preexcited RR in 6/21 pts increased the CL in 7/21 pts and had no effect in 5/21. Digitalis directly related to onset of AF degenerating to VF in 9/21 pts. Each of these 9 had a shortest RR <230 msec during AF baseline. | This study is old but highlights the risk of digitalis in WPW pts w/ AF |
| Bauernfeind RA, et al., 1980  (160)  [7438370](http://www.ncbi.nlm.nih.gov/pubmed/?term=7438370) | Single center study of multiple drugs given IV and then long term for AV node reentry | 21 pts studied acutely; 18 pts followed 6-50 mo | All pts w/ AV node reentry | Drug efficacy at minimal f/u of 6 mo | Pts were tested w/ IV drug to determine if the drug prevented induction of AVNRT. Successful pts were then treated long term w/ oral drugs. 18 pts followed at least 6 mo, 72% w/o recurrence: 3 of 5 pts on digoxin only; 2 of 3 pts on digoxin plus propranolol; 4 of 4 pts on propranolol only; 1 of 3 pts on procainamide; and 3 of 3 pts on quinidine only. | Small number of pts on each medication showing moderate success. |
| Sakurai M  1983  (161)  [6837416](http://www.ncbi.nlm.nih.gov/pubmed/?term=6837416) | Single center study of IV and oral verapamil for PSVT | 15 pts studied acutely and followed 3 to 31 mo (mean 15 mo) | AVNRT in 4 and AVRT in 11 (all w/ a concealed AP) | Drug efficacy at minimal f/u of 3 mo | 13 pts followed 3-31 (mean 15) mo w/ 8 having no recurrent PSVT and 5 having decreased frequency and duration. Mild constipation in 4. | Small, uncontrolled study of oral verapamil for PSVT including some pts w/ AVRT |
| Feld GK  1984  (162)  [6707383](http://www.ncbi.nlm.nih.gov/pubmed/?term=6707383) | EP testing after amiodarone loading and then long term f/u | 10 pts  EP test at ≥4 wk | All pts w/ AP and AVRT | Assessment of EP properties | 9 pts no longer had inducible AVRT. 1 pt had nonsustained AVRT. AP ERP increased by 20% anterograde p<0.05 and 40% retrograde p<0.02  symptomatic control of arrhythmia during 20 mo. 1 pt stopped due to side effects | Amiodarone had favorable effects on AP and long-term rhythm control. Small number of pts |
| Feld GK  1988  (163)  [3336964](http://www.ncbi.nlm.nih.gov/pubmed/?term=3568305) | EP testing and long term assessment of amiodarone | 10 pts  Acute EP study and mean 30 mo f/u | All pts w/ WPW and AF w/ a rapid ventricular response | EP measurement of drug effect and long term f/u of rhythm control | EP study—amiodarone prolonged the AP ERP 38% (p<0.01) and atrial ERP 34% (p<0.01). Amiodarone prolonged the mean RR 90% and minimum RR 104% (p<0.01) during AF.  Long-term f/u—no AF or VF. SVT in 1 who went to surgery.  1 serious and 5 minor side effects | Amiodarone was safe and effective preventing AF in a small number of pts although side effect were significant. |
| Chimienti M 1995  (30)  [8682031](http://www.ncbi.nlm.nih.gov/pubmed/?term=8682031) | Open label, no placebo comparison of flecainide vs. propafenone | 335 pts  12 mo mean f/u | PSVT 135  PAF 200  Unclear number of AVRT or WPW | Arrhythmia recurrence | Probability of 12 mo safe and effective treatment for PSVT was 93% for flecainide and 86% for propafenone p=0.24. For AF it was 77% for flecainide and 75% for propafenone p=0.72.  One VT on propafenone, Two rapid AF on flecainide | Propafenone and flecainide had similar efficacy for PSVT and AF |
| Hopson JR  1996  (164)  [8607395](http://www.ncbi.nlm.nih.gov/pubmed/?term=8607395) | Open-label multicenter trial of flecainide | 151 pts  1 y | PSVT 67  PAF 67  CAF 17, unclear number of AVRT or WPW | Arrhythmia recurrence | At 1 y of treatment, 87% of PSVT, 73% of PAF, and 56% of CAF had improved symptomatically. Proarrhythmia is 3, CHF in 7. 65% w/ visual sx or headache | Poor study design, flecainide effective but important cardiac events. Study done before results of CAST known. |
| Catheter Ablation: Ablation of Standard APs | | | | | | |
| Jackman WM 1991  (165)  [2030716](http://www.ncbi.nlm.nih.gov/pubmed/?term=2030716) | Observational study of RF ablation and short term f/u for WPW | 166 | 166 WPW pts w/ 177 pathways | Acute ablation success and at 8 mo | AP conduction eliminated in 164 of 166 pts (99%) by a median of 3 RF applications. F/u at 8±5.4 mo showed preexcitation or AVRT returned in 15 pts who underwent a 2nd RF. EP study at 3±9 mo after RF in 75 pts verified absence of AP. 3 pts (1.8%) w/ complications – AV block, cardiac tamponade, pericarditis. | Large series reporting success and safety of RF for treating AP in WPW. |
| Calkins H  1992  (166)  [1555278](http://www.ncbi.nlm.nih.gov/pubmed/?term=1555278) | Observational study of RF in WPW | 250 | 183 pts w/ manifest AP and 84 concealed. Failed 2.0+/-1.6 AADs | Acute, 3 mo EP study, and 10±4 mo success | 250 pts w/ 267 APs. 94% w/ both acute success and free of tachycardia at 10 mo. 4% w/ complications: MI-1, AV block-3, valve damage-1, TIA-1, vascular-2 | Large series reporting success and safety of RF in pts w/ APs |
| Kugler J  1994  (167)  [8164700](http://www.ncbi.nlm.nih.gov/pubmed/8164700) | Observational multicenter study of RF ablations in young pts SVT | 652 | 615 APs | Acute and short-term f/u 13.5 mo | Success highest in left free wall APs (89%), high volume centers; lowest in right free wall AP’s (69%), pt weight >80 kg, or presence of CHD. Recurrence in 12-40%, higher in right free wall AP or presence of CHD. 3.7%; one procedural death; AV block, pericardial eff/usion; higher if weight <15 kg; One post procedural death in 5 wk old infant w/ torn mitral valve. | Large multicenter series, RF acceptable treatment for AP w/ attention to pt age and body weight and center experience. |
| Calkins H  1999  (59)  [9892593](http://www.ncbi.nlm.nih.gov/pubmed/?term=9892593) | Multicenter observational study of RF using Atakr for PSVT | 1050 | 500 pts w/ AP; 373 w/ AVNRT; 121 of AV junction | Acute and long term safety and f/u.; median f/u 6.3 mo | Acute AP success 93% for single APs and 86% for multiple APs. 7.8% of pts w/ AP had a recurrence. 3% w/ major complication and 8.2% minor. Death-3, stroke-2, AV block-10, tamponade-6, valve damage-1, MI-1 | Large series showing good acute success, 8% recurrence, and major complications in 3%. This is the most accurate study listing complications. |
| Dagres N  1999  (168)  [10581141](http://www.ncbi.nlm.nih.gov/pubmed/?term=10581141) | Observational study of RF for APs | 519 | All pts w/ APs | Acute and long term f/u at 22.6±12.4 mo | 398 pts responded to f/u questionnaire. 85.4% asymptomatic and 10.6% taking AADs. 41% of pts w/ failed ablations were asymptomatic. | Large series reporting good long term success w/ RF for APs |
| Schlapfer J  2001  (169)  [11259148](http://www.ncbi.nlm.nih.gov/pubmed/?term=11259148) | Observational study of RF for APs followed long term | 180 | Pts. w/ APs undergoing RF failing 1.75+/- 1.25 AADs | Long-term f/u at a median of 48.1 mo | All pts has successful procedure. Pts followed median of 48.1 mo—79% remained asymptomatic. 10% required further RF’ or meds. 4% w/ procedure complications: vascular-5, valve perforation-1, TIA-2 | Large study of acute RF success w/ 21% having sxs by 4 y but only 10% requiring additional therapy. |
| Belhassen B 2007  (170)  [17491219](http://www.ncbi.nlm.nih.gov/pubmed/?term=17491219) | Observational study of RF for APs | 508 | 508 pts w/ 535 APs. | Acute and long term RF results 85±43 mo f/u | 46.8% manifest and 44.4% concealed. 572 procedures in the 508 pts. Acute RF success 93.1% and multiple RF 95.3%. 9.9% recurrence after 1st RF. At 85 mo f/u, 94.9% cure. 2 major complications—pericardial effusion, MI | Large series showing long-term success and safety of RF for APs. |
| Pappone C, et al., 2014  (145)  [25052405](http://www.ncbi.nlm.nih.gov/pubmed/?term=25052405) | Prospective single center registry of WPW pts | 2169 pts | All pts w/ a manifest AP underwent EP±RF. Followed 8 y | Both asymptomatic and symptomatic pts studied at EP to identify risk factors for VF | 1001 pts (550 asymptomatic) did not undergo RF and 1168 (550 asymptomatic) underwent RF. F/u of 8 y. VF occurred in 1.5% of the no-RF group (mean age 11 y) and no VF occurred in the RF treated group (p<0.001). VF was associated w/ a short ERP of the AP w/ an optimal cut-off of 240 msec (p<0.001) and AVRT initiating AF (p<0.001). | Large single center registry showing that EP findings identified pts w/ a manifest AP at high risk for VF and the risk was eliminated w/ ablation. |

AAD indicates antiarrhythmic drugs; ACLS, Advanced Cardiovascular Life Support; AF, atrial fibrillation; AHA, American Heart Association; AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; bpm, beats per min; CAF, chronic atrial fibrillation; CHF, congestive heart failure; CL, cycle length; EP, electrophysiological; ERP, effective refractory period; f/u, follow up; h/o, history of; IV, intravenous; MI, myocardial infarction; N/A, not applicable; NPV, negative predictive value; PAF, paroxysmal atrial fibrillation; PPV, positive predictive value; PSVT, paroxysmal supraventricular tachycardia; pt, patient; FR, radiofrequency; RVR, rapid ventricular response; SVT, supraventricular tachycardia; sx, symptom; TIA, transient ischemic attack; VF, ventricular fibrillation; w/, with; w/o, without; and WPW, Wolff–Parkinson-White syndrome.

Data Supplement 13. Summary of Included Studies – ERC Report (Section 6.2)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study (Author, Year)** | **Study Design** | **Sample Size (N)** | **Participant Characteristics** | **Inclusion Criteria** | **Exclusion Criteria** |
| Milstein S  1986  (171)  [3706161](http://www.ncbi.nlm.nih.gov/pubmed/?term=3706161) | Uncontrolled prospective cohort study. All pts underwent an EP study. | 42 | * Mean age (±SD) 36 y (±12 y); age range 7-77 y * Gender: 21 (50%) men and 21 (50%) women * SHD: --- | * WPW pattern seen on a routine ECG. These pts were considered asymptomatic because they had neither documented arrhythmias nor a h/o sustained palpitations | --- |
| Satoh M  1989  (172)  [2466266](http://www.ncbi.nlm.nih.gov/pubmed/?term=2466266) | Uncontrolled observational cohort study. All pts underwent an EP study. | 95 (34 asymptomatic and 61 symptomatic pts) | * Mean age (± SD) 32 y (± 19 y) * Male 73% * SHD 13% * Intermittent preexcitation 23% | * WPW pattern * Asymptomatic (neither documented tachycardia, nor a h/o palpitations suggestive of paroxysmal tachycardia.) | --- |
| Klein GJ  1989  (173)  [2710202](http://www.ncbi.nlm.nih.gov/pubmed/?term=2710202) | Uncontrolled prospective observational study. All pts underwent an EP study. | 29 | * Age (±SD): 50 y (±18 y) in the preexcitation lost subgroup 39 y (±11 y) in the preexcitation persistent subgroup * Gender: 17/29 (58.6%) men, 12/29 (41.4%) women * SHD: --- | * Asymptomatic WPW ECG pattern * No documented tachycardia and no h/o sustained tachycardia. | --- |
| Leitch JW  1990  (174)  [2225373](http://www.ncbi.nlm.nih.gov/pubmed/?term=2225373) | Uncontrolled prospective observational study. All pts underwent an EP study. | 75 | * Mean age (± SD) 34 y (± 13 y), age range 7-77 y * Male 44 (59%) * SHD 5/75 (7%): (1 w/ CAD, 2 w/ cardiomyopathy, 1 w/ VHD, 1 w/ Ebstein’s anomaly) | * Asymptomatic w/ WPW ECG pattern | * All pts underwent sx-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 preexcitation either at rest or during exercise testing and EP study. |
| Brembilla-Perrot B  2001  (175)  [11707045](http://www.ncbi.nlm.nih.gov/pubmed/?term=11707045) | Uncontrolled prospective observational study. All pts underwent testing w/ transesophageal stimulation. | 92 | * Mean age (±SD): 34 y (±15 y), age range 11-69 y * 68 men, 24 women * No SHD | * Asymptomatic WPW ECG pattern * No documented tachycardia and no h/o sustained tachycardia | * Documentation of SVT at any time |
| Pappone C  2003  (176)  [12535816](http://www.ncbi.nlm.nih.gov/pubmed/?term=12535816) | Uncontrolled prospective observational study. All pts underwent an EP study. | 212 | * Mean age of overall population (± SD): 35.8 y (± 20.5 y), age range 7-63 y. Gender in overall population: N/A. SHD in overall population was present in 10/212 (5%) (5 w/ MVP, 2 w/ HCM, 3 w/ hypertension) * Mean age (±SD) of the 162 pts w/ complete f/u 33.6 y (±14.3 y), age range 7-63 y. Male 105/162 (65%). SHD was present in 4/162 (3 w/ MVP, 1 w/ HCM) | * 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 | --- |
| Pappone C  2003  (177)  [14602878](http://www.ncbi.nlm.nih.gov/pubmed/14602878) | Combined RCT and prospective observational cohort study. All pts underwent EP study. Pts w/ 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 a RCT and 148 low-risk pts enrolled in a prospective observational cohort study) | * 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 SHD in either group. * Median (IQR) age for observational cohort 36 y (27-48 y). Male sex 59% in this cohort. SHD 7%. | * Ventricular preexcitation documented by 12-lead ECG * Absence of arrhythmia-related sxs | * Participation in other investigational protocols * Age <13 y * Pregnancy * Concomitant medical conditions |
| Santinelli V  2009  (178)  [19808453](http://www.ncbi.nlm.nih.gov/pubmed/?term=19808453) | Uncontrolled prospective observational study. All pts underwent an EP study | 293 | * Median age (IQR) 36 y (28-48 y) * Male 61% | * Incidental WPW pattern on ECG * Asymptomatic based on an accurate history | * Participation in other research studies |
| Pappone C  2014  (145)  [25052405](http://www.ncbi.nlm.nih.gov/pubmed/?term=25052405) | Uncontrolled prospective observational study. All pts underwent an EP study. They reported data by treatment w/ catheter ablation. | 2169 (756 asymptomatic and 550 asymptomatic and w/ no ablation and 1413 symptomatic pts) | * Median age 19 y, male preponderance among asymptomatic pts (63%). * SHDs were found in 1.5% of asymptomatic pts | * Asymptomatic and symptomatic pts w/o prior ablation or documented life-threatening arrhythmias who consented to undergo a baseline EP study | --- |

CAD indicates coronary artery disease; ECG, electrocardiogram; EP, electophysiological; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; MVP, mitral valve prolapse; N/A, not applicable; pt, patient; RCT, randomized controlled trial; SD, standard deviation; SHD, structural heart disease; SVT, supraventricular tachycardia; sx, symptom; VHD, valvular heart disease; w/, with; w/o, without; WPW, Wolff-Parkinson-White syndrome; and ---, not available.

Data Supplement 14. Comparators and Outcomes – ERC Report (Section 6.2)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **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 F/u** | **Loss to F/u** |
| Milstein S  1986  (171)  [3706161](http://www.ncbi.nlm.nih.gov/pubmed/?term=3706161) | Group 1: Asymptomatic WPW pattern | N/A | 43 APs in 42 asymptomatic pts. Mean ERP of AP was 333±106 msec in asymptomatic pts vs. 298± 42 msec in asymptomatic pts (p<0.025). Mean shortest RR interval during AF 277±48 msec in the asymptomatic groups vs. 247±51 msec 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, 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 |
| Klein GJ  1989  (173)  [2710202](http://www.ncbi.nlm.nih.gov/pubmed/?term=2710202) | Group 1: Invasive EP study w/o catheter ablation | N/A | 28/29 (97%) pts had only 1 AP and 1/29 (3%) pts had more than 1 AP. The mean (± SD) ERP of pathway(s) at baseline 334 msec (±105 msec) on the initial study and 301 msec (±78 msec) on the f/u study.  The shortest RR interval (±SD) during induced AF was 266 msec (±39 msec). 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 PSVT 2/29 (7%) (during 36-79 mo); 27/29 (93%) remained asymptomatic; 9/29 (31%) lost WPW pattern on ECG. | 36-79 mo | None |
| Satoh M  1989  (172)  [2466266](http://www.ncbi.nlm.nih.gov/pubmed/?term=2466266) | Group 1: Asymptomatic pts w/ WPW pattern | Intermittent preexcitation on ECG recording 23% | Number of pts w/ multiple APs not reported. Baseline mean ERP of AP was 288±29 msec in asymptomatic pts. Shortest RR in AF not reported. AVRT induced in 6/34 (18%) pts in the asymptomatic group, sustained AF was induced in 2/34 (6%) of asymptomatic pts. | No ablation | Group 1: no events  Group 2: 2 pts w/ symptomatic WPW syndrome had VF and were resuscitated successfully | Mean 15 mo (range 2 to 47 mo) | --- |
| Leitch JW  1990  (174)  [2225373](http://www.ncbi.nlm.nih.gov/pubmed/?term=2225373) | Group 1: Invasive EP study w/o catheter ablation | N/A | At baseline, the median ERP of the AP was 293 msec (IQR 280-310 msec), and the median retrograde ERP of the AP was 288 msec (IQR 240-320 msec).  The median shortest RR interval during preexcited AF was 274 msec (IQR 240-325 msec) in 72 pts, was ≤250 msec in 23 pts and was ≤200 msec 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, 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 |
| Brembilla-Perrot B  2001  (175)  [11707045](http://www.ncbi.nlm.nih.gov/pubmed/?term=11707045) | Group 1: Transesophageal stimulation | All pts had 24-h Holter and stress test performed prior to study entry and only those w/o supraventricular arrhythmia were included | The number of APs found was not reported. The ERP of pathway(s) at baseline and during isoproterenol infusion were not reported. Shortest RR interval (<250 msec) during induced AF was present in 20/92 (22%) pts. Atrial tachyarrhythmia was induced in 27% of pts. | No ablation | 3/92 (3%) pts developed symptomatic AF several y later. Of these 3 pts, 1 presented w/ AF and then VF 1 d after an aortic aneursymectomy. 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. | --- | --- |
| Pappone C  2003  (176)  [12535816](http://www.ncbi.nlm.nih.gov/pubmed/?term=12535816) | Group 1: Invasive EP study w/o catheter ablation | N/A | 17/162 (10%) had multiple APs. Baseline mean (± SD) ERP 275.2 msec (± 33.8 msec). Isoproterenol mean (± SD) ERP 246.1 msec (± 30.5 msec). Shortest RR in AF not reported 47/162 (29%) had inducible arrhythmia: nonsustained AF in 17, sustained AF in 19, inducible AVRT that degenerated into totally preexcited sustained AF in 11. | No ablation | 129/209 (62%) remained asymptomatic at the end of follow- up, whereas 33 (16%) developed arrhythmic events: SVT in 25, AF in 8, documented VF in 3/209 (aborted sudden death in 2 (both had developed sxs 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 ref/used the 5-y EP study were excluded from the analysis |
| Pappone C  2003  (177)  [14602878](http://www.ncbi.nlm.nih.gov/pubmed/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 RF applications was 9 (range, 5 to 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 w/ an anteroseptal AP. | 2/37 (5%) pts in the ablation group had an arrhythmic event found on EP study to be due to AVNRT in both pts. W/in 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 sxs) 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, sxs of SVT developed in 6 pts and 20 pts lost ventricular preexcitation. | Ablation group median f/u 27 mo, range 9-60 mo. Control group median f/u 21 mo, range 8-60 mo. | None |
| Santinelli V  2009  (178)  [19808453](http://www.ncbi.nlm.nih.gov/pubmed/?term=19808453) | Group 1: Invasive EP study w/o catheter ablation | N/A | Anterograde ERP of AP ≤250 msec was present in 39/293 (13%) pts.  Multiple APs 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) | --- |
| Pappone C  2014  (145)  [25052405](http://www.ncbi.nlm.nih.gov/pubmed/?term=25052405) | Group 1: Asymptomatic pts w/ WPW pattern (they presented data on symptomatic pts and by whether or not catheter ablation of the AP was done), but the groups were not matched and selection bias was not adjusted for) | --- | No ablation: Multiple APs in 59 (6%), median (IQR) ERP of AP 280 msec (250-300 msec). Inducible AVRT triggering AF on EP study was found in 47 (5%) of pts.  W/ Ablation:  Multiple APs in 80 (7%), median ERP (IQR) of AP 280 msec (250-300 msec). Inducible AVRT triggering AF on EP study was found in 73 (6%) of pts. | 206/756 asymptomatic pts were treated w/ 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 86/756 (11%) of the asymptomatic pts developed benign arrhythmias (AVRT and AF).  W/ 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  W/ ablation: completeness of f/u was 95.5% at 1 y and 90.2% at the end of the study |

AF indicates atrial fibrillation; AP, accessory pathway; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventrial reentrant tachycardia; ECG, echocardiogram; EP, electrophysiological; ERP, effective refractory period; f/u, follow up; IQR, interquartile range; N/A, not applicable; pt, patient; RF, radiofrequency; SD, standard deviation; SVT, supraventricular tachycardia; VF, ventricular fibrillation; w/, with; w/o, without; WPW, Wolf-Parkinson-White syndrome; and ---, not available.

Data Supplement 15. Quality Assesment of Included Studies – ERC Report (Section 6.2)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **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 Follow Up of Cohort (Including Loss to Follow Up)** | **Precision of Findings** |
| Milstein S  1986  (171)  [3706161](http://www.ncbi.nlm.nih.gov/pubmed/?term=3706161) | Yes | N/A (all pts underwent EP study) | All pts underwent EP study | Yes | --- | Yes | Yes | Imprecise due to small sample size |
| Klein GJ  1989  (173)  [2710202](http://www.ncbi.nlm.nih.gov/pubmed/?term=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) |
| Satoh M  1989  (172)  [2466266](http://www.ncbi.nlm.nih.gov/pubmed/?term=2466266) | Yes | N/A (all pts underwent EP study) | All pts underwent EP study | Yes | --- | Yes | --- | Imprecise (no events) |
| Leitch JW  1990  (174)  [2225373](http://www.ncbi.nlm.nih.gov/pubmed/?term=2225373) | Questionable | N/A (no comparator group) | All pts underwent EP study | Yes | --- | Yes | Yes | N/A (no comparator group) |
| Brembilla-Perrot B  2001  (175)  [11707045](http://www.ncbi.nlm.nih.gov/pubmed/?term=11707045) | Yes | N/A (no comparator group) | All pts underwent EP study | Reasonable based on the absence of sxs. Pts had to have a normal ECG, exercise stress test and 24-h Holter monitor | --- | Uncertain as duration of f/u was not reported | F/u and loss to f/u were not reported | N/A (no comparator group) |
| Pappone C  2003  (176)  [12535816](http://www.ncbi.nlm.nih.gov/pubmed/?term=12535816) | Questionable | N/A (no comparator group) | All pts underwent EP study | Yes | --- | Yes | Questionable | N/A (no comparator group) |
| Pappone C  2003  (177)  [14602878](http://www.ncbi.nlm.nih.gov/pubmed/14602878) | Questionable | Yes | Yes | Reasonable based on the absence of sxs | The events were reviewed by an independent committee whose members were unaware of the pts' treatment assignments | Yes | Yes | Fairly precise w/ 95% CI: 0.02-0.33 for arrhythmic events and 95% CI: 0.002-0.104 for event-free survival |
| Santinelli V  2009  (178)  [19808453](http://www.ncbi.nlm.nih.gov/pubmed/?term=19808453) | Questionable | N/A (no comparator group) | All pts underwent EP study | Yes | --- | Yes | --- | N/A (no comparator group) |
| Pappone C  2014  (145)  [25052405](http://www.ncbi.nlm.nih.gov/pubmed/?term=25052405) | Questionable | N/A (no comparator group) | All pts underwent EP study | Yes | --- | Yes | --- | N/A (no comparator group) |

CI indicates confidence intervals; ECG, echocardiogram; EP, electrophysiological; f/u, f/u; N/A, not applicable; pt, patient; SVT, supraventricular tachycardia; sx, symptom; w/, with; and ---, not available.

Data Supplement 16. Randomized Trials Comparing Atrial Flutter – Section 7

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Name, Author, Year** | **Aim of Study** | **Study Type (Size, N)** | **Study Intervention Group (n)** | **Study Comparator Group (n)** | **Pt Population** | | **Endpoints** | | | **P Values, OR: HR: RR: & 95% CI:** | **Study Limitations & Adverse Events** |
|  |  |  |  |  | ***Inclusion Criteria*** | ***Exclusion Criteria*** | ***Primary Endpoint (efficacy) and Results*** | ***Safety Endpoint and Results*** | ***Secondary Endpoint and Results*** |  |  |
| Platia EV  1989  (179)  [2564725](http://www.ncbi.nlm.nih.gov/pubmed/2564725?dopt=Citation) | The effects of esmolol, an ultrashort-acting beta blocker, and verapamil were compared in controlling ventricular response in 45 pts w/ AF or atrial flutter | Randomized, parallel, open-label study. 45 pts | Esmolol (n = 21) | Verapamil (n = 24) | Pts w/ either new onset (less than 48 h, n = 31) or old onset (greater than 48 h, n = 14) of AF or flutter w/ rapid ventricular rate | Uncontrolled CHF, SSS w/o pacemaker, h/o intolerance to beta blockers or ca-channel blockers, AMI <3 d, impaired renal and hepatic function, SVT other that AF or atrial flutter, digitalis toxicity, SBP <100 mm Hg unless it was usual | Drug efficacy was measured by ventricular rate reduction and conversion to sinus rhythm.  HR declined w/ esmolol from 139 to 100 bpm and w/ verapamil from 142 to 97 bpm. 50% of esmolol-treated pts w/ new onset of arrhythmias converted to NSR vs. 12% w/ verapamil. | N/A | N/A | HR decline w/ esmolol (p<0.001); HR decline w/ verapamil (p<0.001).  Conversion w/ esmolol vs. verapamil (<0.03). | Mild hypotension both groups |
| Salerno DM  1989  (180)  [2650517](http://www.ncbi.nlm.nih.gov/pubmed/?term=2650517) | study evaluates the effectiveness and safety of IV diltiazem for the treatment of AF and atrial flutter. | Double-blind, parallel, randomized, placebo-controlled.  113 pts w/ AF or flutt | IV diltiazem 0.25 mg/kg/2 min followed 15 min later by 0.35 mg/kg/2 min if the first dose was tolerated but ineffective.  If a pt did not respond, the code was broken and the pt was allowed to receive open-label diltiazem if placebo had been given. | Identical placebo | 113 pts w/ AF or flutter, a ventricular rate greater than or equal to 120 bpm and systolic BP greater than or equal to 90 mm Hg. | Severe HF | Of 56 pts, 42 (75%) randomized to receive diltiazem responded to 0.25 mg/kg and 10 of 14 responded to 0.35 mg/kg, for a total response rate of 52 of 56 pts (93%), whereas 7 of 57 pts (12%) responded to placebo. | Mild hypotension | N/A | Response to diltiazem vs. placebo (p<0.001) | IV diltiazem was rapidly effective for slowing the ventricular response in most pts w/ AF or atrial flutter. BP decreased slightly. Side effects were mild. |
| Van Gelder IC  1989  (181)  [2511744](http://www.ncbi.nlm.nih.gov/pubmed/?term=2511744) | Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic AF or atrial flutter. | 81 pts | N/A | N/A | Chronic AF or flutter | Age <16 or >80 y; CHF or angina pectoris > III (NYHA); MI <2 y, flecainide intolerance, BBB, SSS w/o pacemaker, antiarrhythmics, severe systemic disease | Multiple regression analysis showed New York Heart Association class I for exercise tolerance (p=0.0004) and flecainide treatment (p=0.01) to be the main factors increasing the arrhythmia-free episode. However, Mantel-Cox lifetable analysis did not reveal significant differences between arrhythmia-free survival curves of both treatment groups. In the flecainide-treated group, 9% of pts experienced side effects, mostly related to negative dromotropic effects. The incidence of ventricular proarrhythmia in this group of pts was low. | N/A | N/A | N/A | 9% of pts treated w/ flecainide had adverse events (e.g,sinus arrest, AV block, rate related LBBB).  Moderate doses of flecainide (not >300 mg) recommended after cardioversion |
| Suttrop MJ  1990  (182)  [2123909](http://www.ncbi.nlm.nih.gov/pubmed/?term=2123909) | Cardioversion w meds: Single blind randomized study of IV propafenone (2 mg/kg per 10 min) vs. flecainide (2 mg/kg per 10 min) | 50 pts w/ AF or atrial flutter | AF or flutter  Group A- 20 pts w/ AF treated w/ propafenone  Group C- 5 pts w/ atrial flutter treated w/ proopafenone | AF or flutter  Group B-20 pts w/ AF treated w/ flecainide  Group D- 5 pts w/ atrial flutter treated w/ flecainide | AF or atrial flutter <6 mo w/ ventricular rate >100 bpm at rest w/ no HF signs | Conduction disturbances more that 1st degree AV block, on class I antiarrythmics, WPW syndrome, SSS, AMI, Hyperthyroidism, cardiac surgery <2 wks, atrial enlargement, w/ AF or atrial flutter w/o appropriate anticoagulants, body weight >100 kg | Conversion to NSR w/in 1 H  11/20 (55%)pts w/ AF treated w/ propafenone  18/20 (90%)pts w/ AF treated w/ flecainide (p<0.02)  2/5 (40%) pts w/ atrial flutter treated w/ propafenone  1/5 (20%) pts w/ atrial flutter treated w/ flecainide. P=NS | QRS lengthening (83±15 to **9920** msec) was observed only in the pts treated w/ flecainide (p<0.001). | N/A | Conversion from AF w/ flecainide vs. propafenone (p<0.02).  Conversion from atrial flutter w/ fleainidec vs. propafenone (p=NS).  Transient AE flecainide vs. propafenone more common (p<0.001) | Flecainide 2 mg/kg in 10 min is more effective than propafenone for conversion of AF to NSR but not for conversion of flutter. Few AE w/ propafenone- may be related to low dose. |
| Ellenbogen KA 1991  (183)  [1894861](http://www.ncbi.nlm.nih.gov/pubmed/?term=1894861) | To demonstrate the safety and efficacy of a continuous IV diltiazem infusion for 24 h heart rate control | Randomized, double-blind, parallel, placebo-controlled | IV diltiazem vs. placebo | Placebo | Pts >18 y w/ AF or atrial flutter w/ duration >24 h and HR >120 bpm | Severe CHF, sinus node dysfunction, 2nd or 3rd degree AV block, WPW syndrome or hypotension | Therapeutic response (ventricular response <100 bpm, ≥20% decrease in heart rate from baseline or conversion to NSR  74% vs. 0% | N/A | N/A | p<0.001 | IV diltiazem is safe and effective at slowing heart rate in AF or flutt |
| Van Gelder IC  1991  (184)  [2058558](http://www.ncbi.nlm.nih.gov/pubmed/?term=2058558) | Cardioversion: reassess prospectively the immediate and long-term results of direct-current electrical cardioversion in chronic AF or atrial flutter, and to determine factors predicting clinical outcome of the arrhythmia after direct-current cardioversion | 246 pts | Multivariate analysis to identify factors predicting short- and long-term arrhythmia outcome following DC cardioversion | N/A | AF or atrial flutter | Sinus rhythm, unstable HF, cardiogenic shock, severs systemic disease, SSS, AMI, contraindication to anticoagulants | Cardioversion successful in 70% of pts w/ AF and in 96% of pts w/ flutter. Stepwise logistic regression analysis revealed that arrhythmia duration, type of arrhythmia and age independently influenced conversion rate.  42 and 36% of pts remained in sinus rhythm during 1 and 2 y, respectively.  Multivariate regression analysis revealed that the type of arrhythmia), low precardioversion functional class and the presence of nonrheumatic mitral valve disease independently increased the length of the arrhythmia-free episode. Rheumatic heart disease shortened this period. | N/A | N/A | Arrhythmia duration (p<0.001); AF vs. atrial flutter (p<0.02) and age (p<0.05) influenced DCV rates. MVanalysis showed arrhythmia type (p=0.0008), functional class (p=0.002) and presence of nonrheumatic disease (p=0.03) increased arrhythmia free period. Rheumatic heart disease decreased arrhythmia free period (p=0.03) | Predictors for successful cardioversion include flutter vs. AF. FC, age and rheumatic heart disease affect cardioversion. |
| Kingma JH  1992  (185)  [1510000](http://www.ncbi.nlm.nih.gov/pubmed/?term=1510000) | Cardioversion w meds: Single-blind randomized study design. Efficacy and safety of IV propafenone (2 mg/kg per 10 min) vs. flecainide (2 mg/kg per 10 min) vs. verapamil 10 mg in 1 min.in pts w/ AF or flutt | 90 | Conversion to NSR w/in 1 hr of start of infusion:  First 40: flecainide and verapamil assessed | Conversion to NSR w/in 1 hr of start of infusion:  Second 50: flecainide and propafenone compared | Consecutive pts w/ AF or flutter | More than 1st degree AV block, class I antiarrhtyhmics, WPW syndrome, SSS, AMI, hyperthyroidism, cardiac surgery <2 wk, left atrial enlargement with AF or atrial flutter >2 d w/o appropriate anticoagulants, body weight >100 kg | Conversion to NSR in:  32/37 (86%) AF w/ flecainide  11/20 (55%) AF w/ PPF  In recent onset AF, flecainide conversion 24/25 (96%) vs. 8/14 (57%) propafenone, p<0.05.  1/8 (13%) atrial flutter w/ flecainide  2/5 (40%) atrial flutter propafenone, p=NS  Overall verapamil 1/20 (5%) | QRS widening occurred in flecainide-treated pts (83±15 to 99±20 msec; p<0.001), but not after propafenone (83±11 to 86±12 msec). | N/A | Recent onset AF flecainide more effective than propafenone at conversion ((p<0.05)  Flutter conversion no difference in conversion w/ flecainide vs. propafenone (p=NS)  Verapamil ineffective.  QRS widening more common w/ flecainide than propafenone (p<0.001) | Flecainide is more effective than propafenone at converting recent onset AF, but not flutter. Verapamil was not effective at converting AF or atrial flutter w/in 1 hr |
| Roberts SA  1993  (186)  [8362772](http://www.ncbi.nlm.nih.gov/pubmed/?term=8362772) | Clinical effectiveness and cost of digoxin at controlling HR in AF and atrial flutter in prospective , observational study at 18 academic centers | 115 pts | Assessed time to HR control w/ digoxin | N/A | 18 y  AF or atrial flutter w/ ventricular rates ≥ 120 BPM | NYHA class III, IV, HF, surgery, AMI | The median time to ventricular rate control (i.e., resting ventricular rate <100 bpm, decrease in ventricular rate of >20%, or sinus rhythm) was 11.6 h from the first dose of digoxin for all evaluable pts (n = 105) and 9.5 h for those only receiving digoxin (n = 64). Before ventricular rate control, the mean ±SD dose of digoxin administered was 0.80±0.74 mg, and a mean of 1.4±1.8 serum digoxin concentrations were ordered per pt. | N/A | N/A | N/A | Observational study |
| Tucker KJ  1993  (187)  [8343321](http://www.ncbi.nlm.nih.gov/pubmed/?term=8343321)  *Pace termination* | Prospective randomized clinical trial: Comparison of safety and efficacy of transesophageal atrial pacing vs. DC cardioversion in pts on medical therapy. | 21 consec pts | Group A- 11 pts treated w/ TAP | Group B- 10 pts treated w/ DC cardioversion | Consecutive pts w/ flutter  - HD stable.  - Had failed 1A or 1C antiarrhythmic therapy  -All pts received digoxin to control HR to <100 BPM | N/A | NSR achieved w/ intervention  Group A- 8/11 TAP pts  Group B- 9/10 DC cardioversion pts  P= 0.31 | Nonsustained VT was more frequent in DC cardioversion  Group A- 0/11 TAP  Group B 6/10 DC cardioversion  P=0.02 | N/A | P=0.31 NSR in TAP vs. DC cardioversion  NSVT p= 0.02 Group A vs. B | TAP is safe and effective and was well tolerated and is as efficacious as DC cardioversion |
| Ellenbogen KA  1995  (188)  [7801862](http://www.ncbi.nlm.nih.gov/pubmed/?term=7801862) | To demonstrate the efficacy of various doses of IV diltiazem for heart rate control | Open label, dose titration study. 84 pts w/ AF, atrial flutter, or both | Bolus dose of diltiazem followed by continuous infusion w/ monitoring of heart rate and BP | N/A | 84 consecutive pts w/ AF or flutter, or both, received an IV bolus dose of diltiazem followed by a continuous infusion of diltiazem at 5, 10, and 15 mg/h. | >18 y, women of child-bearing age, SSS, 3rd degree AV block, WPW, hypotensive SBP <90 mm Hg, allergic to diltiazem. | 94% of pts (79 of 84) responded to the bolus dose w/ a >20% reduction in HR from baseline, a conversion to sinus rhythm, or a heart rate <100 bpm. 78 pts received the continuous infusion. After 10 h of infusion, 47% of pts had maintained response w/ the 5 mg/h infusion, 68% maintained response after the infusion was titrated to 10 mg/h, and 76% after titration from the 5 and 10 mg/h infusion to the 15 mg/h dose. For the 3 diltiazem infusions studied, mean (±SD) heart rate was reduced from a baseline value of 144±14 bpm to 98±19, 107±25, 107±22, 101±22, 91±17, and 88±18 bpm at infusion times 0, 1, 2, 4, 8, and 10 h, respectively. By the end of the infusion, 18% of pts (14 of 78) had conversion to sinus rhythm | Statistically significant change in BP before and after 20 mg bolus during infusion. NS difference in BP, after infustion at h 0, 1, 2, 4, 8, and 10. | N/A | Continuous infusion 10 h response at 5 mg/h (95% CI for 5 mg/h: 36-59; 95% CI for 10 mg/hr: 57-79%) | IV diltiazem is safe and effective at slowing heart rate in AF or flutter.  Treatment related symptomatic hypotension (3.5-13% w/ hypotension) was most common. |
| Hou ZY  1995  (189)  [7671898](http://www.ncbi.nlm.nih.gov/pubmed/?term=7671898) | Cardioversion w meds: Randomized, open label, digoxin-controlled study to observe efficacy and safety of dosing regimen of amiodarone in recent-onset, persistent AF and atrial flutter w/ ventircular rates >130 BPM. | 51 | Randomly assigned to either IV amiodarone (n=26) or digoxin (n=24)  Amiodarone infused over 24 h (decreasing doses/h)  Digoxin inf/used- 0.013 mg/kg in 3 divided doses | Amiodarone vs. digoxin | Potentially useful for a recommendation | Recent-onset, persistent, AF and flutter w/ ventricular rates above 130 beats. | Heart rate control: Mean HR in amiodarone group decreased from 157 + 20 to 122+ 25 BPM in 1 hr (p<0.05) and further stabilized to 96±25 BPM after 6 h (p<0.05).  Fewer HR reductions in digoxin group (p<0.05) | amiodarone infusion was prematurely aborted in two pts due to severe bradycardia and death after conversion in one pt and aggravation of HF in the other | N/A | Amiodarone reduced HR significantly more than digoxin at 1 and 6 h (p<0.05 both time frames) | Demonstrated HR control w/ amiodarone. |
| Sung RJ  1995  (190)  [7900626](http://www.ncbi.nlm.nih.gov/pubmed/?term=7900626) | Cardioversion w meds  Multicenter, randomized, double-blind, placebo controlled study:  Placebo vs. sotalol | 93 | Two phased study:  Phase 1: randomized placebo infusion vs. 1.0 or 1.5 mg/kg IV sotalol. (30 min observation)  Phase 2: if not converted or if HR not fall to <100, 1.5 mg/kg sotalol given | Phase 1 sotalol vs. placebo  Phase 2 no comparetor | Spontaneous or induced SVT (n=45) or atrial flutter/fibrillation (n=48) | N/A | SVT phase 1 conversion to NSR 2/14 (14%) w/ placebo  SVT phase 1 conversion to NSR 10/15 (67%) sotalol 1.0 mh/kg (p<0.05 vs. placebo)  SVT phase 1 conversion to NSR 10/15 (67%) sotalol 1.5 mg/kg (p<0.05 vs. placebo)  SVT open label 7/17 (41%) conversion to NSR w/ 1.5 mg/kg sotalol  AF phase 1 conversion to NSR 2/14 (14%) w/ placebo  AF phase 1- 2/11 (11%) conversion to NSR w/ 1.0 mg/kg sotalol (p=NS vs. placebo)  AF phase 1- 2/16 (13%) to NSR 1.5 mg/kg sotalol (p=NS vs. placebo) | N/A | N/A | Phase 1 SVT sotalol 1.0 mg/kg and 1.5 mg/kg vs. placebo, sotalol superior (p<0.05 for each dose)  Phase 1 sotalol vs. placebo conversion of AF 1.0 mg/kg and 1.5 mg kg not different (p=NS for both doses) | Sotalol was effective at terminating SVT but not AF |
| Doni F  1996  (191)  [8945077](http://www.ncbi.nlm.nih.gov/pubmed/?term=8945077) | Pace termination (randomized):  Comparison of TAP in Type 2 atrial flutter w/ or w/o propafenone | 12 pts w/ type 2 atrial flutter | 12 pts w/ type 2 flutter randomized to 2 groups:  Group A- TAP on no meds | Group B- TAP 2 h after propafenone 600 mg | Mean age = 59 y. Symptomatic atrial flutter, all pts had negative P waves in leads II, III, and aVF. | N/A | NSR achieved in  Group A-0/6 (no meds)  Group B- 4/6 on PPF | Flutter CL: propafenone slowed flutter cycle: 219±33 vs. 168±8 msec, p<0.05 | N/A | NSR in Group A vs. Group B (P<0.05).  Flutter cycle legth propafenone vs. no meds, p<0.05 | Propafenone facilitated pace termination in those pts in whom a slowing of flutter CL occurred but not in those w/ unchanged atrial flutter CL |
| Ellenbogen KA  1996  (192)  [8752805](http://www.ncbi.nlm.nih.gov/pubmed/?term=8752805) | Cardioversion w meds: Randomized to single IV dose Efficacy of IV ibutilide vs. placebo for AF or flutter –dose response study. | 200 pts AF or atrial flutter 3H-90 d | Pts randomized to single IV dose vs. placebo  159 randomized to ibutilde:  41 at 0.005 mg/kg  40 at 0.10 mg/kg  38 at 0.015 mg/kg  40 at 0.025 mg/kg | 41 randomized to placebo | AF or A flutter 3 h- 90 d | Childbearing age, MI <3 m, class I and III antiarrhythmics discontinued for 5 half lives, AF >3 d, anticoags >2 wk before ibutilide | Conversion to NSR during or w/in 60 min of infusion:  24% conversion to NSR in drug treated group vs. 3% in placebo. Conversion rates at successive doses: 12%, 33%, 45%, 46%. | Polymorphic VT occurred in 3.6% | N/A | Placebo and 0.005 mg/kg ibutilide vs. all other groups lower success (p<0.05).  No other statistic | Ibutilide can rapidly terminate AF and flutter |
| Stambler BS  1996  (193)  [8840852](http://www.ncbi.nlm.nih.gov/pubmed/?term=8840852) | Multicenter study . Safety and efficacy study Varying doses of ibutilide | 226  133 AF  133 atrial flutter | Randomized to up to 2 10-min doses Ibutilide separated by 10 min. Ibutilide doses= 1.0 and 0.5 mg or 1.0 and 1.0 mg. | This was compared to placebo. | AF and atrial flutter.  Arrhythmia of 3 h to 45 d duration | Pt could not be <18 y, weight >300lbs, h/o of torsade, on ibutilide previously, MI, cardiac surgery <30 d, have digoxin toxicity, hyperthyroidism, not on class I | Conversion rates were:  47% w/ ibutilide vs. 2% w/ placebo (p<0.001)  Efficacy in flutter >AF: 63% vs. 31%, p<0.001  In AF (but not flutter) conversion rates higher in those w/ shorter duration arrhythmia  The 2 ibutilide dosing regimens did not differ in conversion efficacy (44% vs. 49%). | Polymorphic VT in 8.3% (15 pts) (3 required cardioversion, 12 did not) | N/A | Ibutilide vs. placebo (p<0.001)  Efficacy in flutter vs. AF: (p<0.001)  No difference in conversion at different doses (p=NS) | Ibutilide in repeated doses is effective in terminating AF and flutter |
| Volgman AS  1998  (194)  [9581743](http://www.ncbi.nlm.nih.gov/pubmed/?term=9581743) | Cardioversion w meds: Multicenter study- compare efficacy and safety of ibutilide vs. procainamide for conversion of recent onset AF or flutt | 127 | Conversion to NSR: randomized to either 2 10 min infusions of 1 mg ibutilide separated by 10 min vs. 3 successive 10 mg- /IV infusions of 400 mg procainamide  120 pts eval for efficacy:  60 received ibutilide  60 received proc | (Ibutilide vs. procainamide) | 2 h to 90 d AF or flutter | N/A | 120 evaluated for efficacy of conversion in 1.5 h:  35/60 (58%) ibutilide to NSR  11/60 (18.3%) procain converted to NSR (p=0.0001)  Flutter- ibutilide significantly more effective than procain (76% 13/17 vs. 4% 3/22; p=0.001.  AF- ibutilide significantly more effective than procain (51% 22/43 vs. 21% 8/38; p=0.005. | PMVT- 1 pt in ibutilide group  Hypotension- 7 pt in procainamide group | N/A | Ibutilide more successful at conversion n 1.5 h vs. procainamide (p<0.0001)  Flutter: ibutlide superior to procain (p=0.001)  AF- ibutilide superior to procain (p=0.005 | Ibutilide was superior to procainamide at converting either AF or flutt. Hypotension was major AE for procainamide. Low incidence of serious proarrhythmia wth ibutilide. |
| Vos MA  1998  (195)  [10078083](http://www.ncbi.nlm.nih.gov/pubmed/?term=10078083) | Cardioversion w meds: Randomized to receive one of 2 doses of ibutilde or DL sotalol. To compare safety and efficacy | 308 pts: 251 AF, 57 atrial flutter. | Three treatment groups:  99 received 1 mg ibutilide  106 received 2 mg ibutilide  103 received 1.5 mg/kg DL-Sotalol | N/A | AF or flutter: Duration 3 h - 45 d | Hyperthyroidism, UA, bronchospasm, MI or cardiac surgery <30 ds, 2 and 3rd degree AV block, BBB, WPW, torsade de pointes | Conversion to NSR w/in 1 hr of treatment.  Both drugs were more effective w/ atrial flutter than fib. Ibutilide was more effective than DL-sotalol achieving SNR in atrial flutter in: 70% and 56% vs. 19%.  High dose ibutilide was more effective than DL-Sot in AF (44% vs. 11%) and than low dose ibutilide (44% vs. 20%, p<0.01) | Bradycardia (6.5%) and hypotension (3.7%) were more common side effects w/ DL-sotalol. Of 211 pts given ibutilide, two (0.9%) who received the higher dose developed polymorphic VT, one of whom required direct current cardioversion | N/A | High dose I more effective than. DL Sotalol and than low dose I in AF (p<0.01) | Ibutilide was more effective than DL sotalol. Duration of atrial flutter or AF was predictor of success. |
| Benditt DG  1999  (196)  [10496434](http://www.ncbi.nlm.nih.gov/pubmed/?term=10496434) | Prospective dose finding study | Randomized | Sotalol 80 BID (59)  Sotalol 120 BID (63)  Sotalol 160 BID (62)  Placebo (69) | N/A | 50 pts - outpatient  134 pts - inpatient  SHD 57% | H/o torsade de pointes, CHF, QI >450 msec, hypokalemia, hypomagenesemia, bradycardia. | Time to first recurrent symptomatic AF and/or atrial flutter after reaching drug steady state (p=0.004, significant longer time to recurreance for sotalol 120 mg BID vs. placebo) | No cases of VT/VF/torsade  QT>520 ms in 7 pts (4 in 120 mg BID and 3 in 160 mg BID)  Premature discontinuation due to AEs 25% inpatients, but 6% of outpatients (bradycardia predominantly) | N/A | N/A | It is unrealistic to define efficacy in tx of AF and atrial flutter.  HF pts for AF and atrial flutter not evaluated. |
| Doni F  2000  (197)  [170334595](http://www.ncbi.nlm.nih.gov/pubmed/11194595) | Pace termination of atrial flutter via trans esophageal pacing.  Randomized to 4 groups | 80 | Randomized to 4 groups:  A) Short bursts (5 sec) atrial pacing w/o drug  B) Short bursts (5 sec) atrial pacing after propafenone 600 mg  C) Long burst (30 sec) atrial pacing w/o drug  D) Long burst (30 sec) atrial pacing after propafenone 600 mg | N/A | Atrial flutter- new onset | N/A | Successful flutter pace termination in:  20%  55%  50%  85% | N/A | N/A | (p<0.05: C vs. A)  (p<0.05: D vs. B).  (p<0.05: B vs. A and D vs. C)  No other stats provided | Propafenone + long bursts of atrial pacing was best at terminating atrial flutter |
| Natale A  2000  (198)  [10841241](http://www.ncbi.nlm.nih.gov/pubmed/?term=10841241) | Multicenter prospective randomized comparison of antiarrhythmic therapy vs. first-line RF ablation in pts w/ atrial flutter. | 61 | Group 1: 30 randomized to drug therapy | Group 2: 31 randomized to RFA | Inclusion: At least two symptomatic episodes of atrial flutter in the last four mo.  . | Exclusion:1) prior evidence of AF (AF); 2) the presence of significant left atrial enlargement (≥4.5 cm); and 3) previous treatment w/ antiarrhythmic medications | 1) Rehospitalization: medication group- 63% required one or more rehospitalizations, vs. post-RF ablation, 22% of pts were rehospitalized (p<0.01).  2) Post RF ablation, 29% developed AF vs. 53% of pts receiving medications (p<0.05).  3) Sense of well being (pre-RF 2.0±0.3 vs. post-RF 3.8±0.5, p<0.01) and function in daily life (pre-RF 2.3±0.4 vs. post-RF 3.6±0.6, p<0.01) improved after ablation, but did not change significantly in pts treated w/ drugs. | N/A | N/A | 1) Rehospitalization more common w/ meds (p<0.01)  2) AF more common post RFA than meds (p<0.05)  3) Sense on well being improved w/ RFA but not meds (change in scoe p<0.01) | RF ablation could be considered a first-line therapy due to the better success rate and impact on QOL, the lower occurrence of AF and the lower need for rehospitalization at f/u. |
| Delacretaz E  2001  (199)  [11345382](http://www.ncbi.nlm.nih.gov/pubmed/?term=11345382) | Ablation: Single center, non-randomized trial comparing ablation of multi IART circuits in adults w/ CHD guided by entrainment mapping w/ and w/o 3D electroananatomic mapping | 20 pts (47 circuits) | To define an approach for mapping and ablation, combining anatomy, activation sequence data and entrainment mapping.  a) 7 pts w/ ablation guided by entrainment mapping only | b)13 pts w/ ablation guided by entrainment and 3D electroanatomic mapping | N/A | Recurrent IART refractory to meds.  Late post repair of CHD | Overall 38 (81%) of 47 IARTs successfully ablated. In f/u ranging from 3-46 mo:  a)16 (80%) of 20 pts remains free of recurrence  b)Success similar in both groups but fluoroscopy time decreased from 60 +/- 30 to 24 +/- 9 min/procedure w/ addition of 3D electroanatomic mapping | N/A | N/A | No statistical analysis | Entrainment mapping combined w/ 3D electroanatomic mapping allows delineation of complex re-entry circuits and critical isthmuses as targets for RFA as a satisfactory treatment modality for IARTs related to CHD. |
| Delle Karth G  2001  (200)  [11395591](http://www.ncbi.nlm.nih.gov/pubmed/?term=11395591) | To compare the efficacy of IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion for immediate (4 h) and 24-h rate control during AF | Randomized prospective, controlled | IV diltiazem bolus/infusion vs. IV amiodarone bolus vs. IV amiodarone bolus/infusion | N/A | Critically ill pts w/ recent-onset AF w/ ventricular rate >120 bpm | N/A | Sustained heart rate reduction ≥30% w/in 4 h  70% vs. 55% vs. 75% | Bradycardia or hypotension  35% vs. 0% vs. 5% | Uncontrolled tachycardia  0% vs. 45% vs. 5% | 1° endpoint: NS  2° endpoint  p<0.00016  Safety endpoint  p=0.01 | The study speaks about rate control during recent AF or atrial flutter in really sick pts. |
| DIAMOND  2001  (201)  [11457747](http://www.ncbi.nlm.nih.gov/pubmed/?term=11457747) | RCT, double-blind  To evaluate the efficacy of dofetilide to maintain SR in pt w/ LV dysfunction | 506 pts | Dofetilide 500 mcg/d (249) | Placebo (257) | Inclusion: Persistent AF associated w/ either HF or recent acute MI  Dose reduction for renal insufficiency  BBB), K <3.6 or >5.5, CrCl <20 mL/min | Exclusion: HR: <50 bpm, QTc >460 msec (500 msec w/ | Probability of maintaining SR at 1 y  79% dofetilide  42% w/ placebo  (p<0.001) | No effect on all-cause mortality  Dofetilide associated w/ reduced rate of rehospitalization | N/A | Torsade de pointes occurred in 4 dofetilide pts (1.6%) | Subjects not stratified by rhythm. Differences in population, Lft atrial size, LV diastolic dysfunction, and MR could have influenced results. |
| Gallagher MM  2001  (202)  [11691530](http://www.ncbi.nlm.nih.gov/pubmed/?term=11691530) | Cardioversion: design a more efficient protocol for the electrical cardioversion of atrial arrhythmias | 1838 attempts at cardioversion of AF and 678 attempts at cardioversion of flutter | Analyzed the effects of different energy deliveries at terminating either AF or atrial flutter in pts w/ arrhythmias of varying duration. | N/A | AF or atrial flutter undergoing DC cardioversion | N/A | Conversion rates were:  a) AF of >30 d duration = 5.5% at <200 J; 35% at 200 J and 56% at 360 J.  b) atrial flutter= 68% at 100 J  c) AF of >30 d duration, shocks of <200 J = 6.1%  d) AF >180 d= 2.2% at 200 J | N/A | N/A | For AF >180 d, initial use of a 360 J shock was associated w/ the eventual use of less electrical energy than w/ an initial shock of ≤100 J (581±316 J vs. 758±433 J, p<0.01, Mann-Whitney U test). | An initial energy setting of ≥360 J can achieve cardioversion of AF more efficiently in pts than traditional protocols, particularly w/ AF of longer duration. |
| Wazni O  2003  (203)  [14610012](http://www.ncbi.nlm.nih.gov/pubmed/?term=14610012) | Randomized study comparing combined pulmonary vein-left atrial junction disconnection and cavotricuspid isthmus ablation vs. pulmonary vein-left atrial junction disconnection alone in pts presenting w/ typical atrial flutter and AF. | 108 | Consecutive pts w/ documented symptomatic AF and typical atrial flutter were randomly assigned to have PV-LAJ disconnection combined w/ CTI ablation (group 1, n=49) or PV-LAJ disconnection alone (group 2, n=59). | PV-LAJ disconnection combined w/ CTI ablation (group 1, n=49) or PV-LAJ disconnection alone | Preablation proof of both atrial flutter and AF on ECG, 1 documented episode of typical atrial flutter while not on antiarrhythmics | N/A | W/in the first 8 wk after ablation, 32 of the group 2 pts had typical atrial flutter documented, whereas none was seen in group 1. Twenty of these 32 converted to sinus rhythm after initiating AADs. Twelve were cardioverted, and AADs were started. After 8 wk, all AADs were stopped, and only 3 pts continued to have recurrent sustained typical atrial flutter that was eliminated by CTI ablation. Beyond 8 wk of f/u, 7 pts in group 1 and 6 pts in group 2 (14% and 11%, respectively) continued to have AF. Ten of these 13 pts underwent a repeat PV-LAJ disconnection procedure and were cured. The remaining 3 remained in normal sinus rhythm while taking AADs. | N/A | N/A | N/A | Isolating of all 4 pulmonary vs. is challenging.  No f/u beyond 1 y. |
| LADIP Trial  2006  (204)  [17030680](http://www.ncbi.nlm.nih.gov/pubmed/?term=17030680%5D) | Randomized study comparing amiodarone and RF ablation after the first episode of symptomatic atrial flutter | 104 pts w/ atrial flutter: | group I= 52 pts treated w/ RFA as 1st line | Group2 treated w/ cardioversion and amiodarone as 1st line | 1 episode of symptomatic typical atrial flutter | N/A | Recurrence of flutter: 3.8% after RFA vs. 29.5% w/ amiodarone and cardioversion; p<0.0001 | Complications of treatment:  Five complications (10%) were noted in group II (SSS in 2, hyperthyroidism in 1, and hypothyroidism in 2) and none in group I (0%) (P=0.03). | long-term risk of subsequent AF (AF):  25% after RFA vs. 18% after amiodarone and cardioversion (p=NS) | RFA reduced recurrences of flutter vs. amiodarone and caridoversion (p<0.0001)  RFA not different than amiodarone and cardioversion at occurrence of AF (p=NS). Fewer complications w/ RFA than amiodarone + cardioversion (p=0.03) | RFA should be considered first line therapy even after 1 recurrence of atrial flutter |
| Kuniss M  2009  (205) [19959115](http://www.ncbi.nlm.nih.gov/pubmed/19959115) | Prospective randomized comparison of durability of  bidirectional conduction block in the cavotricuspid isthmus in  pts after ablation of common atrial flutter using  cryothermy and RF energy: The CRYOTIP study | 191 | Cryoablation  Do people use this for atrial flutter ablation? | Vs. standard RFA | Inclusion: 1. One episode of ECG-documented typical atrial flutter symptomatic  w/ eligibility for ablation treatment  2. Age between 18 and 80 y  3. Written informed consent for the ablation procedure and  the invasive f/u procedure after 3 mo. | Exclusion: atypical flutter | Acute success rates: 91% (83/91) in the RF group vs. 89% (80/90) in the cryoablation group (P=NS). Invasive  2) f/u 3 mo EP study available for 60 pts in the RF group and 64 pts in cryoablation group.  3) Persistent BCB confirmed in 85% of the RF group vs. 65.6% of the cryoablation group.  4)The primary end-point= nonpersistence of BCB block was seen in 15% of the RF group vs. 34.4% of the cryoablation group (P<0.014). | N/A | Secondary end-point-pain perception during ablation was significant lower in the cryoablation group (*P*<0.001) | Acute success RFA vs. cryoablation (p=NS)  Pesristent BCB- cryoablation inferior to RFA (p<0.014) | Persistence of BCB in pts treated w/ cryoablation  reinvestigated after 3 mo is inferior to that pts  treated w/ RF ablation, as evidenced by the higher recurrence  rate of common atrial flutter seen in this study. |
| Steinwender C  2009  (206)  [19136164](http://www.ncbi.nlm.nih.gov/pubmed/?term=19136164) | Randomized placebo controlled Trial: Assess pretreatment w/ magnesium for conversion w/ Ibutilide: Randomized 117 pts (58 w/ and 59 w/o pre-injection of magnesium; 65 w/ typical atrial flutter and 52 w/ atrypical atrial flutter. | 117- 65 typical flutter; 52 atypical flutter | 2 randomized groups:  Group 1) 4 g of IV magnesium  sulfate | Vs. Group 2) placebo immediately before administration of a maximum dose of 2 mg of ibutilide fumarate | Typical and atypical atrial flutter | N/A | 1) TAF: pre-injection IV magnesium improved efficacy of ibutilide for conversion (85% w/ magnesium vs. 59% w/ placebo, p=0.017).  Atypical atrial flutter: no significant difference in conversion rates between pts receiving magnesium vs. placebo (48% vs. 56%,p=0.189) | No effect of magnesium on QTc interval.  QTc intervals at 30 min after ibutilitde did not differ between patients w/ and w/o ventricular ectopy | N/A | Preinjcention w/ Mg superior for conversion w/ ibutilide in trypical atrial flutter (p=0.017)  Preinjection w/ Mg for conversion w/ ibutilide no different (p=NS)  Preinjection wih Mg did not affect QT (no statistic offered) | Pre-injection of magnesium significantly enhances the efficacy of ibutilide for the conversion of typical atrial flutter but not of atypical atrial flutter. |
| Bastani H  2012  (207)  [22927662](http://www.ncbi.nlm.nih.gov/pubmed/?term=22927662) | Randomized comparison in pts w/ typical atrial flutter. RFA- 3.5 mm open-irrigated-tip catheter and Cryoablation a 9 F, 8 mm tip catheter. Ablation endpoint was bidirectional  CTI block. | 153 | Ablation RFA- 3.5 mm open-irrigated-tip catheter (N= 75) | Cryoablation a 9 F, 8 mm tip catheter (N=78) | Inclusion: Pts w/ a h/o AF included if they had predominant atrial flutter under chronic treatment w/ class I or III antiarrhythmic agents. | Exculsion: (i) prior ablation for atrial flutter; (ii) atrial flutter related to recently undergone surgery, hyperthyroidism or other severe disease; (iii) inability to adhere w/ the study protocol; (iv) pregnancy; (v) predominant AF; and (vi) contraindication to warfarin. | Primary endpoint: demonstration of long-term efficacy  defined as no symptomatic recurrence of atrial flutter at the 6-mo f/u.  Success rate at 6-mo f/u was 93% (73 of 78) for Cryoablation vs. 97% (73 of 75) for RF (p= 0.86). | safety assessed by the rate of periprocedural complications, procedure and fluoroscopy times, and the level of pain experienced by the pt during the ablation procedure  Procedural time was longer in the cryoablation group (152±54 min) than the RF group (116±41 min) (P<0.001).  Cryoablation was less painful compared w/ RF (mean VAS-Cryoablation 0.7±1.2 vs. VAS-RF 4.6±2.0; P<0.001). | Secondary end-points: acute ablation success defined as bidirectional CTI-block;  Acute success rate 92% for cryoablation vs. 95% for RF (p=0.58). | 1) Acute success rate for Cryoablation vs. RF (p=0.58).  2) Procedural time was longer in the Cryoablation group vs. RF group (p<0.001).  3) Cryoablation was less painful compared vs. RF (p<0.001).  4) Success rate at 6-mo f/u was no different for Cryoablation vs. RF (P= 0.86).  No major adverse events occurred in any group. | Cryoablation is not inferior to RFA for typical flutter |
| Mohanty s  2013  (208) [23572499](http://www.ncbi.nlm.nih.gov/pubmed/?term=23572499) | Single-blind, randomized study- Examined the impact of different ablation strategies on AF recurrence and QOL in coexistent AF and atrial flutter. | 360 pts w/ documented AF and atrial flutter | Blinded and randomized to group 1, AF±atrial flutter ablation (n=182), or group 2, atrial flutter ablation only (n=178). AF recurrence was evaluated w/ event recording and 7-d Holter at 3, 6, 9, and 12-mo f/us. QOL was assessed at baseline and at the 12-mo f/u w/ 4 questionnaires. | AF ± atrial flutter ablation vs. atrial flutter ablation only | 1 antiarrhythmic and preablation evidence of typical atrial flutter by 12-lead surface ECG. | <18 or >85 y old, previous ablation, left atrium size ≥5 cm, or contraindication to oral anticoagulation | At 21±9 mo of f/u, 117 in group 1 (64%) and 34 in group 2 (19%) were arrhythmia free (P<0.001). In group 1, scores on most quality-of-life subscales showed significant improvement at f/u, whereas group 2 pts derived relatively minor benefit. | N/A | N/A | Group 1 vs. Group 2 p<0.001 | Questionnaires didn’t address comorbidities, smaller sample size |

AAD, antiarrhythmic drug; AE, adverse events; AF, atrial fibrillation; AMI, acute myocardial infarction; AV, atrioventricular; BBB, bundle branch block; BCB, bidirectional conduction block; bid, two times per day; BP, blood pressure; bpm, beats per min; CHD, congenital heart disease; CHF, congestive heart failure; CI, confidence interval; CL, cycle length; CrCl, creatinine clearance; CTI, cavotricuspid isthmus; DC, direct current; ECG, electrocardiogram; EP, electrophysiological; f/u, follow up; HF, heart failure; h/o, history of; HR, heart rate; IART, intraatrial reentrant tachycardia; IV, intravenous; LBBB, left bundle branch block; LV, left ventricular; MI, myocardial infarction; MR, mitral regurgitation; N/A, not applicable; NS, non-significant; NSR, normal sinus rhythm; NSVT, non-sustatined supraventricular tachycardia; NYHA, New York Heart Association; pt, patient; PV-LAJ, pulmonary vein-left atrial junction; QTc, corrected QT interval; RCT, randomized controlled trial; RF, radiofrequency; RFA, radiofrequency ablation; SBP, systolic blood pressure; SD, standard deviation; SHD, structural heart disease; SR, sinus rhythm; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; TAP, transesophageal atrial pacing; tx, transplant; VAS, visual analog scale; VF, ventricular fibrillation; VT, ventricular tachycardia; w/, with; w/o, without; and WPW, Wolff-Parkinson-White syndrome.

Data Supplement 17. Nonrandomized Trials, Observational Studies, and/or Registries of Atrial Flutter – Section 7

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| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Van Gelder IC  1989  (181)  [2511744](http://www.ncbi.nlm.nih.gov/pubmed/2511744) | Persistent AF and atrial flutter after cardioversion randomized to flecainide or no therapy to reduce recurrence | 81 pts (16 pts with atrial flutter – 6 in flecainide group and 10 in control group) | Inclusion: Persistent AF and atrial flutter referred for cardioversion. All pts w/ atrial flutter received verapamil 240 mg daily to reduce 1:1 AV conduction.  Exclusion: <16 y or >80 y, CHF, angina, MI <2 y before, bifascicular block or bundle branch block, sick sinus syndrome without pacemaker, severe systemic disease | Arrhythmia-free survival after cardioversion | No significant difference in arrhythmia free survival. However, it postponed time to arrhythmia recurrence.  Adverse effects: 9% flecainide group experience side effects. 3 pts in flecainide group required pacemaker (2 w/ symptomatic sinus arrest and 1 with AV block). 1 pt had increase ventricular ectopy burden requiring discontinuation. | No significant difference in arrhythmia free survival in pts w/ persistent AF or atrial flutter. However, it postponed time to arrhythmia recurrence after cardioversion. |
| Pietersen 1991  (209)  [1900978](http://www.ncbi.nlm.nih.gov/pubmed/?term=1900978) | Randomized, placebo controlled cross over design trial flecainide 150 mg bid vs. placebo. Pts received 3 mo of therapy w/ another 3 mo of crossover therapy. | 43 pts | Inclusion: Paroxysmal AF or atrial flutter >3 episodes <3 mo prior to enrollment  Exclusion: CHF, reduced LV fractional shortening, WPW, syncope, thyroid disease, sinus node dysfunction w/o pacer, more than isolated PVC’s | Number of symptomatic recurrences | Outcome: Significant reduction in number of episodes with flecainide treatment (p<0.002).  Adverse events: 1 pt developed 1:1 conduction of atrial flutter. 1 sudden death in flecainide group (bathing in the cold Norway sea after drinking alcohol). Other minor adverse events occurred in 74% (mostly visual changes, dizziness, and GI side effects) resulting in 2 withdrawals. | Flecainide significantly redcuced the number of recurrent episodes of AF or flutter. |
| Aliot E  1996  (210)  [8607394](http://www.ncbi.nlm.nih.gov/pubmed/?term=8607394) | Randomized, open-label, long-term, parallel, comparative multicenter study comparing propafenone to flecainide | 97 pts (5 with atrial flutter) | Inclusion: adults with paroxysmal AF or atrial flutter on ECG or Holter  Exclusion: MI, recent heart surgery, VT, CHF, PR >280 ms, QRS >150 ms, sinus node dysfunction or heart block in absence of pacemaker | Proportion of pts remaining on therapy at 1 y | 0.619 remained on flecainide 1 y  0.469 propafenone  Adverse events: 1 death in propafenone group. 8.5% flecainide experienced neurological side effects, 16% propafenone group GI side effects | In paroxysmal AF and paroxysmal atrial flutter, flecainide and propafenone not significantly different. Too few pts with atrial flutter to draw conclusions. Rate of side effects was greater with propafenone. |
| Baker  1996  (211)  [8800118](http://www.ncbi.nlm.nih.gov/pubmed/?term=8800118) | Single center trial evaluating efficacy of anatomically based RFA ablation for the treatment of IART in pts w/ previous atrial surgery | 14 pts | H/o atrial surgery and clinical intraatrial reentrant tachycardia | Freedom from recurrence of IART | Successfully terminated in 13 pts (93%). Six pts required repeat ablation for recurrence. Twelve (86%) remained free of IART at 7.5 mo. | RFA is effective technique for IART in pts w/ previous atrial surgery |
| Kalman JM  1996  (212)  [8565168](http://www.ncbi.nlm.nih.gov/pubmed/?term=8565168) | Single center observation cohort study to evaluate the success of RFA for IART in CHD using targeted ablation of critical isthmus | 18 pts | IART and repaired CHD | Acute success | Successful termination in 15 pts (21 arrhythmias). During f/u (mean 17 mo), 11 pts (61%) remained free of recurrence (2 remained on antiarrhythmic drug) | Describes early experience w/ targeted RF to critical isthmus in pts w/ repaired CHD. Successful ablation IART can be achieved w/ ablation to critical isthmus of conduction. |
| Triedman  1997  (213)  [9316535](http://www.ncbi.nlm.nih.gov/pubmed/?term=9316535) | Single center retrospective trial evaluating the short and mid term efficacy of RFA for IART in CHD | 45 pts | Pts w/ CHD w/ IART undergoing RFA  Non-isthmus dependent flutter instead of IART | Freedom from recurrence of IART | 73% acutely successful. Recurrence 53% during mean f/u of 17.4 mo. Seven underwent repeat ablation. | Early experience w/ RFA for IART in CHD reduced events in population of pts. However, recurrence was frequent often w/ new IART circuits. |
| Huang DT  1998  (214)  [9607453](http://www.ncbi.nlm.nih.gov/pubmed/?term=9607453) | Single center trial assessing efficacy of combining pharmacologic and simple ablative therapies in treating AF in small targeted subset of pts | 13 pts w/ AF who converted to electrocardiographic atrial flutter during anti-arrhythmic treatment | “Typical” atrial flutter in 11 pts and “atypical” atrial flutter in 2 suggested by surface ECG.  Intracardiac mapping and entrainment studies found 9 pts w/ CCW isthmus dependent atrial flutter and remaining 4 had complex activation patterns. | Successful ablation w/o recurrence at mean f/u 14.3±6.9 mo | All 9 pts w/ typical atrial flutter had successful ablation and 88.9% maintained sinus rhythm in f/u period (while continued on antiarrhythmic drugs)  None of 4 pts w/ complex activation patterns had successful ablation | In pts who experience conversion of AF to typical isthmus dependent flutter during anti-arrhythmic drug therapy, ablation and continuation of pharmacologic therapy is effective in maintaining sinus rhythm. |
| Chan DP  2000  (215)  [10982544](http://www.ncbi.nlm.nih.gov/pubmed/?term=10982544) | Single center study assessing the importance of atrial flutter isthmus in post-operative IART | 19 postoperative CHD pts w/ IART | All study pts underwent EP study w/ entrainment mapping of atrial flutter isthmuses to determine PPIs. RFA performed at identified isthmus to create line of block. | Successful ablation | 21 IARTS identified in 19 pts  Atrial flutter isthmus part of circuit in 15 of 21 (71.4%)  Sites near atrial incisions or suture lines in remaining 6 of 21  Ablation successful in 19 of 21 (90.4%) of IARTs and in 14 of 15 cases of at the atrial flutter isthmus (93.3%) | When IART occurs late after repair of CHD, atrial flutter isthmus may be part of reentrant circuit and should be evaluated as a target for ablation. |
| Jais  2000  (216)  [10869265](http://www.ncbi.nlm.nih.gov/pubmed/?term=10869265) | Single center retrospective observational trial to assess efficacy of mapping guided RFA | 22 pts | Pts w/ persistent left atrial flutter predominantly in pts w/ SHD. 18 (81%) failed amiodarone. | Acute success and mid-term f/u | Complete activation map achieved in 17/22 pts. 20 pts (90%) in sinus rhythm at the end of procedure.  7 pts required 2 procedures and 1 pt required 3 procedures.  During mean 15 mo f/u, 16 pts (73%) remained free of recurrence (2 remained on antiarrhythmic). | Describes various left atrial reentrant circuits and demonstrated feasibility of mapping guided RFA |
| Reithmann C  2000  (217)  [10775011](http://www.ncbi.nlm.nih.gov/pubmed/?term=10775011) | Single center trial assessing catheter ablation of CTI on amiodarone-induced atrial flutter and subsequent incidence of AF in comparison to CTI ablation of regular typical atrial flutter | 92 consecutive pts w/ typical atrial flutter who underwent CTI ablation | 3 groups  28 pts w/o h/o AF  10 pts w/ atrial flutter following amiodarone treatment for PAF  54 pt w/ AF and atrial flutter | Successful CTI ablation w/ bidirectional block eliminating atrial flutter and recurrence of AF during mean f/u 8±3 mo | Successful ablation achieved in 90% of amiodarone-treated pt’s and 93% of pts w/o amiodarone therapy  Recurrence of AF occurred in 20% amiodarone treated pts which was similar to pts w/o preexisting AF (25%) and markedly lower than pts w/ atrial flutter plus preexisting PAF (76%) | CTI ablation w/ bidirectional block and continuation of amiodarone therapy is effective for treatment of atrial flutter due to amiodarone therapy for PAF.  Hybrid therapy belongs in this guideline? Yes. Merit a rec? Yes. |
| Akar JG  2001  (218)  [11499727](http://www.ncbi.nlm.nih.gov/pubmed/?term=11499727) | Single center study assessing the coexistence of IART and IDAF in pts w/ SVTs after surgical correction of CHD | 16 consecutive pts diagnosed w/ both IART and IDAF | IART and IDAF diagnosed by standard criteria and entrainment mapping. 7 pts had classic atrial flutter morphology on surface ECG, whereas 9 had atypical morphology | Successful ablation w/o procedural complication or recurrence at mean f/u of 24 mo | Successful ablation performed in 13 of 14 (93%) IART and 9 of 10 (90%) IDAF circuits.  1 IART recurrence otherwise none reported at 24 mo  Slow conduction zone involved region of right atriotomy scar in 12 of 14 (86%) IART circuits  No procedural complications | IDAF and IART are the most common and commonly coexistant mechanisms of atrial re-entrant tachyarrhythmias in pts w/ surgically corrected CHD. Majority of IART circuits involve lateral RA and may be successfully ablated by lesion extending to IVC. |
| Nakagawa  2001  (219)  [11156882](http://www.ncbi.nlm.nih.gov/pubmed/?term=11156882) | Characterize the circuit of IART in pts w/ repaired CHD and evaluate success of RFA of w/in channels defined by electroanatomic mapping | 13 pts w/ 15 IARTs | Pts w/ repaired CHD and IART | Acute and medium term success | Ablation acutely eliminated inducibility of all 15 IARTs. During f/u of median 13.5 mo, 13 pts (81%) remained free of recurrence. Large area of low voltage scar identified in all pts w/ macroreentrant tachycardias. | RFA of IART in pts w/ repaired CHD using electroanatomic mapping and targeting channels has a reasonable success rate. |
| Deal BJ  2002  (220)  [12147539](http://www.ncbi.nlm.nih.gov/pubmed/?term=12147539) | Retrospective non-randomized comparison of cryoablation of inferomedial RA vs. extensive modified RA maze in pts undergoing Fontan revision w/ AT | 23 pts | Pts undergoing Fontan revision w/ AT  Maybe shouldn’t be in here since surgical; may be more recent papers breaking down the differences by types of CHD | Inducibility at f/u EP and long-term freedom from recurrence of AT | Inducibility of AT:  62% inferomedial RA ablation  7% modified RA MAZE  P<0.02  Freedom from AT (mean 43 mo f/u):  62% inferomedial RA ablation  0% modified RA MAZE  P<0.001 | Modified RA maze procedure is superior to anatomic isthmus block in treating reentrant AT in postoperative Fontan pts |
| Spector P  2010  (55)  [19699343](http://www.ncbi.nlm.nih.gov/pubmed/19699343) | Meta-analysis of ablation of atrial flutter and SVT. | A meta-analysis of 21 studies RFA in atrial flutter:18 primary studies w/ 22 treatment arms and 1,323 pts) | N/A | Evaluate the safety and efficacy of RFA of typical atrial flutter and AV node-dependent SVT in adult pts | Single-procedure success for atrial flutter was 91.7% (95% CI: 88.4%-94.9%).  Multiple-procedure success was 97.0% (95% CI: 94.7%-99.4%). Postablation arrhythmia was noted in 13.2% of pts (95% CI: 7.5%-18.9%), while repeat ablation was reported in 8% (95% CI: 4.5%-11.4%). | RFA for the treatment of pts w/ atrial flutter and SVT report high efficacy rates and low rates of complications.  70% of pts who got ablation didn’t need it; interrelationship for AF and atrial flutter. When to ablate? 🡪 discussion. AF ablation covered in consensus document. Drive by protein disulfide isomerase vs. drive by flutter ablation. Both ways. |
| Coffey JO  2013  (221)  [23385050](http://www.ncbi.nlm.nih.gov/pubmed/?term=23385050) | Retrospective multicenter cohort study to assess the efficacy of RFA on atypical atrial flutter/AT | 91 pts w/ 171 ATs (1.9 / pt) | Pts w/ atypical atrial flutter/AT in pts w/ prior catheter ablation for AF, MAZE or other cardiac surgery, or idiopathic scar. Pts w/ on CTI-dependent flutter were excluded. | Acute and long-term success | Acute success was 97% for non-septal AT and 77% for septal AT. Long-term success rates 82% in pts w/ no septal AT and 67% in pts w/ 1 or more septal AT. Long-term success rates were 75%, 88%, and 57% for pts w/ ATs associated w/ prior catheter ablation, cardiac sugery/MAZE or idiopathic scar, respectively. | High-density activation mapping combined w/ selective entrainment mapping allows for reasonable successful RFA of non-CTI dependent ATs occurring after AF ablation, cardiac surgery, or in the setting of idiopathic scar. |
| Ghali WA  2005  (222) | Systematic review and meta-analysis of observational studies that investigated risk of thromboembolism associated with atrial flutter. | The meta analysis included 13 studies on embolic risk around time of cardioversion that included 1546 patients. For chronic risk, there were 14 studies involving 17,691 patients. | MEDLINE, EMBASE, bibliographies, and consultation with clinical experts were used to identify studies that report the risk of thromboembolism associated with attempted cardioversion and longer-term risk in patients with atrial flutter. | Risk of thromboembolism associated with atrial flutter around time of cardioversion or over the long term in chronic atrial flutter. | Around the time of cardioversion, the risk of thromboembolic events ranged from 0% to 7.3% depending of clinical factors.  Lower event rates were observed in patients taking anticoagulants.  The long term risk rate of thromboembolism was approximately 3% with sustained atrial flutter. | The findings of this systematic review strongly suggest that atrial flutter does indeed impart a risk of thromboembolism. |

AF indicates atrial fibrillation; AT, atrial tachycardia; AV, atrioventricular; bid, two times per day; CCW, counter-clockwise; CHD, congenital heart disease; CHF, congestive heart failure; CI, confidence interval; CTI, cavotricuspid isthmus; ECG, electrocardiogram; EP, electrophysiological; f/u, follow up; GI, gastrointestinal; h/o, history of; IART, intraatrial reentrant tachycardia; IDAF, isthmus-dependent atrial flutter; IVC, inferior vena cava; LV, left ventricular; MI, myocardial infarction; N/A, not applicable; PAF, paroxysmal atrial fibrillation; PPI, postpacing interval; pt, patient; PVC, premature ventricular contraction; RA, right atrial; RF, radiofrequency; RFA, radiofrequency ablation; SHD, structural heart disease; SVT, supraventricular tachycardia; w/, with; w/o, without; and WPW, Wolff-Parkinson-White syndrome.

Data Supplement 18. Randomized Trials for Junctional Tachycardia – Section 8

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Name, Author, Year** | **Aim of Study** | **Study Type (Size, N)** | **Study Intervention Group (n)** | **Study Comparator Group (n)** | **Pt Population** | | **Endpoints** | | | **P Values, OR: HR: RR: & 95% CI:** | **Study Limitations & Adverse Events** |
|  |  |  |  |  | ***Inclusion Criteria*** | ***Exclusion Criteria*** | ***Primary Endpoint (efficacy) and Results*** | ***Safety Endpoint and Results*** | ***Secondary Endpoint and Results*** |  |  |
| Mamchur SE  2012  (223)  [22978723](http://www.ncbi.nlm.nih.gov/pubmed/?term=mamchur+se%2C+kurilin+my) | Assess the risk of AV block during ablation of parahisian ectopic foci prior to ablation by high-amplitude pace mapping. | RCT (N=20) | Ablation at site where high-amplitude (15-30 mA) pacing revealed absence of His capture (wide QRS complexes) (n=11) | Ablation performed in conventional manner (n=9) | Pts w/ parahisian ectopic foci (i.e., pts w/ focal JT) | Pts w/ SHD | Group 1: Ablation (standard approach) effective in 6/11 (55%); Group 2: Ablation effective w/ high amplitude pacing in 9/9 (100%),  p=0.02 | Group 1: 27% AV block; Group 2: no complications,  p=0.09 | Late recurrence of ectopic activity similar in both groups, p=NS | Group 1: Ablation effective in 6/11 (55%); Group 2: Ablation effective in 9/9 (100%),  p=0.02. Group 1: 27% AV block; Group 2: no complications,  p=0.09. Late recurrence of ectopic activity similar in both groups, p=NS. | Small sample, generalizability unclear. Cannot use method for ectopic focus in right coronary sinus or the aorta. |

AV indicates atrioventricular; NS, non-significant; pt, patient; RCT, randomized controlled trial; SHD, structural heart disease; and w/, with.

Data Supplement 19. Nonrandomized Trials, Observational Studies, and/or Registries of Junctional Tachycardia – Section 8

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| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Pharmacological Therapy | | | | | | |
| Ruder  1986  (224)  [3698238](http://www.ncbi.nlm.nih.gov/pubmed/3698238) | Case report | n=5 | 5 adult pts w/ JT (one pt refused drug therapy) | Control or eradication of arrhythmia | All pts responded to beta-blockers (nadolol, propranolol), and best response w/ beta-blockers w/ procainamide. | First report of JT in adults. Good response to beta-blockers. Only 4/5 pts underwent EP study to definitively identify junctional origin. |
| Cook  1988  (225)  [1951023](http://www.ncbi.nlm.nih.gov/pubmed/1951023) | Case report | n=1 | 19 y w/ refractory JT | Flecainide therapy for JT refractory to AV nodal blockers, burst atrial or ventricular pacing | Flecainide 150 mg bid successful in restoring SR | First report of successful treatment of “incessant” JT w/ class Ic agent. |
| Kuck  1988  (226)  [3144166](http://www.ncbi.nlm.nih.gov/pubmed/3144166) | Case series | n=3 | 16 total pts w/ ectopic atrial tachyarrhythmia in study, 2 spontaneous JT (not inducible), 1 incessant JT | Flecainide and encainide therapy for JT | Flecainide effective in 2 pts w/ spontaneous JT (200 and 300 mg/d). Pt w/ incessant JT had prolongation of H-V interval and hypotension. | Encainide arm not valid for guidelines, but flecainide results valid for treatment of spontaneous JT. Builds on Cook’s data above. |
| Villain  1990  (227)  [2184944](http://www.ncbi.nlm.nih.gov/pubmed/2184944) | Multicenter study; pediatric population | n=26 | Infants w/ JT | AAD therapy in congenital JT, w/ success defined as HR <150 bpm, partial success as HR >150 bpm w/ sx relief | Combinations of digoxin, propranolol, amiodarone, quinidine, flecainide, chlorpromazine, phenytoin. 10 pts treated w/ amiodarone monotherapy —6 successes, 2 partial successes, 2 failures. One death in f/u. Amiodarone combination therapy less effective. | Amiodarone monotherapy is effective for congenital JT, but associated w/ some mortality. Authors comment that ablation should be reserved for drug-refractory JT. Digoxin ineffective in rate control, and may be harmful--specifically, incriminated in producing VF in 4 wk old child; and atrial tachycardia and then atrial flutter in 10 d old infant. |
| Paul  1992  (228)  [1527301](http://www.ncbi.nlm.nih.gov/pubmed/1527301) | Case series; pediatric population | n=4 | Infants w/ congenital JT | Propafenone therapy for congenital JT | Effective at restoring SR w/ doses of 300 mg/m2 w/ f/u ranging 1-36 mo | Efficacy of propafenone in pediatric population can avoid need for ablation in young population, and early toxicity of amiodarone. |
| Heusch  1994  (91)  [7527342](http://www.ncbi.nlm.nih.gov/pubmed/7527342) | Retrospective cohort study; pediatric population | n=3 | 72 pediatric pts w/ supraventricular arrhythmias treated w/ propafenone, only 3 pts had JT | Efficacy of propafenone in suppressing supraventricular arrhythmia | Successful in 2/3 pts w/ JT | Supports results of Paul et al for use of propafenone, despite small subset of pts w/ JT. |
| Raja P  1994  (229)  [7946778](http://www.ncbi.nlm.nih.gov/pubmed/?term=raja+p%2C+hawker+re) | Retrospective cohort study; pediatric population | n=16 | Postoperative (CHD) JET | Efficacy of amiodarone for rate control | Mean HR of 200 bpm, reduced to mean 153-170 in 24-h f/u | Amiodarone effective in HR and hemodynamic control for postoperative JT. |
| Lee  1999  (230)  [10392383](http://www.ncbi.nlm.nih.gov/pubmed/10392383) | Prospective cohort study | n=17 (age 12-83) | Pts developed JT during EP study, and all inducible w/ isoproterenol | Effect of adenosine and verapamil in catecholamine-inducible JT | Adenosine terminated rhythm in all pts, 11 w/ transient AV block. IV verapamil terminated rhythm in all 10 pts given the drug | Supports treatment of JT due to enhanced automaticity w/ adenosine and verapamil. Presence of AV block w/ adenosine suggests differential effect on automaticity and AV conduction. Age range spans pediatric and adult. |
| Sarubbi  2002  (231)  [12117855](http://www.ncbi.nlm.nih.gov/pubmed/12117855) | Retrospective cohort study | n = 9, age 2-6 mo | 5/9 pts w/ family h/o JT;  6/9 w/ decreased ventricular function | Effects of digoxin, propafenone, amiodarone | Digoxin alone ineffective; propafenone alone effective in 2/9 pts; amiodarone in combination w/ propafenone or flecainide effective in 6 pts | Digoxin or propafenone alone ineffective; Amiodarone effective as part of combination therapy w/ propafenone; or flecainide; genetic contribution noted. |
| Ablation Therapy | | | | | | |
| Scheinman MM  1994  (232)  [8074039](http://www.ncbi.nlm.nih.gov/pubmed/8074039) | Case series | n=8 | Adult pts w/ JT | RFA of JT | 6/8 w/ JT underwent ablation, 2 underwent AVJ ablation. Only 2 w/ preserved AV conduction. | Early report establishing that RF ablation may be successful therapy for JT. |
| Hamdan M  1996  (233)  [8960595](http://www.ncbi.nlm.nih.gov/pubmed/?term=hamdan+m%2C+vanhare+gf) | Case series | n=11 | Pts w/ JT (age 1-66) | RFA of JT | RFA successful w/o complications in 9/11 pts (82%). 7/9 successful w/ ablation at site of earliest atrial activation and 2 pts required empiric lesions in posteroseptal area due to lack of VA conduction. CHB developed in 1 pt, and RFA failed in 1 pt. F/u 1-20 mo. | RF ablation a largely successful strategy in series of pts, half of which were adults. |
| Law IH  2006  (234)  [16876738](http://www.ncbi.nlm.nih.gov/pubmed/16876738) | Retrospective cohort study; pediatric population | n=6 (range 7-36 y, median 8 y) | All pts who underwent cryoablation for symptomatic, non-postoperative JT, refractory to AADs (primarily beta-blockers), at 2 hospitals. | Efficacy and safety of cryoablation for JT | 4 pts had no JT at end of procedure. All 5 pts who underwent procedure were free of JT on up to 2 y of f/u. | Early report of cryoablation of JT, safe and effective (except w/ proximity to His-Purkinje system), and may confer long term benefit.  This study studied a small number of primarily pediatric pts at two institutions. Pharmacologic therapy not attempted in all pts. One pt had an ectopic focus proximal to His-Purkinje, and cryomapping resulted in transient CHB, so cryoablation not performed. |
| EP Study Diagnosis | | | | | | |
| Meiltz A  2006  (235)  [16627404](http://www.ncbi.nlm.nih.gov/pubmed/?term=meiltz+a%2C+weber+r) | Retrospective cohort, multicenter | n=49 | Adults w/ PJRT confirmed at EP study, both paroxysmal (53%) and incessant | Describe results of RFA in adults w/ PJRT | RFA successful in 94% w/o complications, and long term success 100% w/o AADs, w/ 49 mo mean f/u. | Rare report of PJRT in adults only, so results pertinent to guidelines, and support RF ablation as first line therapy. |
| Padanilam BJ  2006  (236)  [19007691](http://www.ncbi.nlm.nih.gov/pubmed/19007691) | Prospective cohort study | n=39 | Adults w/ AVNRT, JT, or “clinically indeterminate.” | To distinguish JT or AVNRT based on specific responses to PACs delivered at different phases of the tachycardia cycle | PACs introduced during His refractoriness did not affect tachycardia. Earlier PACs preexcite the immediate His and ventricle, w/o terminating tachycardia, confirming JT. For AVNRT, 61% sensitivity, 100% specificity; for JT, 100% sensitivity and specificity. | The response to PACs during tachycardia can distinguish JT from AVNRT w/ 100% specificity and high sensitivity.  However, PACs introduced during His refractoriness can lead to misdiagnosis of JT as AVNRT if dual AV nodal physiology is present. Furthermore, if double ventricular responses are present, a PAC during AVNRT can advance the His w/ continuation of the tachycardia, misdiagnosed as JT. |
| Srivathsan K  2007  (237)  [17916156](http://www.ncbi.nlm.nih.gov/pubmed/17916156) | Retrospective cohort study | n=35 | Typical AVNRT and evidence of JT during EP study and/or ablation | To assess the utility of delta H-A interval (difference in the H-A intervals observed during tachycardia and basal RV pacing to differentiate AVNRT and JT—delta HA = HA during pacing minus HA during tachycardia. (Helps to distinguish whether H-A interval represents true his conduction to the atria, or whether atria and His activated simultaneously from common focal source.) | Average H-A interval was -10 msec during AVNRT and 9 msec during JT (p<0.00001). Delta HA ≥0 has sensitivity/specificity of 89%/83%, PPV/NPV 84%/88% for diagnosis of JT. | Delta HA is a useful metric that can aid differentiation of AVNRT and JT during EP study. Utility in that JT ablation confers high risk of AV block. Limited in that spontaneous JT may be mechanistically different from JT seen w/ slow path modification. |
| Fan R  2011  (238)  [21220046](http://www.ncbi.nlm.nih.gov/pubmed/?term=fan+r%2C+tardos+jg+2006) | Prospective cohort study | n=21 | Adult pts referred to a single center for EP study and subsequent AVNRT ablation. | To investigate whether the tachycardia response to atrial overdrive pacing at a CL shorter than the tachycardia CL can elucidate whether the tachycardia is JT or AVNRT. | The paced AH interval was shorter for JT compared w/ AVNRT (86±19 msec vs. 338±59 msec, p<0.0001).  The mean CL of JT longer compared w/ AVNRT (614±118 msec vs. 373±65 msec, p<0.0001) | Atrial overdrive pacing during tachycardia can help to rapidly differentiate JT from AVNRT (transiently suppresses JT, entrains AVNRT).  Diagnosis of JT made on clinical grounds, although JT only observed post-ablation. Potential for misdiagnosis of AVNRT as JT. Included only spontaneous JT after AVNRT ablation (excluded “clinical” JT, i.e. not due to AVNRT ablation). |

AAD indicates antiarrhythmic drug; AV, atrioventricular; AVJ, atrioventricular junction; AVNRT, atrioventricular nodal reentrant tachycardia; bid, two times per day; bpm, beats per min; CHB, complete heart block; CHD, congenital heart disease; CL, cycle length; EP, electrophysiological; f/u, follow up; h/o, history of; HR, heart rate; IV, intravenous; JET, junctional ectopic tachycardia; JT, junctional tachycardia; NPV, negative predictive value; PAC, premature atrial contractions; PJRT, permanent junctional reciprocating tachycardia; PPV, positive predictive value; pt, patient; RFA, radiofrequency ablation; SR, sinus rhythm; sx, symptom; VA, ventriculoatrial; VF, ventricular fibrillation; w/, with; and w/o, without.

Data Supplement 20. Nonrandomized Trials, Observational Studies, and/or Registries of Special Populations – Section 9

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Pediatrics: Epidemiology | | | | | | |
| Lundberg A  1982  (239)  [7122164](http://www.ncbi.nlm.nih.gov/pubmed/?term=7122164) | Retrospective, single center | 49 | 49 babies SVT in infancy, 40 SVT, 9 atrial flutter/AF 86% males  F/u mean 24 y | SVT recurrence after infancy | Males w/ WPW: 60% recurrence.  Pts w/o WPW: 30% recurrence | Recurrent SVT after infant SVT: 30-60% |
| Deal BJ  1985  (240)  [3964800](http://www.ncbi.nlm.nih.gov/pubmed/?term=3964800) | Retrospective multicenter | 90 | 90 babies WPW and SVT ≤4 mo of age. SHD 20%. AVRT, one atrial flutter, no AF.  Mean f/u 6.5 y. | WPW outcomes infants w/ SVT | Cardioversion success 87%, chronic digoxin 85 pts. Deaths: 4.4%, 2 w/o SHD: all receiving digoxin. One no SHD developed cardiomyopathy thought due to recurrent high dose cardioversions. | Mortality 4.4%, (2 no SHD), all receiving digoxin.  1/3 pts developing wide QRS tachycardia died. |
| Perry JC 1990  (241)  [2229769](http://www.ncbi.nlm.nih.gov/pubmed/?term=2229769) | Retrospective, single center | 140 | 140 pts WPW w/ SVT <18 y old.  CHD 37%--23% of CHD = Ebstein’s. Multiple AC: 12%. | SVT recurrences vs. age w WPW | SVT age ≤2 mo: 31% recurrent SVT, average age 8 y.  SVT > age 5 y: 78% recurrent SVT during mean f/u 7 y. | SVT recurs more frequently in pts w/ first episode ≥ age 5 y. |
| Wu MH  1994  (242)  [7850817](http://www.ncbi.nlm.nih.gov/pubmed/?term=7850817) | Retrospective, single center | 90 | 90 pts w/ SVT <15 y old, median f/u 215 mo.  CHF 16%. Stroke 1 pt. | Recurrent SVT vs. age onset SVT | SVT age 1-5 y: 40% recurrent SVT prenatal SVT lowest risk recurrent SVT, followed by age <1 y, then 1-5 y; onset >5 y highest risk. | First SVT ≥5 y: highest risk for recurrent SVT vs. age 1-5 y, or age <1 y |
| Riggs TW 1999  (243)  [10393395](http://www.ncbi.nlm.nih.gov/pubmed/?term=10393395) | Retrospective, single center | 70 | 70 pediatric pts w/ SVT, vs. WPW and age.  Recurrent SVT: 29% w/ SVT <1 y, vs. 94% w/ SVT onset >1 y. | Risk recurrent SVT in young pts | Only sig predictor of recurrent SVT was age at presentation  WPW not significant multivariate. 11 | First SVT after age 1 y: high likelihood recurrent SVT vs. onset SVT <1 y (OR: 34.6). |
| Tortoriello TA  2003  (244)  [14583354](http://www.ncbi.nlm.nih.gov/pubmed/?term=14583354) | Retrospective, single center | 150 | All pts SVT <1 y 1/1984-12/00. | Risk recurrent SVT in young pts vs. preexcitation | Pts w/ preexcitation: 88% recurrent SVT, vs. 17% w/o WPW. WPW pts more likely to require multiple drugs. | Presence of WPW associated w/ increased risk recurrent SVT |
| Gilljam T  2008  (245)  [18489621](http://www.ncbi.nlm.nih.gov/pubmed/?term=18489621) | Retrospective, single center | 109 | 109 pts SVT <30 d, 1971-1997.  SVT = AVRT or AVNRT | Outcomes neonatal SVT | Freedom from arrhythmia: 52% 1 y, 82% 5 y, 83% 10 y. Recurrence 31% WPW vs. 6% no overt WPW. | Mortality 2.7% related to arrhythmia/CHF.  Recurrences higher overt WPW, multiple meds, or >6 d to obtain initial arrhythmia control. |
| Santinelli V  2009  (246)  [19147045](http://www.ncbi.nlm.nih.gov/pubmed/?term=19147045) | Prospective, single center | 184 | 1995-2005, 184 pts ≤12 y (median 10 y, 8-12 y) w/ asymptomatic WPW evaluated and followed, median 57 mo. | Natural h/o asymptomatic WPW in children | 72% remained asymptomatic.  28% sxs: 10% considered “POTS life-threatening”: cardiac arrest 1.6%;  Syncope 1.6% | Cardiac arrest 1.6%  Multivariate risk: APERP ≤240 msec (p=.001)  And multiple AC (p= .001) |
| Salerno JC  2011  (247)  [21418251](http://www.ncbi.nlm.nih.gov/pubmed/?term=21418251) | Retrospective multi-center review | 1755 | Reviewed hospital databases 41 children’s hospitals between 1/03-9/08  Discharge dx SVT, age <25 y | Case fatality | Overall 68 deaths (4%)  6% w/ SHD died vs. 1% of pts w/o SHD  Case fatality increased in:  Age <1 mo, OR: 2.41 (95% CI: 1.35-4.32)  SHD, OR: 2.67 (95% CI: 1.22-5.80)  Cardiomyopathy, OR: 6.72 (95% CI: 1.79-25.28) regardless of SHD | Case fatality in absence of SHD is low, 1%,  Vs. 6% in presence of SHD  Case fatality highest in cardiomyopathy regardless of presence of SHD |
| Cain N  2013  (21)  [23827401](http://www.ncbi.nlm.nih.gov/pubmed/?term=23827401) | Retrospective, single center | 446 | 446 pts WPW; median age dx 7 y, 61% male, 9% SHD. Presentation: 64% w/ sxs--SVT 38%; chest pain or palps 27%; syncope 4%, AF 0.4%; cardiac arrest 0.2%. | Natural h/o WPW | During f/u: additional 20% developed sx.  54% SVT, AF 1.6%.  Pts dx ≤3 mo, 35% WPW resolved, vs. 5.8% dx >3 mo.  Sudden death 1.3%, 2.8/1000 pt y. | Sudden death: 1.3%  No heart disease: 1.1/1000 pt y  SHD: 27/1000 pt y. |
| Pediatrics: Mechanisms of SVT | | | | | | |
| Garson A 1981  (248)  [7258098](http://www.ncbi.nlm.nih.gov/pubmed/?term=7258098) | Retrospective, single center | 103 | Intracardiac EP study in pts 2 d-17 y, mean 4.2 y. | Determine mechanisms of SVT in young pts w/ clinical SVT | AVRT 50%, AVNRT 24%, AT 21%  55% of AP tachycardia w/ manifest WPW | Predominance of AP mediated tachycardia in young pts |
| Ko JK  1992  (249)  [1561973](http://www.ncbi.nlm.nih.gov/pubmed/?term=1561973) | Retrospective, single center | 137 | EP study (TEP 110, intracardiac 14, both 13) performed in pts <18 y of age, excluding significant heart disease or neuromuscular disorders | Determine mechanism of SVT in young pts w/ clinical SVT | AVRT 73%, AT 14%, AVNRT 13%. | AVNRT rarely present <2 y of age;  AVRT and AT occurred throughout childhood |
| Weindling SN  1996  (250)  [8554021](http://www.ncbi.nlm.nih.gov/pubmed/?term=8554021) | Retrospective, single center | 112 | SVT in infants, 7/85-3/93. | Mechanism of SVT in infants w/ SVT | AVRT 77%, AVNRT 9%, Atrial reentry 10%, ectopic atrial 4%. 106 pts treated: 70% digoxin, propranolol, or both, Class I or III used in 12% each. 8% ablation failed med rx: 1/9 died related to ablation (VF after discharge). Overall mortality 4.4%, 4/5 w/ SHD. | Ablation for medically refractory SVT.  Neonate w/o SHD died related to complications of ablation.  Recommends ablation for rare infants: fail aggressive med rx, rx comp by ventricular dysfunction, severe sx, complex SHD. |
| Gross GJ 1998  (251)  [9794351](http://www.ncbi.nlm.nih.gov/pubmed/?term=9794351) | Retrospective, single center | 15 | Infants AVNRT <1 y mean age 58 d, 5/15 after CHD palliation. Typical AVNRT 14/15. Mean f/u 45 mo. | Outcome of AVNRT in first y of life | Digoxin: 87%, successful 38%.  40% digoxin + propranolol, successful 4/6. Class III in 3 pts: 2/3 RFA: ages 4.1 and 6.7 y. | All pts alive and well, minority syx beyond infancy. Digoxin questionalble benefit. AVNRT remained inducible in asymptomatic pts. |
| Anand RG  2009  (252)  [19925541](http://www.ncbi.nlm.nih.gov/pubmed/?term=19925541) | Retrospective, multicenter | 3556 | Registry of pediatric EP reviewed for pts undergoing ablation for SVT between 1999-2004.  Ages <7 y: 378; 7-12: 964; 12-21 y: 2214; males 55%; white 82% | Assess influence of age, gender, ethnicity on SVT | AP: 68%; decreased w/ increasing age  AVNRT 32%  In age 12-21 y, females more likely to have AVNRT than AP  Black and Hispanic pts had less SVT than representation in population; whites more SVT than population. | Proportion of SVT due to AP decreases w/ increasing age.  After age 12 y, females more likely to have AVNRT than males.  More whites in registry than expected based on population. |
| Brembilla Perrot  2013  (253)  [23609066](http://www.ncbi.nlm.nih.gov/pubmed/?term=23609066) | Retrospective, single center | 140 | Sxs of palpitations/SVT w/ normal ECG, underwent transesophageal pacing.  Mean age 15±3 y | Utility of TEP to identify SVT in pts w/o preexcitation | 59% AVNRT, AVRT 37%, AT 0.7%, VT 3%.  High risk antegrade conduction over AP >240 bpm baseline or >290 bpm isoproterenol found in 1.4%. | Preexcitation found in 13.5% w/ atrial pacing. |
| Pediatrics: SVT Pharmacological Therapy | | | | | | |
| Pfammatter JP  1998  (254)  [9504781](http://www.ncbi.nlm.nih.gov/pubmed/?term=9504781) | Retrospective single center | 26 | SVT in infants <4 mo of age  Mean age presentation 7 d  SHD 31%; WPW 35%  All AVRT | Digoxin for neonatal SVT | Digoxin successful: 65%  Failure 27%  Mean f/u 54 mo, 73% no meds no recurrences; 8% recurrent SVT | Digoxin success 65%  73% no early recurrences  8% symptomatic recurrences |
| Villain E  1998  (255)  [10223132](http://www.ncbi.nlm.nih.gov/pubmed/?term=10223132) | Retrospective single center | 141 | SVT <1 y of age, 77% <1 mo.  Digoxin first med in 114 pts, 81%; Amiodarone used after failure of digoxin (combo: 26%) or first: 19%. (solo 16%). | Infant SVT: digoxin and amiodarone outcomes | Digoxin effective 65%; amiodarone 97%. Total amiodarone used in 58 pts, no pro-arrhythmia, increase TSH 10%. .  Adverse events 6 pts w/ digoxin: VF in 3 pts | Digoxin: VF in 3 pts, (2/3 WPW) in hospital; one additional baby died at 3 mo, digoxin, no SHD. Total 4 CA on digoxin: 3.5%.  Amiodarone safer, more effective than digoxin. |
| Losek JD 1999  (256)  [9922414](http://www.ncbi.nlm.nih.gov/pubmed/?term=9922414) | Multicenter prospective and retrospective | 82 | 82 pts w/ 95 episodes SVT ≤18 y, in pediatric ED. 25 episodes <1 y of age. 10% SHD. Adenosine doses: low 0.1 mg/kg, medium 0.1-0.2 mg/kg, high ≥0.3 mg/kg. | Adenosine for pediatric SVT | Adenosine success 72%; AV node-dependent SVT success 79%.  Successful dose: low 6%, medium 62%, high 32%. | Adenosine cardioversion 72%; low dose rarely effective. |
| Dixon J  2005  (257)  [16243875](http://www.ncbi.nlm.nih.gov/pubmed/?term=16243875) | Retrospective single center | 35 | SVT rx w/ adenosine 1/98-5/03. 53 episodes. 23 infants, 12 children <16 y. | Dosing of adenosine to terminate SVT | Adenosine efficacy vs. dose:  Infants: 50 mcg/kg, 9%, 150 mcg/kg, 35%; median effective 200 mcg/kg.  Children: 50 mcg/kg: 9%,100 mcg/kg: <50%. median effective dose 150 mcg/kg | Adenosine in recommended dose has low efficacy, <10%.  Recommend minimum dose 100 mcg/kg children, 150-200 mcg/kg infants. |
| Chang PM 2010  (258)  [20194798](http://www.ncbi.nlm.nih.gov/pubmed/?term=20194798) | Retrospective single center | 37 | Refractory SVT: 40 episodes, 37 pts. 7/04-8/06. Median 34 d, 0-19 y. 65 SHD. IV procainamide: 50, Amiodarone 158 pts.  AVRT 11, IART 18, EAT 11. Median dose amiodarone 2.5 mg/kg; procainamide 10 mg/kg. | IV procainamide vs. amiodarone for terminating SV12 | Success: full + partial: Procainamide 71%, amiodarone 34%.  Full success, Procainamide 50%, amiodarone 15%. | IV procainamide more efficacious than IV amiodarone for acute termination of SVT |
| Diza-Parra S 2014  (259)  [24849273](http://www.ncbi.nlm.nih.gov/pubmed/?term=24849273) | Retrospective, single center | 26 | Ped ED: 44 episodes SVT in 26 pts, mean age 3.1 y. 1/07-12/11. Adenosine given to 89%, increasing dosages. | Efficacy of adenosine pediatric SVT | Adenosine efficacy 75%.  30% responded to single dose, mean 112 mcg/kg; 41% 2 doses, mean response dose 188 mcg/kg; 24% 3 doses, mean response dose 249 mcg/kg. 66% discharged home. | Mean effective dose of adenosine 173 mcg/kgm, higher than usual recommended dose.  Mean number doses 1.7. |
| Pediatrics: JET Risk Factors | | | | | | |
| Batra AS  2006  (260)  [16391972](http://www.ncbi.nlm.nih.gov/pubmed/?term=16391972) | Retrospective, single center | 336 | 336 consecutive pts surg for CHD/1 y.  JET 8%, 27/336 pts | Identify risk factors for postop JET | Highest risk: TGA arterial switch, 23%; AVSD 21%; Norwood, 20%.  JET pts younger, longer CPB times, hgher iinotrope schore, longer ischemic time | JET incidence 8%. |
| Andreasen JB  2008  (261)  [18196218](http://www.ncbi.nlm.nih.gov/pubmed/?term=18196218) | Retrospective single center, case-control | 874 | 874 pts <16 y, CHD surgery 1/98-12/05  Among JET pts: 26% had VSD closure; more often in pts w/ high RACHS score; 25% had surgery NOT near the AVN. | Identify risk factors for postop JET | Incidence 10.2%,  CPB >90 min (OR: 2.6); high inotropes (OR: 2.6); high postop CK-MB (OR: 3.1).  Mortality increased: 13.5% vs. 1.7%; 12 deaths. Prolonged LOS. | Rx protocol: sedation/electrolytes; reduced inotropes; reduced core temp to 34-35 d C; muscle relaxation, IV amiodarone. |
| Borgman KY 2012  (262)  [21740877](http://www.ncbi.nlm.nih.gov/pubmed/?term=21740877) | Retrospective Single center, | 36 | CHD pts developing JET postop compared w/ CHD pts w/o JET | Assess genetic polymorphism in CHD pts who develop postop JET | Risks for JET postop included, age, inotrope score, bypass time, crossclamp time. ACE I/D genotype associated w/ 2-fold increase in risk for JET. | ACE I/D polymorphism may be risk factor for JET |
| Makhoul M  2013  (263)  [22987106](http://www.ncbi.nlm.nih.gov/pubmed/?term=22987106) | Single center, retrospective, matched cohorts | 54 | Pts <21 y, CHD surgery 1/06-6/10 Emory. Narrow QRS tach >150 bpm.  Identified JET in 54, incidence 1.4%out of 2450 pts undergoing CPB.  One death in each group, 1.8%. | JET risk factors | ↑risk: weight <4 kg, CPB >100 min; postop lactic acid >20 mg/dL.  Rx: ↓ surface cooling core temp 35 d C, ↓exogenous catech; optimize sedation: used in 96%. Atrial overdrive pacing used 74%.  Amiodarone 78%, Procainamide 9%; esmolol 6%. | Lower mortality and incidence JET than prior studies.  Study not designed to assess drug efficacy. |
| Pediatrics: JET Therapy | | | | | | |
| Pfammatter JP  1995  (264)  [7677480](http://www.ncbi.nlm.nih.gov/pubmed/?term=7677480) | Retrospective single center | 6 | Postop JET treated w/ hypothermia.  6 consecutive pts, surface cooling to rectal temperature 32-34 d C; sedated, vent. Cooling maintained 24-88 h. | Assess rx postop JET w/ hypothermia | Mean interval Dx JET and start hypothermia 4 h.  JET rate ↓from 219 to 165 bpm mean. | Early institution moderate hypothermia effective in lowering HR |
| Walsh EP  1997  (265)  [9120158](http://www.ncbi.nlm.nih.gov/pubmed/?term=9120158) | Prospective, single center | 71 | Staged rx for JET 1986-1994.  71 pts, HR >170 bpm. Stages: ↓catecholamines; correct feve; atrial pacing; digoxin; phenytoine or propranolol or verap; procaine or hypothermia; combine procainamide + hypothermia | Assess rx JET postop | Success: reduce HR <170 w/in 2 h.  Treatment success 70/71 pts.  JET associated w/ young age, transient AV block, VSD closures | Only correction of fever and combined procainamide + hypothermia efficacious. |
| Laird WP 2003  (266)  [12370794](http://www.ncbi.nlm.nih.gov/pubmed/?term=12370794) | Retrospective, single center | 11 | 11 pediatric postop CHD pts w/ JET, mean HR 203 bpm. IV amiodarone 5 mg/kg x2 given, followed by infusion 10-15 mg/kg/d for 48-72 h. | Amiodarone efficacy for postop JET | Amiodarone in higher dose (10 mg/kg vs. 5 mg/kg) achieved control more rapids.  Hypotension/bradycardia 2 pts. | Amiodarone 10 mg/kg IV effective for rapid control of postop JET; continuous infusion necessary. |
| Plumpton K  2005  (267)  [15831155](http://www.ncbi.nlm.nih.gov/pubmed/15831155) | Retrospective, single center | 15 | 15 postop pediatric CHD pts, JET, median 2.6 mo. JET rates 182-229 bpm, median 192 bpm. IV amiodarone | Amiodarone efficacy for postop JET | Amiodarone controlled tachycardia, median time 4.5 h, median dose 5.9 mg/kg. Hypotension or bradycardia in 2 pts. | Amiodarone controlled post-op JET rapidly. |
| Haas NA 2008  (268)  [19026806](http://www.ncbi.nlm.nih.gov/pubmed/?term=19026806) | Prospective observational | 71 | 71 of 2106 CPB pts repair CHD received amiodarone for postop atrial (70) or ventricular (7) tachycardia. Median age 3 mo.  JET 37, ectopic AT 10, atrial flutter 8, AF 1, IART 1.  Early rx: w/in 60 min of arrhythmia detection vs. >60 min. Protocol: reduce inotropes, correct lytes; IV amiodarone. Dose 5 mg/kg over 1-4 h, infusion 5-15 mcg/kg/min. Repeat boluses; infusion 5-10 mg/kg/d. | Assess response of postop tachycardia to IV amiodarone | Early rx postop tachycardia reduced rate (156 vs. 300 bpm, p<0.01); time to control (400 vs. 1038 min, p<0.001), reduced dose (28 vs. 67 mg, p<0.025), and ICU LOS (3.3 vs. 5.3 d, p<0.01). | Early RX w/ amiodarone (60 min) significant improved outcomes. |
| Collins KK  2009  (269)  [19232902](http://www.ncbi.nlm.nih.gov/pubmed/?term=Pediatric+Nonpost-Operative+Junctional+Ectopic+Tachycardia) | Multicenter retrospective | 94 | Non postoperative JET, median age 0.8 y, range fetus – 16 y). .  Time frame 1969-2008.  CHF 16%. *VA dissociated 56%,* 1:1 VA 32%; both 3%, NOS 9%.  Median f/u 4.5 y. | Assess outcomes of rx for non postop JET in pediatric pts | Medications used in 89%; 62% ≥2 medications.  Amiodarone used 60%, alone in 20%, combo w/ beta blocker (15%), procainamide, dif, flecainide, propafenone.  Ablation: indication CHF or refractory to medications; elective 15%. RF 17, cryoablation 27, efficacy 82 vs. 85%, p=NS; recurrence 13-14%; inadvertent CHB 18% of RF pts. AV node ablation 3%, pacer 14%.  Deaths 4%, all age ≤6 mo. 70% no chronic medical rx for JET. | Amiodarone effective in 60%;  Ablation: 47%: efficacy 82-85%, recurrence 13-14%, 18% inadvertent CHB in RF pts; 3% underwent intentional ablation AVN.  Pacers 14% of ablation pts. |
| Kovacikova L  2009  (270)  [19632422](http://www.ncbi.nlm.nih.gov/pubmed/?term=19632422) | Retrospective single center | 40 | Postop CHD pts  IV amiodarone 2 mg/kg boluses, continuous infusion 10=15 mcg/kg/min | Assess IV amiodarone as rx for postop JET | Amiodarone effective 45%; SR in 7, decreased HR 11; allowed effective atrial pacing w/ AV synchrony.  Failure of amiodarone associated w/ higher AV oxygen saturation difference, lower body temp. | Amiodarone achieved SR in 45% as first line; recommend in combo w/ hypothermia. |
| Pediatrics: EP Study/Risk | | | | | | |
| Klein GJ  1979  [492252](http://www.ncbi.nlm.nih.gov/pubmed/?term=492252)  (137) | To assess risk of VF in WPW pts. | 73 | WPW + h/o VF vs. preexcitation, WPW pts w/ no h/o VF | VF | These pts also had high prevelance of reciprocating tachycardia and AF (14 of 25 vs. 18 of 73 [P=0.004]) and multiple APs (5 of 25 vs. four of 73 [P=0.012]). WPW + h/o AF and tachycardia demonstrate rapid conduction over AP during AF. | VF was initial manifestation of WPW in 10% of pts: ages 8,9, 16 y. |
| Timmermans C  1995  (271)  [7653450](http://www.ncbi.nlm.nih.gov/pubmed/?term=7653450) | Retrospective, single center | 15 | 15/690 pts w/ WPW referred 1/79-2/95 presented w/ cardiac arrest.  53% not known to have WPW. EP study done to assess AP characteristics. | Characterize WPW pts w/ arrest | VF initial manifestation in 8 pts.  10/15 exercising. 7 pts known ORT/AF. 9/11 EP study: AP ERP≤250 msec. Multiple AP not a risk. | VF 2.2% of series; all under age 45 y, half under age 30y. |
| Ceresnak SR  2012  (272)  [22324823](http://www.ncbi.nlm.nih.gov/pubmed/?term=22324823) | Retrospective, multi-center | 30 | 1147 pts w/ WPW underwent EP study; 30 pts (2.6%) w/ ADT.  Mean age 16±3 y. | Assess EP characteristics of pts w/ ADT | 7% w/ CHD  13% more than one AP  Left sided AP 53%; right 47% often septal  High risk in 17 pts (57%) | ADT rare in children w/ WPW undergoing ablation, 2.6%  57% w/ ADT had high risk characteristics |
| Brembilla Perot B  2013  (273)  [23148120](http://www.ncbi.nlm.nih.gov/pubmed/?term=23148120) | Retrospective, single center | 63 | 807 pts w/ WPW underwent EP study; ADT induced in 63 pts (8%)  Ages | Assess EP characteristics of pts w/ WPW and ADT | Pts w/ ADT more likely to have AF induction (41 vs. 24%, p<.002), and high risk characteristics (22 vs. 12%, p<.02)  No difference in age, gender, clinical presentation, ORT | Clinical outcome did not differ in pts w/ ADT; older pts less likely to have high risk characteristics |
| Pappone C  2014  (145)  [25052405](http://www.ncbi.nlm.nih.gov/pubmed/?term=25052405) | Prospective single center | 2169 | 2169 pts w/ WPW, 8 y prospective study. 1001: no RFA; 1168: RFA. EP study in all. Median f/u 96 mo. 92% f/u. | Assess VF or malignant arrhythmias in WPW | In no RFA group, 1.5% experienced VF, vs. 0.4% in no RFA group. VF: 13/15 were children, median age 11 y. Associated w/ short AP ERP (APERP <240 msec) (P <0.001) and AVRT initiating AF, but no sxs. Posteroseptal AP more common among VF pts. VF w/ exertion in 4, at rest in 11. | 1.5% VF, almost all in children; risk higher in asymptomatic pts  13/15 pts w/ VF <15 y; 2 age 32 y. |
| Pediatrics: Ablation | | | | | | |
| Kugler JD  1994  (167)  [8164700](http://www.ncbi.nlm.nih.gov/pubmed/?term=8164700) | Retrospective, multi-center | 652 | 652 pts underwent 725 ablation procedures between 1/91-9/92,  Median age 13.5 y, 84% no SHD | Assess outcomes and complications of ablation in young pts | Success rates: AVRT and AVNRT 83%; highest in LFW AP and ↑institutional experience; lower in RFW AP, structural heart disease, body weight >80 kg.  Complications 4.8%, higher in very low weight <15 kg and less institutional experience | Uncontrolled, voluntary registry |
| Kugler J  1997  (274)  [9399718](http://www.ncbi.nlm.nih.gov/pubmed/?term=9399718) | Retrospective, multi-center | 4135 | 46 centers, pts 0.1-20.9 y undergoing ablation 1/91-9/15/96  88% no SHD  58% performed due to family/pt choice | Determine safety and efficacy of ablation in childhood | Success rates: AVRT 90%, higher left >right, 95 vs. 86%;  AVNRT 96%;  Mean fluoroscopy time 47.6±40 min;  Major complications 3.2%  Deaths 4 pts, 1 immediate, 3 late (2 infant deaths)  Freedom from recurrence at 3 y: AP 77%, AVNRT 71%. | Ablation evolving into treatment of choice for SVT in older pts  Deaths in 2 infants noted  Higher recurrence than adult pts, but possibly due to higher f/u. |
| Schaffer msec  2000  (275)  [10980215](http://www.ncbi.nlm.nih.gov/pubmed/?term=10980215) | Retrospective multicenter | 10 | Rviewed 4651 cases in Pediatric RFCA Registry; deaths 0.22%  5/4092 w/ normal hearts 0.12% | Assess incidence/causes of death | Deaths: all in left sided AP; mural injury, perforation, thromboembolism, vent arrhythmia  Weight 32.7 kg vs. 55.6 kg (p=.023)  Number of lesions 26.3 vs. 8.7, (p=.019) | Mortality 0.12-0.22% in left sided AP ablations; lower weight, greater number of lesions |
| Blaufox AD 2001  (276)  [11733398](http://www.ncbi.nlm.nih.gov/pubmed/?term=11733398) | Retrospective multicenter | 137 | Reviewed Pediatric RFCA Registry, 1989-1999, age ≤18 mo, median 0.7 y, weight median 10 kg.  152 procedures, CHD 36%. | Outcomes ablation in age ≤18 mo | Success 87.6%, vs. 90.6%, NS  Major comps 4.6% vs. 2.9%, p=.17 | No difference in success or complications ≤18 mo |
| Blaufox AD 2004  (277)  [14764175](http://www.ncbi.nlm.nih.gov/pubmed/?term=14764175) | Retrospective single center | 18 | 18 RFA in pts <15 kg 1/88-8/01; median weight 5.7 kg, age 5.8 mo; 4 CHD, 4 CHF | Outcomes ablation <15 kg | ORT 9, MAT 1, VT 4; success all AP; no recur.  Complications 3/18 myocardial infarct 1 occluding left circ, CHF, mitral valve replacement; torn mitral leaflet 1 | Complications 16% associated w/ RF dose indexed for body size (duration and number)  Mitral valve replacement |
| Van Hare G  2004  (278)  [15250858](http://www.ncbi.nlm.nih.gov/pubmed/?term=15250858) | Prospective, multi-center | 481 | Pts ≤16 y, w/o significant heart disease, w/ AVRT or AVNRT; compared w/ cohort-eligible registry pts, N =504 | Assess success rates and complications in age <16 y | Acute success: 96%, highest in left sided AP; left 98% vs. right 91%  Complications 4.2%; no deaths;  AV block 1.2% in AVNRT or septal AC | High success rates for AVNRT or AVRT w/o CHD |
| Van Hare G  2004  (279)  [15851152](http://www.ncbi.nlm.nih.gov/pubmed/?term=15250858) | Prospective, multi-center | 481 | 481 pts w/ AVRT or AVNRT, excluding pts w/ significant heart disease  Ages 0.1-16 y  Followed at 2,6,12 mo following ablation | Assess recurrence following successful ablation | Recurrence at 2,6, 12 mo was 7, 9.2, and 10.7%  Recurrence highest right septal AP 24.6%, RFW 15.8%, LFW 9.3%, left septal 4.8%;  AVNRT 4.8% vs. 12.9% for AP at 12 mo | Recurrence after initially successful ablation occurs commonly in children, 10.7%  Recurrence less common for AVNRT 4.8%, most common for right sided AP >25% at one y |
| Aiyagari R 2005  (280)  [16132307](http://www.ncbi.nlm.nih.gov/pubmed/?term=16132307) | Retrospective, single center | 69 | All pts ≤20 kg undergoing ablation between 1/94-1/03  Group 1, <15 kg, 25 pts  Group 2, 15.1-20 kg, 44 pts | Compare safety and efficacy of ablation in pts <15 kg vs. 15.1-20 kg | SHD more common in pts <15 kg 28% vs. 7%, p<0.01.  No difference in mechanism SVT, number lesions, temperature, procedure time, success rates 91% vs. 89%.  Major complications 8% in Group 1, 2.3% Group 2, p=0.39. | Outcomes similar between groups  Complications 8% in smaller children, although not statistically significant |
| Lee PC  2007  (281)  [17461876](http://www.ncbi.nlm.nih.gov/pubmed/?term=17461876) | Retrospective, single center | 228 | 228 pts 5-18 y old undergoing ablation 12/89 to 8/05  Mean age 9±7 y; mean f/u 86±38 mo | Assess results of ablation in pediatric pts 5-18 y | AVRT 61%, AVNRT 29%, AT 5%, atrial flutter 5%.  Success rates 92% AVRT, 97% AVNRT, 82% AT, 91% atrial flutter.  Complications 8.7%, major 0.9% AV block;  Recurrence 4.7% | AVRT incidence higher than in adults;  Success rates lowest for AT 82%; other mechanisms 91-97%.  Complications 8.7%, recurrence 4.7% |
| Chiu SN 2009  (282)  [19609044](http://www.ncbi.nlm.nih.gov/pubmed/?term=19609044) | Retrospective single center | 27 | 27/210 pts underwent RF at age <6 y.  Median age 4.4 y (8 mo-5.9 y).  Median weight 15 kg (6.6-30 kg).  AVRT 55%, atrial flutter 19%, AVNRT 15%.  SHD 33%. | Outcomes ablation <6 y. | Indications: drug refractory SVT, or tach-induced cardiomyopathy.  Acute success 93%, recurrence 7.4%. | Acute success 93%, recurrence 7.4%.  CHB 3.7% in 5 y old. |
| Schneider HE  2009  (283)  [19324303](http://www.ncbi.nlm.nih.gov/pubmed/?term=19324303) | Prospective, single center | 212 | 212 pts ages <21 y undergoing ablation for SVT underwent selective coronary angiography before and 30 min after RFA or cryoablation; CHD present in 15%  Median age 12 y (0.3-20.4 y)  Median weight 47 kg (5.5–130 kg) | Assess incidence of coronary injury following ablation | AP 53%; AVNRT 40%, both 7%  Coronary artery narrowing identified in 2/117 pts (1.7%) w/ AP, both in posteroseptal region. | Coronary artery injury present in 1.7% of AP ablations: both in posteroseptal region  Consider coronary angiography w/ ablation in posteroseptal region |
| Kantoch MJ 2011  (284)  [21621374](http://www.ncbi.nlm.nih.gov/pubmed/?term=21621374) | Retrospective single center | 34 | 1995-2009, 34 pts <2y of age, RFA 42 procedures in 31 pts, mean wt 7.4 kg; 17/34 CHF; 3 pts ECMO | Outcomes ablation <2 y | AVRT 19, Focal 6, atrial flutter 1, VT 3, JET 2  Acute success 74% vs. 91% >2y  No recurrence mean 7.3 y  Major complications 4/34 children; CHB, pacer in 6 wk old infant; RFA occusion x 2, | Major complications 11.8% vs. 0.7% in >2 y of age |
| Buddhe S 2012  (282)  [22452328](http://www.ncbi.nlm.nih.gov/pubmed/?term=22452328) | Retrospective single center | 155 | 1/05-12/09, 155 pts ablation for SVT. Mean age 13.4±3.7 y. 22% African American. RF 107, Cryoablation 11, Both 97.  AVRT 74%, AVNRT 17%; SNRT 5%, His bundle reentry 4%. .  Median f/u 41 mo. | Outcomes ablation during longer f/u | Acute success 98%; 5 y f/u 83% success.  Recurrences higher w/ right anterior-anteroseptal AC (33%), multiple (27%), or broad distribution. Recurrence not statistical different RF (14%) vs. Cryoablation (22%) or both (20%) | 17% recurrence WPW or SVT during mean f/u 38 mo.  Recurrences higher vs. age, 11.7 y vs. 13.6 y (p<0.05). |
| Pediatrics: QOL & Cost Effectiveness | | | | | | |
| Garson A  1997  (285)  [9395176](http://www.ncbi.nlm.nih.gov/pubmed/?term=9395176) | Cost modeling | N/A | Cost-effectiveness modeling for ablation vs. medications or surgery for WPW treatment in pts age 5-21 y | Identify long term cost effectiveness of treatment strategies | Ablation cost 39% of surgical rx, and 57% of medical management.  Estimated mortality ablation 0.15% = 10% of medical rx, and 28% of surgical rx  Morbidity ablation = 32% of medications, and 36% of surgery | Catheter ablation has lower cost, mortality and morbidity than either medical rx or surgery, and is treatment of choice for the child 5 y of age or older w/ WPW and SVT. |
| Pfammatter JP  2004  (286)  [15093993](http://www.ncbi.nlm.nih.gov/pubmed/?term=Impact+of+curative+ablation+on+pharmacologic+management+in+children+with+reentrant+supraventricular+tachycardias) | Retrospective, single center | 88 | Compare drug therapy vs. ablation as first line in 2 time periods: 1989-94, N = 40, and 1995-2000, N = 48.  Early time period: medications only  Later ablation as first line in 16/48 pts. | Assess impact of ablation as first line therapy for SVT in pts >5 y of age | Over time, number of SVT episodes (3.7 to 2), duration of meds (15 mo to 4.6 mo, p<0.05) and numbers of cardioversions declined (1.1/pt to 0.2, p<0.05) | Use of ablation as first line treatment in pts over age 5 y results in fewer episodes of SVT and cardioversions |
| Strieper M 2010  (287)  [21106019](http://www.ncbi.nlm.nih.gov/pubmed/?term=21106019) | Prospective, single group, pre-test-posttest design | 27 | Consecutive pts w/ SVT referred for catheter ablation between 10/04 – 6/06.  Pre and 6 mo post ablation.  Ages 5-18 y. | Assess impact of ablation on QOL scores | Pre test lowest scores in social and physical functioning; post test greatest improvement in physical functioning.  Significant improvement in all QOL scores following successful elimination of SVT | Significant improvement in all QOL scores following successful elimination of SVT |
| Wood KA  2010  (288)  [20109982](http://www.ncbi.nlm.nih.gov/pubmed/?term=20109982) | Prospective, single group, pre-test-posttest design | 52 | Consecutive pts w/ SVT referred for catheter ablation ≥13 y,  Mean age 41±17 y, range 13-85 y  Female 65%  AVNRT 57%, AVRT 31%, AT 12% | Comparison of QOL, sxs before and after ablation procedure for SVT | All sxs decreased but not completely eliminated at 1 mo f/u  Improvements in palpitations, p=0.001,  Fatigue, p=0.001,  Dizziness, p<0.01, resp or chest pressure p<0.001  QOL improvements in number, severity and impact of sxs, p<0.001 | All sxs improved after ablation, women reported larger changes in sxs and QOL than men |
| CHD: Incidence of SVT | | | | | | |
| Engelfriet P  2005  (289)  [15996978](http://www.ncbi.nlm.nih.gov/pubmed/?term=15996978) | Retrospective, multicenter | 4110 | CONCOR national registry >8600 pts ACHD >17y of age: Pts w/ ACHD of 8 major types seen in 1998, w/ complete f/u to 2003: (ASD, VSD, TGA, TOF, single ventricle, coarctation, Marfan’s, cyanotic heart disease); followed until 12/2003 | assess endocarditis, arrhythmias, vascular events | Median age 27.9 y, (21.7-38.6y),  79% <50 y old  median f/u 5.1 y (3.6-5.7 y);  SVA occurred in TOF 20%, TGA 26%; ASD 28%, Fontan 45% | Young population w/ ACHD, overall 18% developed SVA |
| Verheugt C  2008  (290)  [18559697](http://www.ncbi.nlm.nih.gov/pubmed/?term=18559697) | Retrospective, multicenter | 7414 | CONCOR registry, Netherlands, >8600 pts ACHD >17 y old 1/02-1/08; assess outcomes frequencies | Is gender associated w/ outcomes in ACHD | Median age 35 y (17-91); males 50.2%; median f/u 2.7 y; frequencies of arrhythmias 22-44%; females 12% lower risk arrhythmia, NS; females higher risk for pulmonary HTN | 15% developed SVA during f/u 2.7 y |
| Bouchardy 2009  (291)  [19822808](http://www.ncbi.nlm.nih.gov/pubmed/?term=19822808) | Retrospective multicenter | 38,428 | Adult registry Canada; ACHD median age 42 y; 1983-2005; 5812 pts AT | Assess risk of developing atrial arrhythmias as adult | Prevalence 15.1% AT; impact: 20 y risk for 20 y old 7%, 50 y old 38%; adverse event HR 2.5; mortality 1.47; stroke, CHF 2.21 | >50% severe CHD developed AT by age 65 y; 2-3↑ death, stroke, CHF |
| Trojnarska O 2009  (292)  [19437395](http://www.ncbi.nlm.nih.gov/pubmed/?term=19437395) | Retrospective, multicenter | 1304 | National Polish registry, ACHD pts followed 1995-2004; mean age 29.4±10.6 y, mean f/u 3.5±1.8 y | Assess outcomes of SVA | SVA developed in 10.3% of pts; multivariable predictors; presence of HF (HR: 4.66) CHD complexity (HR: 2.31), age (HR: 1.32) gender NS | 10.3% developed SVA  Increased w/ CHF, complex CHD, increasing age |
| Bernier M  2010  (293)  [20691314](http://www.ncbi.nlm.nih.gov/pubmed/?term=20691314) | Retrospective multicenter | 71,467 | Quebec database; ACHD ≥18 y; study period 1/88–12/05; ACHD pts *arrhythmia free* by age 18 y in 1/1988 | assess risk of developing AT vs. type CHD | 11% developed SVA; 30 y risk for 18 y old: 18% for right sided CHD, 11% for left sided herat disease | ACHD pts arrhythmia free by age 18 y: risk greater in pts w/ right-sided disease vs. left-sided |
| Khairy P  2010  (294)  [20713900](http://www.ncbi.nlm.nih.gov/pubmed/?term=20713900) | Retrospective, multicenter | 566 | AARCC (Alliance for Adult Research in Cong Card); 11 centers; ACHD ages ≥18 y; study period 9/07-10/08 | Assess arrhythmia prevalence in TOF adults | Mean age 36.8±12 y; f/u;  Prevalence SVA 20.1%; risk factors reentrant AT: right atrial enlargement (OR: 6.2); HTN (OR: 2.3), number of cardiac surgeries (OR: 1.4); ventricular arrhythmias 14.6% | 20.1% of TOF w/ SVA |
| Cuypers JA 2013  (295)  [23886606](http://www.ncbi.nlm.nih.gov/pubmed/?term=23886606) | Retrospective single center | 85 | 135 pts, Netherlands; surgical ASD closure <15 y of age, (mean 7.5± 3.5 y) between 1968-1980; f/u on 131 pts | Assess SVA development late after ASD closure | Mean f/u 35 y (30-41 y), 16% developed SVA; 12% developed AF | 16% AT in f/u ASD |
| Valente AM 2014  (296)  [24179163](http://www.ncbi.nlm.nih.gov/pubmed/?term=24179163) | Multicenter, prospective | 873 | Repaired TOF Median age 24.4 y, undergoing standard eval ECG, Exercise, MRI | Assess TOF primary outcome of VT or death | SVA developed in 11% (7% atrial flutter, 4% AF); total 3.7% death or VT; Risk for VT or sudden death included ↑RV mass (HR: 5.04), ↓LVEF (HR: 3.34) or h/o atrial arrhythmia (HR: 3.65) | TOF pts develop SVA in 11%;  SVA significant risk factor for VT or sudden death, HR: 3.65 |
| CHD: Mechanisms of SVT | | | | | | |
| Collins KK 2000  (297)  [11053709](http://www.ncbi.nlm.nih.gov/pubmed/?term=11053709) | Retrospective, single center | 88 | ACHD, 110 AT macro-reentry circuits, median age 23.4 y, repaired CHD: TGA/atrial repair, 17%,; biventricular CHD 27%; Fontan 49%, other 7 | Sites of successful ablation for AT | Non-Fontan: CTI 57-67%, lateral RA wall 22-43%, anterior RA 11%. Fontan pts: isthmus 15%, lateral RA 53%, anterior 25%, septum 7% | CTI involved in right AT in ~60% non-Fontan AT;  Fontan multiple RA circuits esp lateral RA wall |
| Akar JG 2001  (218)  [11499727](http://www.ncbi.nlm.nih.gov/pubmed/?term=11499727) | Retrospective single center | 16 | Consecutive repaired ACHD pts, EP study & ablation, mean ages 32±18 y; 24 circuits. Mean f/u 24 mo  ASD/VSD 9; TOF 3, UVH 4.  ECG: 44% typical atrial flutter; 56% atypical. | Frequency of typical atrial flutter vs. IART in CHD | 19% typical atrial flutter only; 37% IART alone; 44% both atrial flutter/IART;  Isthmus dependent 86% IART;  92% successful ablation; only failure=Fontan | 44% both atrial flutter and IART:  Surface ECG did not predict mechanism  7% recurrence 2 y. |
| Delacretaz E 2001  (199)  [11345382](http://www.ncbi.nlm.nih.gov/pubmed/?term=11345382) | Retrospective, single center | 20 | 47 Atrial reentry circuits mapped in 20 pts, repaired CHD, ASD 10, TOF 6; mean age 43 ±15 y | Assess sites of reentry circuits | Lateral RA wall 40%, CTI 38%; ASD patch 17%.  Acute success 80% pts; mean f/u 19 mo, 20% recurrence. | ALL RA macro-reentry, largely ASD or TOF pts; Circuits in 3 sites: lateral RA wall ≅ CTI |
| De Groot NM 2006  (298)  [16648056](http://www.ncbi.nlm.nih.gov/pubmed/?term=16648056) | Retrospective single center | 43 | 43 consecutive pts repaired ACHD undergoing EP study/ablation for SVT, mean age 37 y, | Assess mechanism of SVT and success of ablations | IART 77% including scar-related 43%, CTI 34%; Focal 16%; AF 3%.  Ablation success 70% IART, atrial flutter,focal 100% | RA macro-reentry: 77%  Focal 16%  AF 3% |
| Mah DY  2011  (299)  [21539636](http://www.ncbi.nlm.nih.gov/pubmed/?term=21539636) | Retrospective, single center | 58 | Repaired TOF or DORV pts, 1/97 to 3/10; 58 pts w/ 127 AT circuits, mean age 35 y | Assess atrial reentry circuits in TOF | RA reentry 75%; focal/ectopic 13%; AF 12%; CTI 53% of IART; CTI and lateral RA wall = 85% of IART; AT ablation acute success 90%; 34% recurrence w/in 3 y | 13% focal; AF 12%; IART 75%:  Of IART 53% involve isthmus; acute success high, recurrence moderate; target both isthmus and lateral RA wall |
| Koyak Z  2013  (300)  [23993125](http://www.ncbi.nlm.nih.gov/pubmed/?term=23993125) | Retrospective multicenter | 92 | ACHD pts, CONCOR Dutch database; First onset SVT 1/08-1/11 mean age 51±16 y; AF/atrial flutter >80%; septal defects 50%, left sided CHD 21%. | Mech of SVT in ACHD | Mechanism of SVT described as AF 68%, atrial flutter 14%, AVNRT 8%, “AT” 7%, unspecified 3% | AF 68%, atrial flutter 14%  AVNRT 8%  AT ? focal 7% |
| Wasmer K 2013  (301)  [23540398](http://www.ncbi.nlm.nih.gov/pubmed/?term=23540398) | Retrospective, single center | 54 | 54 pts repaired ASD, mean age 47.3 y at study, 11/95-12/01, 2 pts w/ AF, 10 no inducible AT: 42 pts studied; f/u 7.7 y | Assess RA reentry circuits in ASD | CTI dependent 69%, of which 40% were clockwise; scar related 17%, both 12%; CTI ablation performed in non-inducible/AF; acute success ~90%; 60% arrhythmia free at 7.7 y | ASD Ablation aimed at CTI highly successful; 11% developed AF |
| CHD: Pharmacological Therapy | | | | | | |
| Fish FA  1991  (302)  [1906902](http://www.ncbi.nlm.nih.gov/pubmed/?term=1906902) | Retrospective multi-center | 455 | 455/579 rx for SVT (79%);  369 pts rx flecainide (81%) . encainide 19%,  Mean age of flecainide death or CA: 9.9 y, range 4d-26 y | Pro-arrhythmia, cardiac arrest or death w/ flecainide/encainide in young pts | Overall death/CA; 25 pts; 18/25 w/ CHD;  Flecainide for SVT: efficacy 7.1%, proarrhythmia 7.4%; cardiac arrest 2.3%;  12 pts cardiac arrest; 8/12 CHD:  7/8 mild-mod ventricular dysfunction or single vent or systemic RV  Flecainide efficacy SVT 70%; pro-arrhythmia 7.4%; | Flecainide rx SVT + CHD: 8.3% death or CA. vs. 0.3% w/o CHD.  Deaths flecainide + CHD, average 16.1 y    4 flecainide deaths in structurally normal hearts, 3 of 4 normal function. |
| Thorne SA 1999  (303)  [10402444](http://www.ncbi.nlm.nih.gov/pubmed/?term=10402444) | Retrospective single center | 92 | ACHD, mean age 34.9 y, receiving amiodarone for ≥6 mo; case-control group. Mean duration 3 y, mean dose 191 mg | Review side effects of chronic oral amio | 36% developed thyroid dysfunction: 19 hyper, 14 hypothyroid. Sig risk factors: Female gender (OR: 3.0) cyanotic HD (OR: 7.0); Fontan (OR :4.0); dosage >200 mg/d (OR: 4.0) | Pts w/ CHD at higher risk for amiodarone adverse effects, especially women, cyanosis, Fontan, or dose >200 mg |
| Pass RH 2000  (304)  [11009280](http://www.ncbi.nlm.nih.gov/pubmed/?term=11009280) | Retrospective single center | 10 | IV diltiazem for AT w/ rapid response. Includes 3 adults w/ AT and repaired CHD, ages 18-21 y. | Efficacy diltiazem for AT | Diltiazem 0.25 mg/kg over 5 min + infusion 0.11 mg/kg/h. HR median 166 pre-treatment, fell to 23 bpm w/in 10 min. No HTN. | Diltiazem effectively decreased ventricular rate w/in 10 min. |
| Hoyer AW 2007  (305)  [17669084](http://www.ncbi.nlm.nih.gov/pubmed/?term=17669084) | Retrospective single center | 19 | 15 w/ CHD, 4 w/ normal hearts.  74 episodes of atrial flutter 4 AF. Median age 16 y. | Evaluate efficacy of ibutilide | 71% successful cardioversion;  No symptomatic bradycardia.  1 TdP, 1 NSVT | W/ careful monitoring, ibutilide can be an effective tool for cardioversion of flutter. |
| Khairy P  2008  (306)  [19808416](http://www.ncbi.nlm.nih.gov/pubmed/?term=19808416) | Retrospective multicenter | 37 | 37 pts w/ intra-atrial baffle repair of TGA, 7 sites, ages 28±7.6 y, w/ AICD: primary prevention 62%, secondary 38%. | ICD and outcomes TGA | Annual rates approximately shock: 0.5% primary, 6% secondary. SVT preceded VT in 50%. | Lack of beta-blockers use: HR: 16.7; beta-blockers seem protective for SVT initiating VT |
| Miyazaki A  2008  (307)  [18931451](http://www.ncbi.nlm.nih.gov/pubmed/?term=18931451) | Retrospective single center | 27 | 44 ACHD, mean age 23±12 y, f/u 13±12 mo; oral sotalol 2002-2007; 27 pts SVT | Efficacy & safety sotalol in ACHD | Overall 41% control;  for SVT 52% complete control;  Not effective for AF | AT w/ AF risk factor for rx failure, OR: 18.3  One death 34 y old, AT + AF |
| Rao SO  2009  (308)  [18653253](http://www.ncbi.nlm.nih.gov/pubmed/?term=18653253) | Prospective, non-randomized | 19 | 19 pts ACHD, mean age 20 y; present in AT, given oral sotalol 2 mg/kg as inpatients | Sotalol for conversion | Focal AT 21%, IART 79%;  84% conversion w/in 98-145 min; 75% of focal and 87% IART. One fatality after 2 d: thromboembolism. | High efficacy 84% for oral sotalol in ACHD acute conversion of AT |
| Wells R  2009  (309)  [19691680](http://www.ncbi.nlm.nih.gov/pubmed/?term=19691680) | Retrospective multicenter | 20 | ACHD pts, 4 institutions, 7 y, rx w/ dofetilide, median age 30 y, 19-53 y.11/20 pts Fontan surgeries.  AF 4, IART 13, AF + IART 3.  Dosage 125-500 mcg bid.  Median f/u ~ 12 mo. | Dofetilide efficacy AT in ACHD | Conversion to SR: 85%.  Torsades de pointes: 10%, immediate.  Recurrent AT: 65%.  55% taking dofetilide at 1 y. | Dofetilide effective acute termination of AT (85%) w/ 10% Torsades de pointes.  65% recurrent AT in 12 mo.  ie 35% control AT x 1 y. |
| Garnock-Jones KP 2012  (310)  [22191799](http://www.ncbi.nlm.nih.gov/pubmed/?term=22191799) | Meta-analysis of databases |  | MEDLINE, EMBASE, and AdisBases databases searched for esmolol and tachycardia, and heart surgery, through 11/2011. | Review of databases using esmolol | Includes comparison trials w/ other meds: placebo, propranolol, diltiazem, ibutilide, for treatment of SVT and for prophylaxis during heart surgery | Hypotension in 2-40% of SVT pts. Resulted in discontinuation in 3-23% |
| Koyak Z 2013  (300)  [23993125](http://www.ncbi.nlm.nih.gov/pubmed/?term=23993125) | Retrospective multicenter | 92 | ACHD pts, CONCOR databse; First onset SVT 1/08-1/11  mean age 51±16 y;  AF/atrial flutter >80%; septal defects 50%, left sided CHD 21%.  Sotalol used in 34%, (mean dose 156 mg) ) and amiodarone 15%,( mean dose 350 mg) | Long term efficacy of AA meds | 90% achieved sinus rhythm. 84% rx w/ chronic oral agents; f/u 2.5±1.4 y; 45% free from SVT.  Sotalol or Amiodarone: significantly fewer recurrences, (HR: 0.5); 22% adverse events;  all amiodarone pts w/ side effects, thyroid 80%, AVB 20%. | Class III agents sotalol and amiodarone more efficacious in maintaining SR; sotalol considered as first choice med  Relatively high dose amiodarone associated w/ significant adverse events |
| Banchs JE  2014  (311)  [23947935](http://www.ncbi.nlm.nih.gov/pubmed/?term=23947935) | Prospective non randomized | 13 | ACHD, 4 TOF, 1 pulmonary atresia, 2 ASD, 1 dextro-TGA ; 2 L-TGA, 2 tricuspid atresia, 1 asd and vsd, 1 vsd pulmonary atresia, 1 noncompaction; mean age 40±11; median f/u 16 mo | Dofetilide efficacy and safety for AT in ACHD | Mechanism of SVT described as AF, atrial flutter or AT  70% conversion  15% control of recurrences  Average time to recurrence 5.5 mo  39% ddischarge medication due to recurrence | Dofetilide well tolerated,  Effective for conversion in 70%  Recurrence still frequent. |
| Stan MN  2014  (312)  [22518347](http://www.ncbi.nlm.nih.gov/pubmed/?term=22518347) | Retrospective single center | 23 | ACHD pts developing amiodarone-induced thyrotoxicosis after ≥3 mo amiodarone, Mayo Clinic 1987-2009; median f/u 3.1 y. | Identify incidence and risk factors amiodarone thyrotoxicosis | 13.6% (23/169) ACHD pts developed amiodarone thryrotoxicosis. | Highest Risk: low BMI <21, cyanotic heart disease |
| CHD: Atrial Pacing | | | | | | |
| Olshansky B 1988  (313)  [3339174](http://www.ncbi.nlm.nih.gov/pubmed/?term=3339174) | Retrospective single center | 12 | Rapid atrial pacing ≥15 sec at ≥10 msec shorter than AT, 12 adult pts, mean 55 y, 2/12 ACHD: VSD, VSD +ASD; mean atrial CL 233 msec | Conversion rates of AT/atrial flutter w/ rapid atrial pacing | 2/12 converted w/ rapid atrial pacing  10 pts received procaine then repeat rapid atrial pacing: successful in 10 pts | Procaine needed to assist RAP conversion in pts w/ ACHD |
| Silka MJ  1990  (314)  [2305688](http://www.ncbi.nlm.nih.gov/pubmed/2305688?dopt=Citation) | Retrospective single center | 21 | 21 pts, CHD, AT or VT and anti-bradycardia pacing.  Mean age 11 y (2-19 y) | Assess impact of anti-brady pacing on frequency of AT | 14 pts w/ AT. Prevention of bradycardia by pacing: significant decrease in SVT (p=0.008) and VT | SVT reduced, but not atrial flutter |
| Ragonese P  1997  (315)  [9455751](http://www.ncbi.nlm.nih.gov/pubmed/9455751?dopt=Citation) | Retrospective single center | 18 | 18 ACHD pts, recurrent late IART, implanted atrial pacemakers programmed for atrial pacing >80% of time. | Atrial anti-brady pacing effect on IART recurrence | Recurrent AT in 29% in first 6 mo.  Late recurrences in 11%; 83% arrhythmia free, 2 pts on AA meds. | Chronic atrial pacing reduced IART recurrences to 11%.  One late sudden death. |
| Brockmeier K  2002  (316)  [12539114](http://www.ncbi.nlm.nih.gov/pubmed/?term=12539114) | Retrospective single center | 39 | 62 conversions in 39 pts, 31 postop CHD, median age 12.5 y (0.1-33 y); “typical atrial flutter 21”, median CL 235 msec | TEP conversion of AT in CHD | 81% successful conversions w/ TEP; 19% underwent CDDV  Used AEST 4-6 x (CL-20) to minimum 120 msec; mA 24-28 | TEP converted 81% atrial flutter or ART |
| Stephenson EA  2003  (317)  [14516898](http://www.ncbi.nlm.nih.gov/pubmed/?term=14516898) | Retrospective multicenter | 28 | ATP in 28 ACHD pts, age 30 ±18 y.  Medtronic AT500 pacer. ≥2 episodes AT in 12 mo. Mean f/u 10 mo. | ATP detection and termination of AT | 57% of pts had AT after implant, mean 54 episodes. | ATP efficacy for termination: 54%. |
| CHD: DC Cardioversion | | | | | | |
| Ammash NM 2012  (318)  [20934227](http://www.ncbi.nlm.nih.gov/pubmed/?term=20934227) | Retrospective single center | 63 | 63 ACHD underwent 80 DCCV 6/00-7/03. Flutter most common 46%. f/u 387 d | Outcome of DCCV | DCCV successful in 94%.  60% ACHD pts recurred during f/u  all cause mortality was 11% during one y f/u. | DCCV safe and effective in ACHD. Recurrence rate is 60%/1 y; AF predicted recurrence, and spontaneous echocardiography contrast in LA |
| CHD: Catheter Ablation - NOS | | | | | | |
| Triedman JK  1995  (319)  [7828297](http://www.ncbi.nlm.nih.gov/pubmed/?term=7828297) | Retrospective single center | 10 | 10 consecutive ACHD pts, median age 18.4 y (12-43 y).  Fontan 6, TGA atrial 2, 2 biVS.  30 IART circuits. Ablate 22 circuits. Median f/u 4 mo. | ACHD ablation outcomes | Circuits in 4 areas of RA.  77% acute success (circuits)  50% recurrence short term | 77% acute success, 50% recurrence short term 4 mo |
| Kalman JM  1996  (212)  [8565168](http://www.ncbi.nlm.nih.gov/pubmed/?term=8565168) | Retrospective single center | 18 | 18 consecutive ACHD pts, 26 IART circuits, mean age 26 ±15 y map & Ablation 1992-1995.  ASD 50%, Fontan 22%, TGA atrial switch 22%, Rastelli 5%; conventional mapping, f/u mean 17 mo. | ACHD ablation outcomes | Acute success 83%  Fontan 50% success | Acute success 83%,  50% asymptomatic, no medications during f/u.  33% recurrence, plus 7% AF |
| Tanner H  2004  (320)  [15851168](http://www.ncbi.nlm.nih.gov/pubmed/?term=15851168) | Multicenter retrospective | 36 | 36 consecutive ACHD pts, median age 46 y.  ASD 20, TOF 8, TGA 5, VSD 1, UVH 1, cc-TGA 1.  Mean f/u 17 mo | ACHD ablation outcomes | 52 IART circuits; 48 ablations.  65% CTI dependent. 27% incisional, 8% LA.  Acute success: 87%. | 87% acute success ablation ACHD (2 ventricles predominantly)  25% on chronic AA meds  92% free of recurrence  14% developed AF |
| Lukac P  2005  (321)  [15851267](http://www.ncbi.nlm.nih.gov/pubmed/?term=15851267) | Retrospective single center | 52 | 52/83 pts postop ACHD, median age 36 y  ASD 21, TOF 11, TGA 9; UVH 4, VSD 2  Median f/u 27 mo | ACHD ablation outcomes | CTI dependent 71%  Fontan pts multiple circuits;lateral RA wall | CTI dependent 71%-most common, except in Fontan pts  31% chronic AA meds  24% recurrence  13% died or OHT |
| De Groot NM 2010  (322)  [20194797](http://www.ncbi.nlm.nih.gov/pubmed/?term=20194797) | Retrospective single center | 53 | Ablation in 53 ACHD pts, age 38±15 y. | Examine characteristics of recurrences after ablation ACHD | Atrial flutter 51%; IART 42%; Focal 9%.  Acute success 65%; recurrence 59% w/in one y.  Repeat ablation 15: 7 similar mechanism.  f/u: 5± 3 y: death 9%; AA meds 57%;  31% recurrent AT | ACHD: High recurrence 59%;  57% meds; 9% death  Recurrent AT may be different mechanism. |
| Yap SC  2010  (323)  [21029876](http://www.ncbi.nlm.nih.gov/pubmed/?term=21029876) | Retrospective single center | 130 | 193 ablations performed in ACHD 130 pts, mean age 40 ±13 y; median f/u 3.4 y. Type of CHD ASD 21%, TGA 18%; UVH 20%; TGA 18%, other 12% | Acute & long term outcomes ablation of IART in ACHD | Acute success 69%; 5% major comps; pacers 3%; 62% discharged on AA meds;  IART recurrence: 4 y =51%; repeat ablation 35%; death 4%. Older age and Fontan palliation predictors of recurrence. | Differential outcomes of ablation based on type of CHD: in Fontan pts, 4 y r freedom from recurrence 15% vs.~42% in ASD, TOF, Mustard |
| Ueda A  2013  (324)  [23685536](http://www.ncbi.nlm.nih.gov/pubmed/?term=23685536) | Retrospective single center | 116 | Ablation 116 ACHD pts, mean age 41 y; 154 procedures, 228 circuits using remote navigation, 3D mapping. F/u mean 20 mo, Group A: manual mappping/ablation; B: remote navigation; C: remote navigation +difficult access. | Assess outcomes ablation ACHD | Compare simple vs. complex lesions or complex vascular access. AVNRT 5-13%; AVRT 4-7%; Focal 11-26%; atrial flutter 11-39%; IART 23-45%; AF 6-18%.  No difference acute success 82-91%, recurrence 20-24%. | ACHD population: ablation  Acute success >80%; 20-25% recurrence w/in 20 mo |
| CHD: Catheter Ablation – ASD | | | | | | |
| Teh AW  2011  (325)  [21208243](http://www.ncbi.nlm.nih.gov/pubmed/?term=21208243) | Retrospective single center | 20 | Ablation AT after ASD repair; mean age 53±13 y; post ASD closure interval 29±15 y. | ASD Outcome atrial flutter ablation in | All CTI dependent atrial flutter; + other circuits.  Acute success 100%; 25% repeat abl at 13 mo. F/u 3.2±1.6 y, 30% documented AF; stroke 5%; 35% AF intervention | Excellent acute ablation success ASD: 100%; 25% recur-repeat ablation,  30% AF in 3 y of f/u |
| Wasmer K 2013  (301)  [23540398](http://www.ncbi.nlm.nih.gov/pubmed/?term=23540398) | Retrospective single center | 54 | Consecutive Repaired ASD pts underwent EP study & ablation, mean age 47 y. Mean 22 y postop.  f/u in 83%, 7.7 y. Mean AT CL 270 msec. | ASD ablation & mechanisms of AT | AT at EP study in 78%: RA macroreentry in 100%; CTI dependent 69%; typical atrial flutter 41%.  10% not inducible. CTI ablation in AF or non-inducible. Ablation acute success: 93% | 93% acute success ablation ASD.  4% recurred w/ different mechanism.  60% arrhythmia free during f/u  11% developed AF |
| Scaglione M  2014  (326)  [24843050](http://www.ncbi.nlm.nih.gov/pubmed/?term=24843050) | Retrospective single center | 46 | 46 repaired ASD pts, mean age 49 y; 89% secundum ASD.  ECG atrial flutter 48%, atypical atrial flutter 35%, AT 17%. 41% also AF.  Onset AT 19±12 y postop.  Complete f/u, 7.3 y | ASD mechanisms & ablation outcomes | Typical AF: 48%, atypical 35%, AT 17%. CTI dependent 26%, 74% atriotomy dependent;  Ablation acute success 100%; recur 24%  Recur same mechanism w/ gaps.  70% atypical atrial flutter had ECG concordance. | ALL RA macro-reentry; no focal.  High success ablation for ASD:  100%, 24% recurrence  20% repeat ablations |
| CHD: Catheter Ablation – Ebstein’s | | | | | | |
| Cappato R 1996  (327)  [8759079](http://www.ncbi.nlm.nih.gov/pubmed/?term=8759079) | Retrospective single center | 21 | Ebstein pts w/ AVRT: EP study + attempted RFA. 34 right sided AP in 21 pts. Mean age 28±14 y.  Mean f/u 22 mo. | Ebstein’s ablation outcomes | 76% acute success ablation AP.  24% recurrent SVT (5 pts, including 4/5 w/ acute success)—4/16 successful ablations-rec SVT= | Cath ablation success 76%;  25% recurrence in 22 mo in pts w/ acutely successful ablation. |
| Reich JD 1998  (328)  [9869537](http://www.ncbi.nlm.nih.gov/pubmed/?term=9869537) | Retrospective multi-center | 65 | 65 Ebstein’s pts, age 9.8±5.4 y, 82 accessory connections: 62% right, 34% septal, 4% left; only 52% w/ single AP; 9% AP plus atrial tachycardia; 9% non-AP tachycardia. | Ebstein’s ablation outcomes | Acute success 75-89%.  Mild tricuspid regurgitation and BSA <1.7 predicted acute success. | SVT related to AC 82%; 18% other atrial tachycardia mechanisms. |
| CHD: Catheter Ablation – UVH | | | | | | |
| De Groot NM 2009  (329)  [19808474](http://www.ncbi.nlm.nih.gov/pubmed/?term=19808474) | Retrospective single center | 19 | 19 Pts w/ UVH, age 29±9 y; 41 SVT circuits; | Procedural outcomes of ablation in UVH | Mechanisms: IART 73%; Typical atrial flutter 10%; Focal 15%; AF 2%.  Acute ablation success: 73% IART; 75% atrial flutter; 100% focal  f/u 53±34 mo: 16% died; 11% transplant | UVH pts: Acute success ~78%  Death or OHT : 27%  Recurrence: 27% by 53 mo |
| Yap SC  2012  (330)  [22035149](http://www.ncbi.nlm.nih.gov/pubmed/?term=22035149) | Retrospective single center | 11 | Ablation in Fontan pts vs. 30 other ACHD pts; atriopulmonary and AV Fontan, mean age 33±0 y. | Assess AT substrate after Fontan surgery | Fontan pts larger RA (p<.001), larger low-voltage area (p=.01). Acute success Fontan 54% vs. 83% other CHD (p=.04).  F/u 2.3±1.6 y, IART recurrence 47%. | Fontan pts lower acute success vs. other ACHD  high recurrence 47% at 2.3 y all pts;  Fontan 50 ±19%, vs. 32 ±10% non-Fontan pts at 2 y  Larger RA size and low voltage areas predicted IART recurrence |
| Correa R  2015  (331)  [25583982](http://www.ncbi.nlm.nih.gov/pubmed/25583982?dopt=Citation) | Retrospective single center | 32 | 52 consectutive pts underwent 57 EP studies 2006-2012. Mean age 18.4±11.8 y, all with TCPC type Fontans. 32 ablations, 31 for SVT. VT induced in 5/52 pts studied. No f/u in 19%. In others, median f/u 18 mo. | Procedural outcomes of ablation in UVH. | 47 procedures w/ 54 defined SVT mechanisms. IART 46%, AVNRT 24%, focal 15%, AP 7%, twin AVN 7%. Additional 21 undefined AT. Ablation for SVT acute success 80%. Two major adverse events 6%: death, pulmonary embolus. 50% recurrence short term, improved arrhythmia scores. | 78% acute success for SVT. 50% recurrence short term; improved arrhythmia scores. 6% major adverse cardiac events. |
| CHD: Catheter Ablation – TGA | | | | | | |
| Jones DG  2013  (332)  [23219079](http://www.ncbi.nlm.nih.gov/pubmed/?term=23219079) | Retrospective single center | 9 | AT ablations TGA Mustard; 9 procedures, 12 circuits between 2007-2012, median age 38 y (18-56 y), used Carto and irrigated tips. Median f/u 15 mo. | Ablation outcomes TGA atrial switch pts | Transbaffle puncture in all. AT mechs:  CTI dep: 75%, focal 25% (pulmonary venous ¾). Acute success 100%; 25% recurrence w/in 16 mo. Death 11% (1/9); recurrent AT w/ CHF.  ICD’s in 3/9. | Ablation in pulmonary venous atrium needed in all pts.  Acute success 100%, recurrence 25% short-term. |
| Wu J  2013  (333)  [23355133](http://www.ncbi.nlm.nih.gov/pubmed/?term=23355133) | Retrospective single center | 26 | Ablation in 26 TGA pts s/p atrial switch repairs, mean age 28.7±6.7 y; 34 ablation procedures. | Assess outcomes ablation in TGA atrial switch pts | 34 AT: IART 88%; AVNRT 12%. Acute success 85% of circuits.  Mean f/u 34±24 mo, 30% recurrence IART. | TGA atrial switch: high acute success, 34% recurrence <3 y |
| CHD: Surgical therapy | | | | | | |
| Pressley JC 1992  (334)  [1394922](http://www.ncbi.nlm.nih.gov/pubmed/?term=1394922) | Retrospective, single center | 38 | 38 pts, WPW and Ebstein anomly, surgical AP ablation and repair. Mean age 26.3 ±12.3 y, 1968-88. Compared to 384 pts undergoing AP surgery w/o Ebstein.  76% documented AVRT; 42% AF. F/u 6.2± 3.8 y. | Assess surgical impact AP ablation during Ebstein repair. | Mult AP 50%, right sided 79%, posteroseptal 58%, left 7.9%.  Surgery mortality 5.3%, both <15 y old. 28/38 surgery repair + AP ablation;  Successful AP ablation: 95%. 82% NS arrhythmias during f/u. | Pts w/ Ebstein anomaly improved after surgery w/ AP ablation.  Late AF reduced from 42% to 9%, p<.001. |
| Misaki T 1995  (335)  [8523883](http://www.ncbi.nlm.nih.gov/pubmed/?term=8523883) | Retrospective, single center | 42 | 42 pts WPW = Ebstein, surgery 1973-1993. Mean age 35±14 y. 52 APs, 48 right or posteroseptal. Division of AP at surgery; 35 TV operation. | Assess outcome WPW surgery in Ebstein | All 52 AP successfully rx at surg.  2 reops due to SVT: additional AP.  Hospital mortality 7.1%. no late deaths f/u mean 94 mo | N/A |
| Theodoro DA  1998  (336)  [9456109](http://www.ncbi.nlm.nih.gov/pubmed/?term=9456109) | Retrospective, single center | 18 | 18 ACHD pts mean age 34.9 y underwent RA Maze for AT/atrial flutter or AF:  Ebstein 15, tricuspid regurgitation 2, ASD1. Mean f/u 8 mo. | Assess outcome RA maze in ACHD | No early deaths. Early postop SVT 3.  RA maze performed, even in pts w/ AF. | Inclusion RA maze in ACHD pt w/ RA dilatation and AT is effective in eliminating or reducing AT. |
| Huang CJ 2000  (337)  [11145402](http://www.ncbi.nlm.nih.gov/pubmed/?term=11145402) | Retrospective, single center | 30 | 30 pts w/ Ebstein:surg repair 1973-1997. Preop EP study performed in 11 after 1980: surg ablation performed in 10/11: WPW 4, AVNRT 2, atrial flutter/AF 3, VT1. | Assess survival difference w/ op ablation Ebstein. | No mort in ablated pts.  7/30 died: 1-infection, 6 died suddenly. None of 6 sudden deaths underwent preop EP study. | Detailed preop EP study in Ebstein: “mandatory”:  Aggressive surg intervention for arrhythmia may reduce risk of sudden death. |
| Mavroudis C 2001  (338)  [11689789](http://www.ncbi.nlm.nih.gov/pubmed/?term=11689789) | Retrospective, single center | 40 | 40 Fontan conversions w/ arrhythmia surgery; mean age 18.7±9 y. All pts w/ AT; AF in 15. | Assess impact of arrhythmia surgery on AT in Fontan | Isthmus ablation 10 pts, RA Maze 16, Biatrial maze 14. No mortality. Mean f/u 2.5±1.9 y, OHT 7.5%. Arrhythmia recurrence 12.5% | Largely AP Fontan population; arrhythmia recurrence 12.5% at 2.5 y |
| Deal BJ  2002  (220)  [12147539](http://www.ncbi.nlm.nih.gov/pubmed/?term=12147539) | Retrospective, single center | 23 | Comparison isthmus ablation (8) w/ RA maze (15) in AP Fontan pts w/ AT; median age 10.9 y (2-33 y) | Assess efficacy of operative ablation techniques Fontan. | Isthmus ablation: 62% recurrent AT; f/u 5.6 y  RA maze: no recurrence, f/u 2.8 y | RA maze superior to isthmus ablation in Fontan pts |
| Khositseth A  2004  (339)  [15573066](http://www.ncbi.nlm.nih.gov/pubmed/?term=15573066) | Retrospective single center | 83 | 83129 adult Ebstein pts w/ SVT underwent arrhy procedure w/ surgery for Ebstein. 41: AP, mean age 18 y; 7 AVNRT, mean 18 y ; 48 atrial flutter/AF (RA maze 38, isthmus 10), mean 33 y. | Assess arrhythmia surgery in Ebstein | Incidence SVT: atrial flutter/AF 54%, AP 32%, AVNRT 8%. Surgical outcomes:  AP or AVNRT: 0 recurrence 48 mo;  Atrial flutter/AF 75% freedom from recurrence at 34 mo. | Arrhy surg interventions should be added to surgical repair Ebstein in pts w/ SVT: AP, AVNRT, or atrial flutter/AF. AS AT present in 54% and increases w/ age, recommend AT surgery as well as AP surgery. |
| Bockeria L 2005  (340)  [16179193](http://www.ncbi.nlm.nih.gov/pubmed/?term=16179193) | Retrospective, single center | 53 | 53 pts, Ebstein + SVT, mean age 21.6±10.7 y. Surgery + operative ablation: 32 pts; preop RFablation later surg: 21 pt.  WPW 26, AVNRT 3, focal 3. | Assess combined arrhythmia surgery in Ebstein vs. RFA + surgery. | Mortality 3.1% in combined ablation operation vs. 0% in 2 staged. Efficacy:  Surgery ablation 94% op vs. 76% catheter.  Surgery efficacy WPW 92%, AVNRT 100%, focal 66%. | Combined operative ablation + surg repair showed improved AT elimination vs. catheter ablation approach followed by surgery. |
| Giamberti A 2006  (341)  [16996928](http://www.ncbi.nlm.nih.gov/pubmed/?term=16996928) | Retrospective, single center | 15 | 15 ASD pts, >40 y, surgical closure ASD w/ intraop RF ablation. All SVT: 8 AF, 7 AT/atrial flutter. 2002-2004. RA Maze 8, biatrial cox maze iii 7 pts. F/u mean 24 mo. | Assess op ablation AT in ASD pts | No mortality, one pacemaker.  AF recurrentce 6.5%, no AT recurrence. | Rec add intraop RF ablation to surgical ASD closure, safe & effective. |
| Karamlou T 2006  (342)  [16631673](http://www.ncbi.nlm.nih.gov/pubmed/?term=16631673) | Retrospective, single center | 249 | 1969-2005, TOF or DORV pts undergoing reop for PVR or TVR; AT in 41 pts. Median age 23 y. Assess RA maze vs. no maze on late outcome. | Assess impact of RA ablation on arrhythmia outcomes TOF. | Atrial flutter: isthmus ablation; AF RA maze.  AT recurrence: ablation pts, 9%, vs. 78% AT occurence in non-ablation; 7.5 y.  AT pts older, longer QRS duration | RA Maze at time of surgery improved long term AT free status.  QRS duration >160 msec predicted risk of AT in TOF |
| Stulak JM  2006  (343)  [16631672](http://www.ncbi.nlm.nih.gov/pubmed/?term=16631672) | Retrospective, single center | 99 | 1993-2003, 99 pts RA maze w/ ACHD repair. Median age 43 y. *Did not distinguish between AT and AF.* Ebsteins 47, TR 19, UVH 11, ASD 8, TOF 8, other 6. | Impact arrhythmia surgery on AT: ACHD. | 6% early mortality. 28% early AT  Arrhythmia recurrence 7%, f/u 2.7 y; AA medications 55%. | ACHD: 55% on AA meds;  93% not in AT at 2.7 y |
| Mavroudis C 2007  (344)  [17954046](http://www.ncbi.nlm.nih.gov/pubmed/?term=17954046) | Retrospective, single center | 111 | 1994-2007, 111 Fontan conversions w/ arrhythmia surgery; mean age 22.5 y. Mainly AP Fontan. | Assess arrhythmia recurrence, survival Fontan | Early mortality 0.9%, late death/OHT 11%. Late AT 13.5%, f/u 7.9 y | Late AT in Fontan 13.5% at ~ 8 y; |
| Giamberti A  2008  (345)  [17689722](http://www.ncbi.nlm.nih.gov/pubmed/?term=17689722) | Retrospective, single center | 50 | 50 ACHD adults undergoing surgery; mean age 39 y. 31 RA Maze,  13 biatrial, 6 VT ablations. | Assess surgical arrhythmia outcome ACHD. | Mortality 4%; Mean f/u 28 mo: 4/48 on medications; 43 sinus rhythm, 4 recurrent AF | ACHD: 86% sinus rhythm, no medications during short term f/u |
| Mavroudis C  2008  (346)  [18721574](http://www.ncbi.nlm.nih.gov/pubmed/18721574) | Retrospective, single center | 100 | Arrhythmia operations, 11 no HD; 89 associated CHD (33 UVH); mean age 15.9 y. SVT 87, VT 13 | Assess surgical arrhythmia outcome ACHD | Mechs AT: ART 45, AF 11, AC 19, AVNRT 6, Focal 6; early mortality 3%, late death/OHT 6%; 10 y Freedom from AT 85%, 68% VT | Freedom from AT at 10 y: 85% in mixed population ACHD |
| Aboulhosn J  2010  (347)  [21087427](http://www.ncbi.nlm.nih.gov/pubmed/?term=21087427) | Retrospective, single center | 27 | 27 atriopulm Fontan adults converted to TCPC; 67% extracardiac. 89% w/ atrial tach. 21/27 w/ arrhythmia surg: RA 12, RA + LA 9.  Mean age 30 y (18-52 y)  Mean f/u 4.2 y. | Assess arrhythmia recurrence after Fontan arrhythmia surgery. | Operative mortality 7.4%.  Arrhythmia recurrence 14% (3/21)  PLE 3; 1 died 27 mo postop, 2 resolved. | Recurrrent AT in 14% w/ 4 y f/u |
| Gutierrez SD  2013  (348)  [23280242](http://www.ncbi.nlm.nih.gov/pubmed/?term=23280242) | Retrospective, single center | 24 | 24 ACHD pts w/ AA undergoing surgery, mean age 40.9 y; incorporated cox maze procedure. 2004-2010. TOF 8, AVSD 4; RVOT repair 10, TV repair 8, ASD 7. Mean F/u 2.8 y, (.1-5.7 y). | Assess outcome of cox maze procedure in ACHD | Preop AT: 19, AF 5.  Mortality: 16.5%, (12.5% early, 1 late)  74% of survivors arrhythmia free. | Pts w/ CHD and atrial arrhythmias, majority free of arrhythmias w Cox Maze procedure. |
| Terrada T  2013  (349)  [24887891](http://www.ncbi.nlm.nih.gov/pubmed/24887891) | Retrospective, single center | 25 | 25 consecutive pts undergoing Fontan conversion 1/04-3/12. Mean age 21 6.3 y.  24/25 underwent arrhyth surg: RA maze 15, isthmus 3, biatrial 6.  Mean f/u 21 mo(11-86 mo) | Assess outcome Fontan arrhythmia surgery. | Late AT recurrence 12.5%  Operative mortality: 0.  16/25 no pacemaker implanted.  5 pts reoperation to implant pacer. | Recurrent AT 12. 5%, |
| Said SM  2014  (350)  [24786860](http://www.ncbi.nlm.nih.gov/pubmed/?term=24786860) | Retrospective, single center | 70 | 70 Fontan pts underwent Fontan conversion 1994-2011.  Median age 23 y (4-46 y)  AT present 89%  TCPC intra-atrial 59%; extracardiac 26%, Lateral tunnel 16%.  49/70 arrhythmia surgery.  Mean f/u 5 y. | Assess outcome Fontan arrhythmia surgery. | Late Recurrent AT in 16% of pts w/ arrhythmia surgery  Operative mortality 14%.  10 y survival 67%  Periop death predictors:  Age >27 y, AV valve regurgitation, males. PLE improved in 1/7 pts. | Late Recurrent AT in 16% |
| Pregnancy: Acute Conversion of AV Node-Dependent Tachycardia | | | | | | |
| Ghosh N  2011  (351)  [21272431](http://www.ncbi.nlm.nih.gov/pubmed/21272431) | Review of all reports published 1950-2010 on acute termination of SVT | 138 pts | Variety of drugs. Most common adenosine w/ 58 cases. Also electrical DCCV 18 cases | Successful termination of SVT | Adenosine was most successful at terminating SVT.  Beta blockers and verapamil second, led to more hypotension. Antiarrhythmic drugs not very effective. | Variety of interventions was reported on acute termination of SVT. Most common adenosine w/ 58 cases. Also electrical DCCV 18 cases, verapamil 16 cases and beta blockers 13 cases. Diversity of antiarrhythmic drugs as well. Most effective was adenosine w/ 84% success, followed by beta blockers and verapamil. Cardioversion safe. |
| Pregnancy: Catheter Ablation | | | | | | |
| Damilakis J  2001  (352)  [11514375](http://www.ncbi.nlm.nih.gov/pubmed/11514375) | Conceptus radiation dose and risk determination for catheter ablation procedures. | 20 | 20 women of childbearing ages who underwent ablation procedures | Estimation of radiation dose using phantom pregnancy | Typical dose to conceptus was <1 mGy | A typical ablation procedure results in very small increase in risk of harmful effects to the conceptus. |
| Berruezo A  2007  (353)  [17897139](http://www.ncbi.nlm.nih.gov/pubmed/17897139) | Case report of ablation w/ low radiation exposure | 2 pts | Pt w/ drug refractory SVT; ablation of SVT w/ radiation dosimeter | Successful ablation; adverse effects | All pathways eliminated successfully | Both pts treated, fetus dose was very low, below dangerous limit. |
| Szumowski  2010  (354)  [20158563](http://www.ncbi.nlm.nih.gov/pubmed/20158563) | Observational, multicenter report experience w/ ablation of SVT in pregnancy | 9 pts | Pt w/ severe SVT refractory to medical therapy; ablation w/ low radiation exposure | Successful ablation; adverse effects | All pathways eliminated successfully | All pts treated successfully, w/ either no radiation at all to very low dose. |
| Pregnancy: Prophylactic Antiarrhythmic Drug Therapy | | | | | | |
| Wen Z  1998  (41)  [9851958](http://www.ncbi.nlm.nih.gov/pubmed/9851958) | Prospective cohort study | 133 | AVRT (n=85)  AVNRT (n=48)  EP study to induce PSVT by PES  Excluded atrial flutter, AF organic heart disease or other systemic diseases involving the autonomic function (e.g., diabetes), those who could not blow into an aneroid manometer to maintain a pressure of 35 mm Hg for 20 sec, and those w/ unstable hemodynamics during tachycardia. | Termination of PSVT | Vagal maneuvers more effective in terminating AVRT than AVNRT (53 vs. 33%, p<0.05).  AVNRT: vagal maneuvers terminated tachycardia in antegrade slow pathway (14%) or in retrograde fast pathway (19%).  Baroreflex sensitivity was poorer but isoproterenol sensitivity test better in pts w/ AVNRT. | Vagal maneuvers effective, more so for AVRT.  Limited in that study conducted during EP study. |
| Lydakis C 1999  (355)  [10371362](http://www.ncbi.nlm.nih.gov/pubmed/10371362) | Retrospective study on the effect of Atenolol and other drugs on fetal growth | 78 | Atenolol given to 78 pregnant women and compared to other drugs. | Comparison of adverse effects to fetal growth | Increased risk of fetal growth retardation | Possible increased risk of fetal growth retardation on atenolol compared to other drugs, risk related to duration of treatment. |
| Von Dadelszen P 2000  (356)  [10675164](http://www.ncbi.nlm.nih.gov/pubmed/?term=10675164) | Metanalysis of different drugs, mainly beta blockers, inpregnancy | 3773 | Meta analysis of different drugs for pregnancy induced HTN to try to determine if growth retardation is due to drugs or disease. | The association of treatment-induced difference in mean arterial pressure with measures of fetoplacental growth | Relationship was observed between fall in MAP and growth retardation, but was not related to drugs. | Beta blockers mainly safe during pregnancy, growth retardation likely due to fall in BP. |
| Bartalena  2001  (357)  [11263469](http://www.ncbi.nlm.nih.gov/pubmed/?term=11263469) | Review of case reports when amiodarone was given during pregnancy | 64 | Review of case reports when amiodarone was given. There were 64 identified and effect on babies was reported. | Adverse effects documented on progeny of mothers who received amiodarone. | Hypothyroidism reported in 17%, which most of the time was transient. Some developmental disabilities seen even in euthyroid. | Maternal use of amiodarone can cause hypothyroidism in progeny and occasionally neurodevelopmental abnormalities. |
| Qasqas SA 2004  (358)  [15191632](http://www.ncbi.nlm.nih.gov/pubmed/15191632?dopt=Citation) | Review article on all cardiovascular drugs in pregnancy. | N/A | This is a review article. | N/A | All drugs are describe in detail and references made to all case reports. | This is a comprehensive compendium of all antiarrhythmic agents give during pregnancy. |
| Jaeggi ET 2011  (359)  [21931080](http://www.ncbi.nlm.nih.gov/pubmed/21931080?dopt=Citation) | Nonrandomized multicenter comparison of different drugs administered for transplacental therapy of fetal SVT | 159 | The authors reviewed 159 consecutive referrals w/ fetal SVT (n=114) and AF (n=45). Of these, 75 fetuses w/ SVT and 36 w/ AF were treated nonrandomly w/ transplacental flecainide (n=35), sotalol (n=52), or digoxin (n=24) as a first-line agent. | Effectiveness of different drugs reported. | Flecainide and digoxin were superior to sotalol for fetal SVT. | This was a study for fetal SVT, but showed that flecainide sotalol and digoxin are well tolerated in pregnant women. |
| SVT in the Elderly | | | | | | |
| Chen SA 1995  (360)  [7490388](http://www.ncbi.nlm.nih.gov/pubmed?term=((chen%5BAuthor%5D)%20AND%201370)%20AND%201995) | Observational | 66 pts w/ AVRT and AVNRT w/ initial sx onset after age 65 vs. 440 pts w/ sxs onset before age 30 | All pts underwent EP study and RFA;  4 mm tip temperature control deflectable catheter | Compare clinical characteristics in the older vs. younger grooups | Older group: 32/66 had AVRT, 34/66 had AVNRT  Younger group: 283/440 AVRT, 157/444 AVNRT  Sxs of syncope and cardioversion were similar between two age groups; older pts had more atrial and ventricular ectopic beats on Holter; dispersion of anterograde ERP was greater in older pts; Success rate was 97-98% in all groups; Recurrence was similar (6-7%; f/u duration was not stated in the paper); complications were significantly higher (13-14% in older pts than younger pts (1%) (for AVRT: 2 arterial thrombosis, 1 TIA, 1 DVT; for AVNRT: 1 DVT, 1 AV block) | Greater dispersion of ERP and increased atrial and ventricular ectopic beats may explain the later onset of sxs in older pts. |
| Chen SA  1996  (361)  [8540455](http://www.ncbi.nlm.nih.gov/pubmed?term=((((chen%5BAuthor%5D)%20AND%201996)%20AND%2077)%20AND%2041)%20AND%2046) | Observational | 3966 consecutive EP study and 2593 ablation procedures | Tertiary referral center in Taiwan, 1987 – 1994  4 mm tip temperature control deflectable catheter | Risk factors associated w/ complications | Overall complications, RFA vs. EP study, 3.1% vs. 1.1% (p 0.00002); Older (≥65 y) vs. younger, 2.2% vs. 0.5% (p 0.0002) for EP study and 6.1% vs. 2.0% for RFA. Older age and presence of systemic disease are independent predictors for complications.  Complications included pericardial eff/usion, tamponade, AVB, vascular injury, systemic emboli) | Data suggest older age is an independent risk for EP study and RFA. These data are somewhat out dated. Older pts had more co-morbidies and the presence of systemic diseases (co-morbidities) is an independent predictor of acute complications. |
| Boulos M  1998  (362)  [9708674](http://www.ncbi.nlm.nih.gov/pubmed/9708674) | Observational | 271 consecutive pts | AVNRT from a single center undergoing RFA, 1991 – 1995.  4 mm tip deflectable catheter were used to map and ablate | Slow pathway ablation | Acute success rate 98.1%, recurrence rate 4.1%; CHB 2.2%, 2% for pts <65 y of age, 8% in older pts; Older age is associated w/ higher risk of CHB. | Data are historical.  The focus was on AVB complicating slow pathway ablation; no other complications were reported. |
| Kalusche  1998  (9)  [9812187](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kalusche+D%2C+Ott+P%2C+Arentz+T%2C+Stockinger+J%2C+Betz+P+Roskamm+H) | Retrospective cohort study | 395 pts undergoing AVNRT RFA. 85 (22%) ≥65 y (mean 70 y). | Consecutive pts from a single center in Germany, 1992 – 1997  9 pts were excluded due to more than one tachycardia inducible  4 mm tip temperature controlled deflectable catheter | Clinical presentation and outcomes in young vs. elderly during AVNRT ablation | Similar to younger pts, elderly more often had organic heart disease (CAD w/ or w/o MI,19.3% vs. 2.6%; P<0.02), syncope or presyncope w/ AVNRT (43.2% vs. 29.8%; P<0.05). 17.5% vs. 6.5% (P<0.05) the fast pathway approach was chosen as the first therapy. The overall success rate (96.8% vs. 95.3%) and recurrence rate (5.8% vs. 4.9%) were similar in both pt groups.  Details of complications not listed: “minor complications such as hematoma; severe complications such as need of a PM” (2 in older group, 1 in younger group); f/u 2-68 mo. | Elderly pts have more severe sxs and more comorbid illnesses, but RFA safe. |
| Zado  2000  (363)  [10676694](http://www.ncbi.nlm.nih.gov/pubmed/?term=Zado+ES%2C+Callans+DJ%2C+Gottlieb+CD%2C+Kutalek+SP%2C+Wilbur+SL%2C+Samuels+FL.+Efficacy+and+safety+of+catheter+ablation+in) | Prospective cohort study | 695 pts were divided into: ≥80 y (n=37), 60-79 (n=275), and <60 y (n=383) | Ablation for SVT, VT (only 8% VT, 43% His ablation) | Determine whether catheter ablation is safe and effective in pts >80 y. | Overall success rate 95% (e groups (97% ≥80 y; 94% 60-79 y; 95%, <60 y). The overall complication rate for the entire group was 2.6%; no difference in complication rates among the groups (0%, ≥80 y; 2.2%, 60 to 79 y; 3.1%, <60 y) | RFA safe in elderly. However ,only 37 pts were >80 y. |
| Li YG  2001  (364)  [11133214](http://www.ncbi.nlm.nih.gov/pubmed/11133214) | Observational | 18 pts among 346 pts w/ prolong PR at baseline | Slow pathway ablation in pts w/ AVNRT  4 mm tip temperature control deflectable catheter | Late occurrence of AVB after complete short pathway ablation in AVNRT | 18/346 pts w/ prolong PR before RFA, age 62±7; Holters were obtained before, 1 d, 1 wk, 1, 3, 6 mo after ablation. Incidence of delayed AVB occurred in 6/18 pts w/ preexisting PR prolongation; antepgrade ERP was longer in the study group | Risk of AVB is increased after short pathway ablation in pts w/ pre-existing PR prolongation. These data have not been confirmed in the contemporary era. |
| Porter MJ  2004  (365)  [15851189](http://www.ncbi.nlm.nih.gov/pubmed/15851189) | Observational | 1754 consecutive pts, 1856 PSVT from a single center 1991-2003 | PSVT undergoing RFA; exclude IAST, flutter and fibrillation, age <5  Mapping and ablation techniques were not described. | Age and gender correlation to PSVT | Mean age 49±19 (5-96), women 62%; AVNRT 1042 (56%), AVRT 500 (27%), AT 315 (17%); AVRT decreases w/ age in both genders; AVNRT and AT increased w/ older age; majority (54.6%) of AVRT were men; majority of AVNRT and AT were women; In women, 63% had AVNRT, 20% AVRT and 17% AT; in men, 45% AVNRT, 39% AVRT, 17% AT | SVT is age and gender dependent in this single center study among pts referred for RFA. It is unknown whether this reflects the epidemiology in the general population due to the evolution of ablation from 1990 – current and whether referral bias, specifically related to age.  This is an age and gender dependent mechanism study; not an outcome study |
| Rostock 2005  (366)  [15946358](http://www.ncbi.nlm.nih.gov/pubmed/?term=Rostock+T%2C+Risius+T%2C+Ventura+R%2C+Klemm+HU%2C+Weiss+C%2C+Keitel+A.+Efficacy+and+safety+of+radiofrequency+catheter+ablation+of) | Retrospective cohort study | <75 y (n=508) and pts ≥75 y (n=70) | All pts w/ symptomatic AVNRT referred for slow-pathway ablation | Determine whether catheter ablation is safe and effective in pts ≥75 y. | Preexisting prolonged PR interval was present in 3.3 vs. 37% in pts <75 vs. older, p<0.0001). Following successful slow-pathway ablation, no induction of an AV block was observed in >75 y group. No recurrences occurred pts ≥75 y. | Slow-pathway ablation in elderly pts effective and safe and should be considered as first line therapy in this pt population. Challenges evidence that preexisting PR prolongation found to be associated w/ a higher risk of developing a delayed high-degree AV block. |
| Kihel J  2006  (367)  [16687422](http://www.ncbi.nlm.nih.gov/pubmed?term=((kihel)%20AND%202006)%20AND%20416) | Observational, case control | 42 pts ≥75 y vs. 234 pts <75 y | Consecutive pts w/ AVNRT from a single center in France, 1997 – 2004.  4 mm tip deflectable catheters were used for mapping and ablation | Determine whether catheter ablation is safe and effective comparing older vs. younger pts | Success rate 100% in the elderly vs. 99.6% in the younger pts; 1 minor complication of groin hematoma occurred in older pts (2.4%), 4 (1.7%) in younger pts including one PE, one pericardial effusion, 2 hematoma. Recurrent was 0 in older pts, 3.4% in the younger pts (p 0.5)  F/u duration was 28 mo and 35 mo in older and younger groups, respectively. | Catheter ablation for AVNRT is reasonable w/ high success rate and low complication rate. The data are more contemporary.  No difference between older and younger groups. |
| Dagres N 2007  (368)  [17434888](http://www.ncbi.nlm.nih.gov/pubmed?term=((dagres%5BAuthor%5D)%20AND%202007)%20AND%20477) | Observational | 131 consecutive pts ≥80 y old undergoing ablation | Consecutive pts from 3 centers: Greece, Germany and Switzerland, 1998 – 2004  “Temperature guided” approach | Determine pt characteristics and ablation outcomes | Flutter most common (54%), AVNRT 22%, AF 18%. 52% had SHD. AVN ablation was performed in pts w/ AF. Overall success rate was 97% w/ one pts had a CVA after isthmus ablation for flutter. Minor complications such as hematoma occurred in 3.1% of study population | In selected elderly pts, ablation is highly successful for flutter, AVNRT and AVN ablation. More than half of the elderly pts have SHD when undergoing RFA. The consistent theme w/ other contemporary studies is that elderly have more co-morbid conditions but the overall ablation outcomes are highly successful w/ acceptable low complications. None of these studies are randomized studies; selection bias cannot be excluded. |
| Haghjoo M 2007  (369)  [17069836](http://www.ncbi.nlm.nih.gov/pubmed/17069836) | Observational case control | 268 consecutive pts underwent RFA for AVNRT; 2001 - 2005 | Dichotomized at 65 y of age | Ablation outcomes | 156/112 : younger/older; CL longer in older pts; success rate, complications, the recurrences were similar between older and younger pts | No significant differences in outcomes between the two age groups dichotomized at 65 y of age |
| Pedrinazzi C  2007  (370)  [17823861](http://www.ncbi.nlm.nih.gov/pubmed/17823861) | Observation | Total of 605 pts | Consecutive pts undergoing RFA for all arrhythmias in a single center in Italy, 2000-2005  4 mm tip temperature control deflectable catheter | RFA outcomes | Older pts had more co-morbidities; 69% <70 y of age, 24% 70-79 y, 7% ≥80 y; complications were similar 1.2 vs. 1.4 vs. 2%; Complications included pneumothorax, pericardial eff/usion, and hematoma;  success rates were similar 92 vs. 88 vs. 88%; recurrence was followed up to 12 mo; AT and flutter had higher recurrence rate than AVNRT or AVRT | Outcomes of RFA for SVT and VT were similar in younger and older pt groups.  No major complications |
| Yangni N’Da’ O  2008  (371)  [18477940](http://www.ncbi.nlm.nih.gov/pubmed/18477940) | Observational | 141/816 (17%) elderly >70 y of age admitted for recurrent SVT | Paroxysmal junctional tachycardia actually included AVNRT and AVRT  Temperature controlled catheter | Clinical outcomes after RFA | In the acute setting: Cardiac decompenstation 10, syncope 26, ACS 14, vascular event 5; typical AVNRT 73%; atypical AVNRT more common in older pts than in younger pts (15% vs. 4%); ablation was performed in 79% of the older pts vs. 57% in the younger pts; complications more common 7% vs. 2.5% in older pts; more AF induced during study (19% vs. 5%) | Older pts have more severe sxs associated w/ SVT at baseline; Atypical AVNRT is more common in older pts. Complications are higher in older pts.  Very difficult paper to understand; did not specifically, or clearly, state the types of complications. |
| Hoffman BA  2011  (372)  [21315834](http://www.ncbi.nlm.nih.gov/pubmed/?term=21315834) | German registry; 48 trial centers in Germany | 3234 consecutive pts undergoing AVNRT ablation from 3/2007 to 5/2010 | AVNRT pts: >50 y  Group 1, n=1,268 [39.2%]; median age 40 y (95% CI: 30.0–45.0 y), 74.1% women,  Group 2 50–75 y old  (n=1,707 [52.8%]; 63.0 y [95% CI: 58.0–69.0] y, 63.0%  women)  Group 3 >75 y old (n =259 [8.0%]; 79.0 [95% CI: 77.0–82.0] y, 50.6% women). | Acute and long term success rate, complications and recurrence | No differences were observed among the three groups w/ regard to primary CA success rate (98.7% vs. 98.8% vs. 98.5%; *P=0*.92)  Hemodynamically stable pericardial eff/usion occurred in five group 2 (0.3%) and two group 3 (0.8%) pts  but in none of the group 1 (*P=0*.05) pts  AV block requiring permanent pacemaker implantation occurred  in two pts in group 1 (0.2%) and six pts in group 2  (0.4%) but none in group 3 (*P=* 0.41)  During a median f/u of 511 d, recurrence rate was 5.7% in all pts | Catheter ablation for AVNRT is highly effective and safe and does not pose an increased risk for complete AV block in pts over 75 y of age, despite a higher prevalence of structural heart  disease. |
| Ghali WA  2005  (222) | Systematic review and meta-analysis of observational studies that investigated risk of thromboembolism associated with atrial flutter. | The meta analysis included 13 studies on embolic risk around time of cardioversion that included 1546 patients. For chronic risk, there were 14 studies involving 17,691 patients. | MEDLINE, EMBASE, bibliographies, and consultation with clinical experts were used to identify studies that report the risk of thromboembolism associated with attempted cardioversion and longer-term risk in patients with atrial flutter. | Risk of thromboembolism associated with atrial flutter around time of cardioversion or over the long term in chronic atrial flutter. | Around the time of cardioversion, the risk of thromboembolic events ranged from 0% to 7.3% depending of clinical factors.  Lower event rates were observed in patients taking anticoagulants.  The long term risk rate of thromboembolism was approximately 3% with sustained atrial flutter. | The findings of this systematic review strongly suggest that atrial flutter does indeed impart a risk of thromboembolism. |

AA indicates antiarrhythmic; AARCC, Allicance for Adult Research in Congential Cardiology; AC, atrioventricular connections; ACE I/D, angiotensin converting enzyme insertion/deletion; ACHD, adult congenital heart disease; ACS, acute coronary syndrome; ADT, antidromic tachycardia; AF, atrial fibrillation; AICD, automatic implantable cardioverter defibrillator; AP, accessory pathway; APERP, accessory pathway effective refractory period; ART, atrioventricular tachycardia; ASD, atrioventricular septal defect; AT, atrial tachycardia; ATP, antitachycardia pacing; AVB, atrioventricular block; AVN, atrioventricular node; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; AVSD, atrioventricular septal defects; BMI, body mass index; bpm, beats per min; BP, blood pressure; BSA, body surface area; CAD, coronary artery disease; cc-TGA, congenitally corrected transposition of the great arteries; CHD, congenital heart disease; CHF, congestive heart failure; CK-MB, creatinine kinase myocardial enzyme; CL, cycle length; CONCOR, Interuniversity Cardiology Institute of the Netherlands and the Netherlands Heart Foundation; CPB, cardiopulmonary bypass; CTI, cavotricuspid isthmus; CVA, cerebral vascular accident; DCCV, direct current cardioversion; DOVR, double outlet right ventricle; DVT, deep vein thrombosis; dx, diagnosis; EAT, ectopic atrial tachycardia; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; ED, emergency department; EP, electrophysiological; ERP, effective refractory period; f/u, follow up; HF, heart failure; h/o, history of; HR, heart rate; HTN, hypertension; IART, intraatrial reentrant tachycardia; IAST, inappropriate sinus tachycardia; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; intraop, intraoperative; IV, intravenous; JET, junctional ectopic tachycardia; LA, left atrium; LFW, left free wall; LOS, length of stay; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MAT, multifocal atrial tachycardia; MI, myocardial infarction; MRI, magnetic resonance imaging; NOS, nitric oxide synthase; NS, non-significant; NSVT, nonsustained ventricular tachycardia; OHT, orthotopic herat transplant; OR, odds ratio; ORT, orthodromic tachycardia; PES, programmed electrical stimulation; PLE, protein-losing enteropathy; postop, postoperative; POTS, postural tachycardia syndrome; preop, preoperative; PSVT, paroxysmal supraventricular tachycardia; pt, patient; QOL, quality of life; RA, right atrium; RACHS, risk adjustment for congenital heart surgery; RF, radiofrequency; RFA, radiofrequency ablation; RFCA, radiofrequency catheter ablation; RFW, right free wall; RV, right ventricular; RVOT, right ventricular outflow tract; rx, therapy; SHD, structural heart disease; s/p, status post; SR, sinus rhythm; SVA, supraventricular arrhythmia; SVT, supraventricular tachycardia; sx, symptom; TCPC, total cavopulmonary connection; TEP, transesophageal pacing; TGA, transposition of the great arteries; TIA, transischemic attack; TOF, tetralogy of Fallot; TSH, thyroid stimulating hormone; TV, tricuspid valve; UVH, univentricular heart; VA, ventriculoatrial; VF, ventricular fibrillation; VSD, ventricular septal defect; VT, ventricular tachycardia; w/, with; w/o, without; and WPW, Wolff-Parkinson-White syndrome.

**Data Supplement 21.** Randomized Trials Comparing Special Populations – Section 9

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| **Study Name, Author, Year** | **Aim of Study** | **Study Type (Size, N)** | **Study Intervention Group (n)** | **Study Comparator Group (n)** | **Pt Population** | | **Endpoints** | | | **P Values, OR: HR: RR: & 95% CI:** | **Summary/Conclusions** |
|  |  |  |  |  | ***Inclusion Criteria*** | ***Exclusion Criteria*** | ***Primary Endpoint (efficacy) and Results*** | ***Safety Endpoint and Results*** | ***Secondary Endpoint and Results*** |  |  |
| Saul JP 2005  (373)  [16316969](http://www.ncbi.nlm.nih.gov/pubmed/?term=16316969) | IV amiodarone efficacy/safety | Multicenter randomized double-blind (N=61) | Ages <16 y, median 1.6 y. SVT 26, JET 31.  71% SHD. | Dosages: low 1 mg/kg, medium 5 mg/kg, high 10 mg/kg, plus 47 h maintenance. 30 d f/u. | N/A | Ages <16 y, median 1.6 y, SVT 26, JET 31.  71% SHD. | Amidarone use <3 mo, drug intereaction w/ amiodarone, imminent death, intentional hypothermia to <35 degrees C | Endpoint: time to success. Success low 47%, medium 80%, high 73%. | Adverse events 87%, 5 deaths, 2 related to drug: profound hypotension medium and high dose. | N/A | Medium or high dose effective 2.1-2.6 h.  Efficacy JET 67-83%.  SVT 33-89%. |
| Lim SH  2009  (38)  [19261367](http://www.ncbi.nlm.nih.gov/pubmed/?term=19261367) | Compare efficacy of bolus adenosine vs. slow calcium channel blockers in ED rx SVT | Prospective randomized trial (N=206). Mean ages 48.3±18.6 y. | 104 pts; adenosine 6 mg followed by 12 mg given as needed. Stopped w/ SVT conversion | 102 pts infusion verapamil 1 mg/min to max 20 mg, or dilitazem 2.5 mg/min to max 50 mg. Stopped w/ SVT conversion. | Pts ≥10 y in ED w/ narrow QRS tachycardia, ECG dx SVT, not converting w/ vagal maneuvers. | N/A | Conversion to SR: calcium channel blockers 98% vs. adenosine 86.5% (RR: 1/13; p= 0.002) | N/A | Drop in BP more common in calcium blockers group, mean SBP ↓13-7 mm Hg vs. no change w/ adenosine. | N/A | Calcium channel blockers effective and safe alternative to adenosine for conversion SVT; implications for cost. |
| Manrique AM 2010  (374)  [19819469](http://www.ncbi.nlm.nih.gov/pubmed/?term=19819469) | Assess magnesium sulfate supplementation during CPB on risk of JET | Randomized, double-blind, controlled trial (N=99) | 2/05-8/06, pts <17 y undergoing CPB repair CHD randomized to receive MgSO4 during rewarming | Placebo: 3 groups: Mg 25 mg/kg, 50 mg/kg or placebo. | Pts from birth-17 y w/ elective cardiac surgery. | Pts with Mg supplements for malnutrition, sepsis, pancreatitis, neonates. | Total incidence JET 7.0%.  JET incidences: Placebo 31%, low Mg 10%; higher Mg 0%. | N/A | N/A | Younger age <1 mo, complex CHD Aristotle score ≥4, prior CHF correlated w/ JET. | MgSO4 reduced incidence of postop JET |
| Sanatani S  2012  (375)  [22962431](http://www.ncbi.nlm.nih.gov/pubmed/?term=22962431) | Compare digoxin vs. propranolol for control of infant SVT | Multicenter randomized double-blind (N=61) | Digoxin (27) | Propranolol (34) | Infants <4 mo w/ SVT, AVRT or AVNRT. | Excluding manifest WPW. | Recurrent SVT. 27 digoxin, 34 propranolol  SVT recurred 19% digoxin, 31% propranolol (p=0.25, NS). Recurrence free status 79% digoxin, 67% propranolol, NS. | No deaths, no serious adverse events. | Time to recurrence, adverse events. No first recurrence after 10 d. | N/A | No difference between digoxin and propranolol in preventing recurrent SVT.  As recurrences did not occur >110 d, may not need prolonged rx. |

AVNRT indicates atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; BP, blood pressure; CHD, congenital heart disease; CHF, congestive heart failure; CPB, cardiopulmonary bypass; dx, diagnosis; ECG, echocardiogram; ED, emergency department; IV, intravenous; JET, junctional ectopic tachycardia; N/A, not applicable; NS, non-significant; pt, patient; rx, therapy; SBP, systolic blood pressure; SHD, structural heart disease; SR, sinush rhythm; SVT, supraventricular tachycardia; w/, with; and WPW, Wolff-Parkinson-White syndrome.

Data Supplement 22. Nonrandomized Trials, Observational Studies, and/or Registries of Quality-of-Life Considerations – Section 10

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| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| Lau CP  1995  (376)  [7770362](http://www.ncbi.nlm.nih.gov/pubmed/?term=Lau+et+al.+PACE+1995%3B+18%3A424-32) | QOL and exercise capacity in pts w/ PSVT due to AP treated medically vs. ablation | N=55  Random allocation to ablation vs. medical therapy | Pts w/ PSVT (including WPW) on stable medications for 3 mo  Randomly selected for ablation or continuing medical therapy | QOL questionnaire and ETT performed at baseline and every 3 mo for 1 y  Assessed PSVT frequency/duration of episodes; hemodynamic disturbance, presence of preexcited AF | 46 pts selected for ablation and 9 for medical therapy  36/46 successfully ablated, and they improved in QOL at 3 mo post ablation (total scores on General Health Questionnaire, Somatic Symptoms Inventory and Sickness Impact Profile) P<0.01for all 3  Improvements held at 1 y  Exercise capacity increased from 13.1±5.5 to 14.9 ±4.5 min at 3 mo after successful ablation (p<0.002) (due mostly to suppressing exercised induced PSVT).  Medical group or those w/ unsuccessful ablation had no change in QOL or exercise capacity | While pts randomly assigned to ablation vs. medical therapy, only 9 pts allocated to medical therapy  Population – WPW, not other forms of PSVT |
| Bubien RS  1996  (377)  [8840848](http://www.ncbi.nlm.nih.gov/pubmed/?term=Bubien+RS%2C+Knotts-Dolson+SM%2C+Plumb+VJ%2C+Kay+GN) | Prospective cohort study, QOL of PSVT | 188 | AVNRT (n=59)  AVRT (n=46)  AF s/p AVJ ablation (n=22)  Atrial flutter/AT (n=22)  VT (n=10)  QOL before, compared w/ 1 and 6 mo after RFA using SF-36 and disease-specific sx checklist—Frequency and Severity Scale | RFA associated w/ significant improvement in QOL sustained over 6 mo (p<0.005).  RFA followed by improved performance of ADLs and a marked decrease in number of visits to physicians and emergency rooms in the 6 mo after RFA compared w/ 6 mo before.  Pt's perception of impact of arrhythmias on health improved after ablation, maintained between 1 and 6 mo after ablation.  90% of pts indicated that heart rhythm problems influenced health perception at baseline, and declined to 59% at 1 mo and 58% at 6 mo. | N/A | Overall demonstrates benefit of RFA on variety of arrhythmias.  Tried to minimize response bias w/ anonymous mail surveys, self-reporting methods may be confounded by under-reporting of undesirable characteristics and over-reporting of socially desirable behaviors. |
| \*Bathina MN  1998  (378)  [9732885](http://www.ncbi.nlm.nih.gov/pubmed/?term=9732885) | Prospective comparison of the impact of QOL and CE between RFA and pharmacologic therapy for PSVT | 79 w/ newly-documented PSVT  Average number of drugs 1.35/pt  (CCB, BB, most common) | Exclusions: drug-refractory pts, prior treatment, AF, atrial flutter, preexcitation | SF-36 used to measure QOL after 12-mo f/u | RFA vs. medication  Bodily pain:  63±24 vs. 81±20  p<0.005  General health:  69±21 vs. 79±21  p<0.05  Vitality:  55±21 vs. 66±22  p<0.05  Role emotion:  78±36 vs. 94±17  p<0.05  Ablation resulted in complete amelioration of sxs in 33% vs. 74%. | First study to prospectively evaluate QOL and resource utilization between RFA vs. medical therapy.  Both effective, but RFA improves QOL to a greater extent. |
| Larson msec  1999  (379)  [10468092](http://www.ncbi.nlm.nih.gov/pubmed/10468092) | Retrospective single center evaluation | 161 pts w/ RFA for drug-refractory AVNRT | Not specified | Duke Activity Status Index used for physical function, Symptom Checklist—Frequency and Severity Scale, both used in telephone survey | Mean number of sxs declined from 5.8🡪3.1 (p<0.001)  Moderate-severe sxs declined 4.6🡪1.1 (p<0.0001)  Urgent care visits declined from mean of 4.6🡪0.4/y (p<0.001)  Heath score increased from mean of 56.6🡪77.3 (p<0.0001)  Pt utility increased from mean of 0.71 to 0.88 (p<0.0001) | RFA effective in improving QOL.  Although single center, Kaiser is a large health care system.  Susceptible to recall bias |
| \*Goldberg AS  2002  (380)  [11988206](http://www.ncbi.nlm.nih.gov/pubmed/?term=goldberg+as%2C+bathina+mn) | Prospective comparison on long-term effects of QOL between RFA and pharmacologic therapy for PSVT | 83 pts w/ newly-diagnosed symptomatic PSVT  Average number of drugs 1.49/pt  (BB most common)  39 w/ initial RFA, 44 w/ initial medical therapy (of which 22/44 underwent RFA) | Referred specifically for ablation  Excluded AF and atrial flutter  AVNRT (67%)  AVRT w/ AP (28%)  AT (5%) | SF-36 used to measure QOL after 1-y and 5-y f/u  At 5-y f/u, both RFA and pharmacologic therapy w/ improved scores (cumulative p<0.05 and p<0.001, respectively)  RFA significantly improved in physical function, physical role, emotional role, mental health (p<0.05)  At 5-y f/u, there was greater sx reduction in RFA group (p<0.01) compared to medical therapy  Improvement in sxs who underwent initial RFA or cross-over to RFA after 5 y, compared to medical therapy (p<0.05)  Over 5 y, the average cumulative cost for pts in the ablation therapy group was $7,507± $1,098. The cumulative cost for pts in medical therapy group was significantly lower than in pts initially treated w/ ablation therapy: $6,249±$1,421, p<0.05. | N/A | RFA was associated w/ higher QOL in all health concepts at 1 y; this improvement was sustained in the physical function, emotional role, physical role, and mental health subsets at 5 y.  Cost estimated to be higher in RFA group.  Offers 5 y f/u and includes pts who were not drug-refractory. |
| Walfridsson U  2005  (15)  [15733177](http://www.ncbi.nlm.nih.gov/pubmed/15733177) | Impact of PSVT on perceived ability to drive | N=301  Interview w/ structured questions | Pts referred for ablation, of which 226 were active drivers | N/A | Sxs among drivers (irrespective of driving): fatigue 77%, dizziness 47%, cold sweat (52%), near syncope (50%), syncope (14%). Women more symptomatic than men (p<0.05).  57% had sxs while driving, 42% of those pts needed to stop driving and 24 pts regarded their tachycardia as an obstacle to driving, w/ correlation (p<0.001) if near syncope was a sx | PSVT common while driving. Correlation of near syncope as sx w/ deciding that PSVT was obstacle to driving. |
| Meissner A  2009  (381)  [19158961](http://www.ncbi.nlm.nih.gov/pubmed/?term=meissner+a%2C+stifoudi+s) | QOL pre-post RFA | 309 | AVNRT (n=230)  AVRT (n=66)  AT (n=13) | QOL following ablation, measured w/ SF-36 and Symptom Checklist-Frequency and Severity Scale | F/u 4.5±1.3 y  QOL significantly improved in AVNRT (p<0.0005) and AVRT (p<0.04); AT p=NS  Pre-RFA sxs of tachycardia (91.5%), increased incidence of tachycardia episodes over time (78.1%), anxiety (55.5%), reduced physical capacity in daily life (52%) significantly improved post RFA (p<0.0001) | Large series w/ long-term f/u. |
| Walfridsson U  2009  (19)  [19702600](http://www.ncbi.nlm.nih.gov/pubmed/19702600) | QOL Survey | Pts w/ AVRT and AVNRT referred for RFA | AVNRT (n=97)  AVRT (n=79) | QOL scores measured by SF-36 and EuroQol, and disease-specific questions, compared w/ reference group | QOL scores were significantly lower for pts w/ AVNRT compared to AVRT in several SF-36 measures (physical functioning, general health, and bodily pain) as w/ EuroQol.  Scores significantly affected by occurrence >once a mo, arrhythmia duration, and whether sxs occurred not only during exercise but also at rest | Arrhythmia recurrence important to consider when setting priorities for treatment w/ RFA. |
| Wood KA  2010  (288)  [20109982](http://www.ncbi.nlm.nih.gov/pubmed/20109982) | QOL pre-post RFA | 52 | AVNRT (n=30)  AVRT (n=16)  AT (n=6) | QOL following ablation, measured w/ Patient Perception scale, 3 subscales of SF-36, 2 subscales from Medical Outcomes Study, disease-specific measures | Significant improvement in most sxs post-ablation (p<0.05)  No sxs completely eliminated at one mo f/u  Effect greater in women | Ablation improves QOL on several measures, both generic and PSVT-specific measures.  Short f/u. |
| Yildrim O  2010  (382)  [23280027](http://www.ncbi.nlm.nih.gov/pubmed/23280027) | QOL pre-post RFA | 50 | AVNRT (n=28)  AVRT (n=22) | WHOQOL-BREF and STAI domains | Prior to RFA, greater than average anxiety score (p<0.05)  All items significantly improved post-RFA—anxiety, QOL, and health satisfaction scores | RFA improves anxiety and QOL.  Limited by 3 mo f/u, but consistent w/ prior work. |
| Farkowski MM  2014  (383)  [24919538](http://www.ncbi.nlm.nih.gov/pubmed/24919538) | Prospective cohort, gender-related differences in outcomes pre-post RFA | 64 | AVNRT (n=40, 32 women, 8 men)  AVRT (n=26, 11 women, 15 men)  (2 pts did not complete f/u) | QOL measured by PPAQ, EQ-5D-3L | 41 women completed survey.  No significant baseline differences except AVNRT prevalence, and HRQOL by gender  Women reported higher severity of sxs on PPAQ than men (p<0.001)  At 2 mo after RFA, women reported higher severity of sxs (p=0.02) on PPAQ and more heart skipping than men (p=0.0014)  No significant difference in healthcare resource utilization during the y preceding RFA  AADs more often prescribed to women pre-procedure (p=0.022) | Small but significant gender-related difference in outcome of RFA in pts w/ AVNRT or AVRT measured w/ a disease-specific instrument  No significant difference in QOL or access to healthcare resources between women and men. |

\*Study addressed both CE and QoL

AAD indicates antiarrhythmic drug; ADL, activities of daily living; AF, atrial fibrillation; AP, accessory pathway; AT, atrial tachycardia; AVJ, atrioventricular junction; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; BB, beta blocker; CCB, calcium channel blocker; CE, cost effectiveness; EQ-5D-3L, EuroQol Research Foundation questionnaire; ETT, exercisetreadmill test; f/u, follow up; HRQOL, health-related quality of life; N/A, not applicable; PPAQ, Patient Perception of Arrhythmia Questionnaire; PSVT, paroxysmal supraventricular tachycardia; pt, patient; QOL, quality of life; RFA, radiofrequency ablation; SF-36, Short Form (36) Health Survey; s/p, status post; STAI, State and Trait Anxiety Inventory; sx, symptom; VT, ventricular tachycardia; w/, with; WHOQOL-BREF, World Health Organization Quality of Life Scale; and WPW, Wolff-Parkison-White syndrome.

Data Supplement 23. Nonrandomized Trials, Observational Studies, and/or Registries of Cost Effectiveness – Section 11

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Name, Author, Year** | **Study Type/**  **Design** | **Study Size** | **Inclusion/Exclusion Criteria** | **Primary Endpoint** | **Results/p Values** | **Summary/Conclusions** |
| De Buitlier M  1990  (384)  [2371949](http://www.ncbi.nlm.nih.gov/pubmed/?term=2371949) | Retrospective cohort study to evaluate CE of AP RFA c/w surgical ablation | 22 | Pts w/ APs who underwent RFA or surgical ablation  (n=11 RFA)  (n=11 surgical ablation) | Health care cost, w/ secondary endpoint LOS | RFA success: 73% (all w/ posteroseptal AP)  Surgical success: 100% (right, left lateral, posteroseptal AP)  RFA LOS 6±2 d  Surgical LOS 8±4 d  RFA cost: 14,116±4,493 c/w 34,175±5,434 in surgical group (p<0.0001).  Mean time lost from work or school was 10± 5 d in RFA group c/w 60±16 d in surgical group (p<0.01). | 1988 dollars  RFA of APs substantially lower in cost and LOS c/w surgical ablation. |
| De Buitlier M  1991  (385)  [1746469](http://www.ncbi.nlm.nih.gov/pubmed/?term=1746469) | Retrospective cohort study to evaluate CE of AP RFA c/w surgical ablation | 50 | Pts w/ APs who underwent RFA or surgical ablation  (n=25 RFA, 1990)  (n=25 surgical ablation, 1989) | Health care cost, w/ secondary endpoint LOS | Success rate was 96% for both groups.  Mean LOS was 3±1 d in RFA group and 9±4 d in surgical group (p<0.0001).  RFA total cost $14,919 c/w $53,265 in the surgical group (p<0.0001). | 1990/1991 dollars  RFA of APs substantially lower in cost and LOS c/w surgical ablation. |
| Kalbfleisch SJ  1992  (386)  [1593054](http://www.ncbi.nlm.nih.gov/pubmed/1593054) | Retrospective review to establish cost-advantage of RFA for AVNRT | 15 | Symptomatic AVNRT who underwent RFA | RFA cost of $15,893 would be advantageous after 10 y in pts who visit ED once per y (in study medical therapy more expensive after 2 y due to frequent ED visits in study population).  Perspective: pt  Outcomes: annual charges | N/A | 1991 dollars  Early report using hospital charges showing cost advantage of RFA for AVNRT  Medical therapy at the time more expensive given drugs may not have been at generic prices. |
| Hogenhuis W  1993  (387)  [8222191](http://www.ncbi.nlm.nih.gov/pubmed/?term=8222191) | CE of management in WPW | Markov model, none-specified, but costs estimated from convenience sample of 13 pts | N/A | Evaluation of 5 different strategies:  -observation  - observation until SCD  -therapy guided by noninvasive monitoring,  -initial RFA  -initial surgical ablation  Perspective: largely pt-perspective  Outcomes: QALY and mortality, using Markov Model | RFA yields life expectancy greater than or equal to other strategies  40 y-old pt:  Observation: $2360  RFA: $5,150-6,250  Surgery: $15,120  Observation w/ RFA at cardiac arrest: $16,860  Drug therapy: $20,250  In cardiac arrest survivors and pts who have had PSVT/AF w/ hemodynamic compromise, RFA should both prolong survival and save resources  For pts w/ PSVT/AF w/o hemodynamic compromise, the marginal cost-effectiveness of attempted RFA ranges from $6,600 per QALY gained for 20-y old pts to $19,000 per QALY gained for 60-y old pts.  For asymptomatic pts, RFA costs from $174,000 per QALY gained for 20-y old pts to $540,000 per QALY gained for 60-y old pts | Supports RFA in WPW syndrome who survive cardiac arrest or who experience PSVT/AF. but also supports the current practice of observing asymptomatic pts |
| Kalbfleisch SJ  1993  (388)  [8436736](http://www.ncbi.nlm.nih.gov/pubmed/?term=8436736) | Prospective cohort study to evaluate safety, feasibility, and cost of AP RFA as an outpt | 137 | Exclusion: <13 or >70 y, anteroseptal AP, obesity, or clinical indication for hospitalization | RFA of AP cost as outpt procedure | 97% success rate, w/ 73% performed as outpatients.  In 70 cases the pt was discharged the d of ablation, and in 30 cases the pt required a short (≤18 h) overnight stay due to scheduling issues.  Mean duration of observation was 4.8±1.5 h for outpts and 15±1.4 h for pts who underwent overnight hospitalization.  Mean cost of the procedure was $10,183±$1,082 in 30 pts studied for cost analysis.  22 outpts vs. 8 overnight pts :  Total charges: $9,873 vs. $11,034 (p<0.01)  Professional fees: $6,163 vs. $6,286 (p=NS)  Hospital charges: $3,710 vs. $4,748 (p<0.01)  2 pts w/ complications: femoral artery pseudoaneurysm notes 3-4 wk after procedure, one in outpt, one after 13 h overnight stay. | Outpt ablation of AP, w/ possible overnight observation, is feasible in low-risk pts |
| Kertes PJ  1993  (389)  [8240167](http://www.ncbi.nlm.nih.gov/pubmed/8240167) | CE of RFA compared to AADs in Australia | 26 | AVNRT (n=16)  WPW (n=10) | Mean cost of RFA $4067, c/w AAD of $700/ y  *NOTE: these are likely Australian dollars, although authors do not specify*  Extrapolating over 20 y and allowing for an annual 5% inflation factor, RFA becomes cost saving in 5.5 y  Over 20 y, AAD estimated at 4-5 times more expensive than RF  Perspective: pt and societal perspective  Outcomes: cost analysis w/ “cost-saving” criterion used to define effectiveness, on the assumption that RFA is at least as effective as AADs in long-term control of PSVT; authors used annual charges | N/A | RFA more cost-effective than AADs.  Limited to Australian population, but results consistent w/ other series.  Used pt data in constructing cost-analysis, not simulation. |
| Ikeda T  1994  (390)  [7823285](http://www.ncbi.nlm.nih.gov/pubmed/7823285) | Prospective cohort, CE evaluation of CE of RFA for PSVT | 20 | Symptomatic PSVT, on AADs, all w/ successful RFA  AVNRT (n=5)  WPW (n=15) | Mean total charge for ablation 982,806 yen and 5.7 times the outpt charges in the previous y  Mean total life-expectancy charges w/ AADs were estimated at 7,064,726 yen, 41.0 times the outpt charges  Total RFA charge 14% of total estimated charges of estimated lifetime medical treatment w/o RFA (p<0.001)  Perspective: pt-perspective, societal component  Outcomes: total life-expectancy charges, total ablation charges | N/A | Small study, limited to Japan, but suggests RFA effective and reduces medical costs.  Utilizes hospital charges, and not a cost-simulation model. |
| \*Bathina MN  1998  (378)  [9732885](http://www.ncbi.nlm.nih.gov/pubmed/9732885) | Prospective comparison of the impact of QOL and CE between RFA and pharmacologic therapy for PSVT | 79 w/ newly-documented PSVT  Average number of drugs 1.35/pt  (CCB, BB, most common) | Exclusions: drug-refractory pts, prior treatment, AF, atrial flutter, preexcitation | SF-36 and direct costs  Perspective: pt-perspective  Outcomes: direct hospital charges | RFA vs. medication  Potential long-term costs similar, but w/ specific assumptions about ED visits, pharmacologic costs will exceed RFA | First study to prospectively evaluate QOL and resource utilization between RFA vs. medical therapy.  Cumulative cost of medical therapy equal to, or less than RFA. This is in contrast to studies by Cheng and Ikeda, which have stronger methodology. |
| Cheng CH 2000  (60)  [11103056](http://www.ncbi.nlm.nih.gov/pubmed/11103056) | Comparison of CE of RFA w/ medical management of PSVT | Symptomatic pts w/ 4.6 unscheduled visits/y for arrhythmia while on long-term drug therapy | RFA:  Estimated population:  AVNRT: 65%  AVRT w/ concealed AP: 30%  Efficacy estimates:  AVNRT: 97%  AVRT w/ concealed AP: 93%  Recurrence estimates:  AVNRT: 5%  AVRT w/ concealed AP: 8%  Drug efficacy: 60% | Perspective: societal  Outcomes: Costs (office visit, annual drug rx, EP study, RFA, PPM, PPM replacement)  QALY  Life-ys  Marginal CE ratios | W/ monthly episodes of PSVT, RFA most effective and least expensive option  RFA reduced lifetime medical expenditures by $27,940 compared w/ long-term pharmacologic therapy  Lifetime costs:  RFA:  $61,880  Long-term drug rx:  $89,820  Episodic drug rx:  $143,530  RFA improved quality-adjusted life expectancy by 3.10 QALYs. | RFA improves QOL and reduces costs when treating highly symptomatic pts.  Effects in less symptomatic not studies |
| Dewland TA  2013  (391)  [24983868](http://www.ncbi.nlm.nih.gov/pubmed/24983868) | Observational cohort | Pts w/ atrial flutter in the California HCUP database, 2005-2009 (n=33,004), median f/u 2/1 y | Exclusion: Non-California residence, concomitant AF, missing admission date data | Whether catheter ablation of atrial flutter associated w/ reductions in healthcare utilization, AF, or CVA | 2,733 (8.2%) underwent catheter ablation. Atrial flutter ablation (in 8.2% of pts) lowered adjusted risk of inpt hospitalization and ED visits (p<0.001); overall hospital-based healthcare utilization (p = 0.001); and 11% reduction in AF( p = 0.01). Risk of CVA not reduced after ablation (p = 0.57). | Robust registry data supports early atrial flutter ablation to significantly reduce hospital-based healthcare utilization and risk of AF. |

\*Study addressed both CE and QoL

AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AP, accessory pathway; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular tachycardia; BB, beta blocker; CCB, calcium channel blocker; CE, cost effectiveness; CVA, cerebrovascular accident; c/w, consistent with; ED, emergency department; EP, electrophysiological; HCUP, Healthcare Cost and Utilization Project; LOS, length of stay; N/A, not applicable; NS, non-significant; PPM, permanent pacemaker; PSVT, paroxysmal supraventricular tachycardia; pt, patient; QALY, quality-adjusted life year; QOL, quality of life; RF, radiofrequency; RFA, radiofrequency ablation; rx, therapy; SCD, sudden cardiac death; SF-36, Short Form (36) Heatlh Survey; w/, with; and w/o, without.

# Appendix 1. Acute Drug Therapy for SVT, Intravenous Administration\*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug†** | **Initial Dose** | **Subsequent or Maintenance Dose** | **Potential Adverse Effects** | **Precautions (Exclude or Use With Caution) and Interactions** | |
| **Nucleoside** | | | | | |
| Adenosine | 6-mg rapid IV bolus (injected into IV as proximal or as close to the heart as possible), administered over 1–2 s, followed by rapid saline flush | If no result within 1–2 min, 12-mg rapid IV bolus; can repeat 12-mg dose 1 time. The safe use of 18-mg bolus doses has been reported (392). | Transient AV block, flushing, chest pain, hypotension, or dyspnea, AF can be initiated or cause decompensation in the presence of pre-excitation, PVCs / ventricular tachycardia, bronchospasm (rare), or coronary steal. Minor side effects are usually transient because of adenosine’s very short half-life. | | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Reactive airway disease * Concomitant use of verapamil or digoxin * WPW |
| **Beta blockers** | | | | | |
| Esmolol | 500-mcg/kg IV bolus over 1 min | Infusion at 50–300 mcg/kg/min, with repeat boluses between each dosing increase | Hypotension, worsening HF, bronchospasm, bradycardia | | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Decompensated systolic HF * Hypotension * Cardiogenic shock * Reactive airway disease * Renal dysfunction * Drugs with SA and/or AV nodal–blocking properties |
| Metoprolol tartrate | 2.5–5.0-mg IV bolus over 2 min | Can repeat 2.5- to 5.0-mg IV bolus in 10 min, up to 3 doses | Hypotension, worsening HF, bronchospasm, bradycardia | | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Decompensated systolic HF * Hypotension * Reactive airway disease * Drugs with SA and/or AV nodal–blocking properties |
| Propranolol | 1 mg IV over 1 min | Can repeat 1 mg IV at 2-min intervals, up to 3 doses | Hypotension, worsening HF, bronchospasm, bradycardia | | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Cardiogenic shock * Reactive airway disease * Decompensated HF * Hypotension * Hepatic or renal dysfunction * Drugs with SA and/or AV nodal–blocking properties |
| **Nondihydropyridine calcium channel antagonists** | | | | | |
| Diltiazem | 0.25-mg/kg IV bolus over 2 min | Infusion at 5–10 mg/h, up to 15 mg/h | Hypotension, worsening HF in patients with pre-existing ventricular dysfunction, bradycardia, abnormal liver function studies, acute hepatic injury (rare) | | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * WPW with AF / atrial flutter * Hypotension**‡** * Decompensated systolic HF/LV dysfunction * Drugs with SA and/or AV nodal–blocking properties * Hepatic or renal dysfunction * Diltiazem is a substrate of CYP3A4 (major) and a moderate CYP3A4 inhibitor * Apixaban, itraconazole, bosutinib, ceritinib, cilostazol, cyclosporine, everolimus, ibrutinib, idelalisib, ivabradine, lomitapide, olaparib, posaconazole, ranolazine, rifampin, simeprevir, voriconazole |
| Verapamil | 5–10-mg (0.075–0.15-mg/kg) IV bolus over 2 min | If no response, can give an additional 10 mg (0.15 mg/kg) 30 min after first dose; then infusion at 0.005 mg/kg/min | Hypotension, worsening HF in patients with pre-existing ventricular dysfunction, pulmonary edema in patients with hypertrophic cardiomyopathy, bradycardia | | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Decompensated systolic HF/ LV dysfunction * Drugs with SA and/or AV nodal–blocking properties * Hypotension‡ * Cardiogenic shock * WPW with AF / atrial flutter * Hepatic or renal dysfunction * Verapamil is a moderate CYP3A4 inhibitor and also inhibits P-glycoprotein * Contraindicated with dofetilide * Itraconazole, bosutinib, ceritinib, cilostazol, colchicine, cyclosporine, everolimus, dabigatran, edoxaban, flecainide, ibrutinib, ivabradine, olaparib, posaconazole, ranolazine, rivaroxaban, rifampin, silodosin, simeprevir, rivaroxaban, rifampin, simvastatin, topotecan, trabectedin, vincristine, voriconazole, grapefruit juice |
| **Cardiac glycosides** | | | | | |
| Digoxin | 0.25–0.5-mg IV bolus | Can repeat 0.25-mg IV bolus, up to maximum dose of 1.0 mg over 24 h (i.e., maximum loading dose 8–12 mcg/kg), given at 6–8-h intervals; maintenance dose based on patient’s age, lean body weight, renal function, and concomitant drugs (IV 2.4–3.6 mcg/kg/d) | Anorexia, nausea, vomiting, visual changes and cardiac arrhythmias if digoxin toxicity (associated with levels >2 ng/mL, although symptoms may also occur at lower levels) | | * Renal dysfunction * WPW with AF / atrial flutter * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Drugs with AV nodal-blocking properties * Digoxin is a P-glycoprotein substrate * Dronedarone (reduce dose by at least 50%), amiodarone (reduce dose by 30%–50%) * Verapamil, clarithromycin, cyclosporine, erythromycin, flecainide, itraconazole, posaconazole, propafenone, voriconazole: Monitor digoxin levels * A large retrospective study suggested an increased risk in mortality in patients who were treated with digoxin for newly diagnosed AF or atrial flutter; although the data were collected from a population that was different from SVT patients, digoxin should be used with caution (393). |
| **Class III antiarrhythmic agents** | | | | | |
| Amiodarone | 150 mg IV over 10 min | Infusion at 1 mg/min (360 mg) over next 6 h; then 0.5 mg/min (540 mg) over remaining 18 h | Hypotension, bradycardia, phlebitis, QT prolongation, torsades de pointes (rare), increased INR | | * Sinus or AV conduction disease (in absence of pacemaker) * Inflammatory lung disease (acute) * Hepatic dysfunction * Drugs with SA and/or AV nodal–blocking properties * Amiodarone is a substrate of and inhibits p-glycoprotein and CYP2C9 (moderate), CYP2D6 (moderate), and CYP3A4 (weak); amiodarone is a substrate for CYP3A4 (major) and CYP2C8 (major);amiodarone is an inhibitor of OCT2 * Reduce warfarin dose by 50% and reduce digoxin dose by 30%–50% * Agalsidase alfa, agalsidase beta, azithromycin, bosutinib, ceritinib, colchicine, dabigatran, edoxaban, flecainide, ivabradine, ledipasvir/sofosbuvir, lopinavir, lopinavir/ritonavir, lovastatin, nelfinavir, pazopanib, propafenone, simvastatin, ritonavir, rivaroxaban, saquinavir, sofosbuvir, topotecan, vincristine, grapefruit juice |
| Ibutilide | Contraindicated when QTc >440 ms**║**; 1 mg over 10 min (if ≥60 kg); if <60 kg, then 0.01 mg/kg | Can repeat 1 mg once, if the arrhythmia does not terminate within 10 min§ | QT prolongation, torsades de pointes, AV block | | * Prolonged QT interval * History of torsades de pointes * Avoid other QT interval–prolonging drugs * Concurrent administration of high-dose magnesium has been associated with enhanced efficacy and safety (206, 394) |

Note: For this reference table, drugs are presented in alphabetical order within the drug classes, not by COR and LOE.

\*When 1 drug is used in combination with other drugs, appropriate dosing adjustments should be made with consideration of at least additive effects during dosage titration. All potential drug–drug interactions are not included in this list. For a more detailed list of drug–drug interactions, clinicians should consult additional resources.

‡If hypotension is a consideration, a slow infusion of diltiazem (2.5 mg/min) or verapamil (1 mg/min) for up to 20 minutes may lessen the potential for hypotension (38).

§The infusion should be stopped as soon as the arrhythmia is terminated or in the event of sustained or nonsustained ventricular tachycardia or marked prolongation of QT or corrected QT interval.

**║**QTc calculation used the Bazett’s Formula in most clinical studies. Patients should be observed with continuous ECG monitoring for at least 4 h after infusion or until QTc has returned to baseline.

AF indicates atrial fibrillation; AV, atrioventricular; BID, twice daily; CrCl, creatinine clearance; ECG, electrocardiogram/electrocardiographic; HF, heart failure; INR, international normalized ratio; LV, left ventricular; QD, once daily; QID, four times a day; QTc, corrected QT interval; SA, sinoatrial; SVT, supraventricular tachycardia; TID, 3-times a day; and WPW, Wolff-Parkinson-White.

# Appendix 2. Ongoing Drug Therapy for SVT, Oral Administration\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug†** | **Initial Daily Dose(s)** | **Maximum Total Daily Maintenance Dose** | **Potential Adverse Effects** | **Precautions (Exclude or Use With Caution) and Interactions** |
| **Beta blockers** | | | | |
| Atenolol | 25–50 mg QD | 100 mg QD  (reduced dosing in patients with severe renal dysfunction) | Hypotension, bronchospasm, bradycardia | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Decompensated systolic HF * Hypotension * Reactive airway disease * Severe renal dysfunction * Drugs with SA and/or AV nodal–blocking properties |
| Metoprolol tartrate | 25 mg BID | 200 mg BID | Hypotension, bronchospasm, bradycardia | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Decompensated systolic HF * Hypotension * Reactive airway disease * Drugs with SA and/or AV nodal–blocking properties |
| Metoprolol succinate (long-acting) | 50 mg QD | 400 mg QD | Hypotension, bronchospasm, bradycardia | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Decompensated systolic HF * Hypotension * Reactive airway disease * Drugs with SA and/or AV nodal–blocking properties |
| Nadolol | 40 mg QD | 320 mg QD  (reduced dosage with renal impairment) | Hypotension, bronchospasm, bradycardia | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Reactive airway disease * Cardiogenic shock * Decompensated HF * Hypotension * Renal dysfunction * Drugs with SA and/or AV nodal–blocking properties |
| Propranolol | 30–60 mg in divided or single dose with long-acting formulations | 40–160 mg in divided or single dose with long-acting formulations | Hypotension, worsening HF, bronchospasm, bradycardia | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Reactive airway disease * Decompensated systolic HF * Hypotension * Drugs with SA and/or AV nodal–blocking properties |
| **Nondihydropyridine calcium channel antagonists** | | | | |
| Diltiazem | 120 mg daily in divided or single dose with long-acting formulations | 360 mg daily in divided or single dose with long-acting formulations | Hypotension, worsening HF in patients with pre-existing ventricular dysfunction, bradycardia, abnormal liver function studies, acute hepatic injury (rare) | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Hypotension‡ * Decompensated systolic HF / severe LV dysfunction * WPW with AF / atrial flutter * Drugs with SA and/or AV nodal–blocking properties * Diltiazem is a substrate of CYP3A4 (major) and a moderate CYP3A4 inhibitor * Apixaban, itraconazole, bosutinib, ceritinib, cilostazol, cyclosporine, everolimus, ibrutinib, idelalisib, ivabradine, lomitapide, olaparib, ranolazine, rifampin, simeprevir |
| Verapamil | 120 mg daily in divided or single dose with long-acting formulations | 480 mg daily in divided or single dose with long-acting formulations | Hypotension, worsening HF in patients with pre-existing ventricular dysfunction, pulmonary edema in patients with hypertrophic cardiomyopathy, bradycardia, abnormal liver function studies | * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Decompensated systolic HF / severe LV dysfunction * Hypotension‡ * WPW with AF / atrial flutter * Verapamil is a moderate CYP3A4 inhibitor and also inhibits P-glycoprotein * Contraindicated with dofetilide * Itraconazole, bosutinib, ceritinib, cilostazol, colchicine, cyclosporine, everolimus, dabigatran, edoxaban, flecainide, ibrutinib, ivabradine, olaparib, ranolazine, rivaroxaban, rifampin, silodosin, simeprevir, rivaroxaban, rifampin, simvastatin, topotecan, trabectedin, vincristine, grapefruit juice |
| **Cardiac glycosides** | | | | |
| Digoxin | *Loading*: 0.5 mg, with additional 0.125–0.25-mg doses administered at 6–8-h intervals until evidence of adequate effect (maximum dose 8–12 mcg/kg over 24 h) | 0.25 mg QD  *Maintenance*: 0.125–0.25 mg QD, with dosing based on patient’s age, lean body weight, and renal function and drug interactions; occasionally down to 0.0625 mg in cases of renal impairment (trough serum digoxin level 0.5 to 1 ng/mL) | Bradycardia, heart block, anorexia, nausea, vomiting, visual changes and cardiac arrhythmias in cases of digoxin toxicity (associated with levels >2 ng/mL, although symptoms may also occur at lower levels) | * Renal dysfunction * WPW with AF / atrial flutter * AV block greater than first degree or SA node dysfunction (in absence of pacemaker) * Drugs with SA and/or AV nodal–blocking properties * Reduce dose by 30%–50% when administering with amiodarone and by 50% when administering with dronedarone * Monitor digoxin concentrations with verapamil, clarithromycin, erythromycin, itraconazole, cyclosporine, propafenone, flecainide |
| **Class Ic antiarrhythmic agents** | | | | |
| Flecainide | 50 mg every 12 h | 150 mg every 12 h  (PR and QRS intervals should be monitored. May consider monitoring flecainide plasma levels, keeping trough plasma levels below 0.7–1.0 mcg/mL) | Atrial flutter with 1:1 AV conduction§, QT prolongation, torsades de pointes, worsening HF, bradycardia | * Sinus or AV conduction disease (in absence of pacemaker) * Cardiogenic shock * Avoid in structural heart disease (including ischemic heart disease) * Atrial flutter (unless concomitant AV nodal therapy to avoid 1:1 conduction) * Brugada syndrome * Renal dysfunction * Hepatic dysfunction * QT-prolonging drugs * Amiodarone, digoxin, ritonavir, saquinavir, tipranavir |
| Propafenone | 150 mg every 8 h (immediate release);  225 mg every 12 h (extended release) | 300 mg every 8 h (immediate release);  425 mg every 12 h (extended release)  (PR and QRS interval should be monitored. Consider dosage reduction with hepatic impairment) | Atrial flutter with 1:1 AV conduction§, QT prolongation, torsades de pointes, bradycardia, bronchospasm | * Sinus or AV conduction disease (in absence of pacemaker) * Cardiogenic shock * Hypotension * Reactive airway diseaseAvoid in structural heart disease (including ischemic heart disease) * Atrial flutter (unless concomitant AV nodal therapy to avoid 1:1 conduction) * Brugada syndrome * Hepatic dysfunction * QT-prolonging drugs * Drugs with SA and/or AV nodal–blocking properties * Amiodarone, ritonavir, saquinavir, tipranavir |
| **Class III antiarrhythmic agents** | | | | |
| Amiodarone | 400–600 mg QD in divided doses for 2-4 wk (loading dose); followed by 100–200 mg QD (maintenance dose) | Up to 1200 mg QD may be considered in an inpatient monitoring setting (loading dose); up to 200 mg QD maintenance (to minimize long-term adverse effects) | Bradycardia, QT prolongation, torsades de pointes (rare), gastrointestinal upset, constipation, hypothyroidism, hyperthyroidism, pulmonary fibrosis, hepatic toxicity, corneal deposits, optic neuritis, peripheral neuropathy, photosensitivity, adult respiratory distress syndrome after cardiac or noncardiac surgery (rare) | * Sinus or AV conduction disease (in absence of pacemaker) * Inflammatory lung disease * Hepatic dysfunction * Hypothyroidism, hyperthyroidism * Peripheral neuropathy * Abnormal gait / ataxia * Optic neuritis * Drugs with SA and/or AV nodal–blocking properties * Amiodarone is a substrate of and inhibits p-glycoprotein and CYP2C9 (moderate), CYP2D6 (moderate), and CYP3A4 (weak); amiodarone is a substrate for CYP3A4 (major) and CYP2C8 (major); amiodarone is an inhibitor of OCT2 * Reduce warfarin dose by 50%, and reduce digoxin dose by 30%–50% * Agalsidase alfa, agalsidase beta, azithromycin, bosutinib, ceritinib, colchicine, dabigatran, edoxaban, flecainide, ivabradine, ledipasvir/sofosbuvir, lopinavir, lopinavir/ritonavir, lovastatin, nelfinavir, pazopanib, propafenone, simvastatin, ritonavir, rivaroxaban, saquinavir, sofosbuvir, topotecan, vincristine, grapefruit juice |
| Dofetilide | * 500 mcg every 12 h (if CrCl >60 mL/min) * 250 mcg every 12 h (if CrCl 40–60 mL/min) * 125 mcg every 12 h (if CrCl 20 to <40 mL/min) * Not recommended if CrCl <20 mL/min * Adjust dose for renal function, body size, and age * Initiate for minimum of 3 d in a facility that can provide continuous ECGmonitoring and cardiac resuscitation * Contraindicated if the baseline QTc interval or QTc >440 ms║ or 500 ms in patients with ventricular conduction abnormalities | Repeat ECG 2–3 h after administering the first dose to determine QTc; if the QTc increased by >15% compared with baseline or if QTc is >500 ms**║** (550 ms in patients with ventricular conduction abnormalities), subsequent dosing should be downtitrated by 50%; at 2–3 h after each subsequent dose, determine QTc (for in-hospital doses 2–5); if at any time after the second dose the QTc is >500 ms**║** (550 ms in patients with ventricular conduction abnormalities), dofetilide should be discontinued | QT prolongation, torsades de pointes | * Severe renal dysfunction (contraindicated if CrCl <20 mL/min) * Prolonged QT * History of torsades de pointes * Concomitant use of hydrochlorothiazide, cimetidine, dolutegravir, itraconazole, ketoconazole, megestrol, trimethoprim, prochlorperazine trimethoprim/sulfamethoxazole or verapamil, contraindicated * Avoid other QT-prolonging drugs |
| Sotalol | 40–80 mg every 12 h  (Patients initiated or reinitiated on sotalol should be placed in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring for a minimum of 3 d.  Contraindicated if the QTc║ interval is >450 ms.  CrCl should be calculated before dosing. If CrCl >60 mL/min, then dosing frequency is twice daily. If CrCl 40-60 mL/min, dosing interval is every 24 h. If CrCl <40 mL/min, should not be used.) | 160 mg every 12 h  (During initiation and titration, the QT interval should be monitored 2–4 h after each dose. If the QT interval prolongs to ≥500 ms, the dose must be reduced or the drug discontinued.) | QT prolongation, torsades de pointes, bradycardia, bronchospasm | * Prolonged QT * Renal dysfunction * Hypokalemia * Diuretic therapy * Avoid other QT-prolonging drugs * Sinus or AV nodal dysfunction (in absence of pacemaker) * Decompensated systolic HF * Cardiogenic shock * Reactive airway disease * Drugs with SA and/or AV–nodal blocking properties |
| **Miscellaneous** | | | | |
| Ivabradine | 5 mg BID | 7.5 mg BID | Phosphenes, AF | * Concomitant drugs that can exacerbate bradycardia * Contraindicated in decompensated HF * Contraindicated if BP <90/50 mm Hg * Contraindicated in severe hepatic impairment * Hypertension * Ivabradine is a substrate of CYP3A4 (major) * Avoid use with concomitant strong CYP3A4 inhibitors (boceprevir, clarithromycin, indinavir, itraconazole, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, telaprevir, posaconazole, voriconazole) * Avoid use with strong CYP3A4 inducers (carbamazepine, phenytoin, rifampin, St. John’s wort) * Avoid use with diltiazem, verapamil, grapefruit juice |

Note: For this reference table, drugs are presented in alphabetical order within the drug classes, not by COR and LOE.

\*When 1 drug is used in combination with other drugs, appropriate dosing adjustments should be made with consideration of at least additive effects during dosage titration. All potential drug–drug interactions and adverse reactions are not included in this list. For a more detailed list of drug interactions and adverse responses, clinicians should consult additional resources; for example, www.crediblemeds.org may be consulted for potential prolongation of the QT interval.

§Recommended given in conjunction with a beta blocker or nondihydropyridine calcium channel antagonist.

║QTc calculation used the Bazett’s Formula in most clinical studies.

AF indicates atrial fibrillation; AV, atrioventricular; BID, twice daily; BP, blood pressure; CrCl, creatinine clearance; ECG, electrocardiogram/electrocardiographic; HF, heart failure; INR, international normalized ratio; LV, left ventricular; QD, once daily; QID, 4 times a day; QTc, corrected QT interval; SA, sinoatrial; SVT, supraventricular tachycardia; TID, 3 times a day; and WPW, Wolff-Parkinson-White.

# Appendix 3. Success and Complication Rates for Ablation of SVT\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Arrhythmia** | **Acute Success** | **Recurrence Rate** | **Major Complications** | **References** |
| **Common SVTs** | | | | |
| AVNRT | 96%–97% (55, 59) | 5% (59) | * Overall 3% (55) * PPM 0.7% (55) * Death 0% (55) | (55, 59) |
| AVRT / accessory pathway | 93% (55, 59) | 8% (59) | * Overall 2.8% (55) * PPM 0.3% (55) * Death 0.1% (55) * Tamponade 0.4% (55) | (55, 59) |
| CTI-dependent atrial flutter | 97% (55) | 10.6% atrial flutter (395), 33% atrial fibrillation (395) | * Overall 0.5% (55) * PPM 0.2% (55) * Pericardial effusion 0.3% (55) | (55, 59, 395) |
| **Less common SVTs** | | | | |
| Focal AT | 80%–100% | 4%–27% | <1%–2% | (89, 93, 97, 99, 105, 106, 396, 397) |
| JT | 82%–85% | 0–18% | 0–18% CHB (overall complications N/A) | (233, 234, 269) |
| Non–CTI-dependent atrial flutter | 73%–100% | 7%–53% | 0–7% | (106, 211, 213, 215, 216, 218, 219, 221, 398) |

\*Data in this table are derived from multiple observational studies and registries, and as such may not always reflect current practice.

AT indicates atrial tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; CHB, complete heart block; CTI, cavotricuspid isthmus; JT, junctional tachycardia; N/A, not available; PPM, permanent pacemaker; and SVT, supraventricular tachycardia.

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