Potential New Therapeutic Option for the Treatment of SVT in Acute and Chronic Settings

News in SVT Diagnosis and Management

A. John Camm

16th April 2023

Conflicts of Interest

Consultant/Advisor/Speaker: Acesion, Allergan, InCarda, Menarini, Milestone, Sanofi, Anthos, Bayer, Daiichi Sankyo, Pfizer, Abbott, Biosense Webster, Biotronik, Boston Scientific, Medtronic, Johnson and Johnson

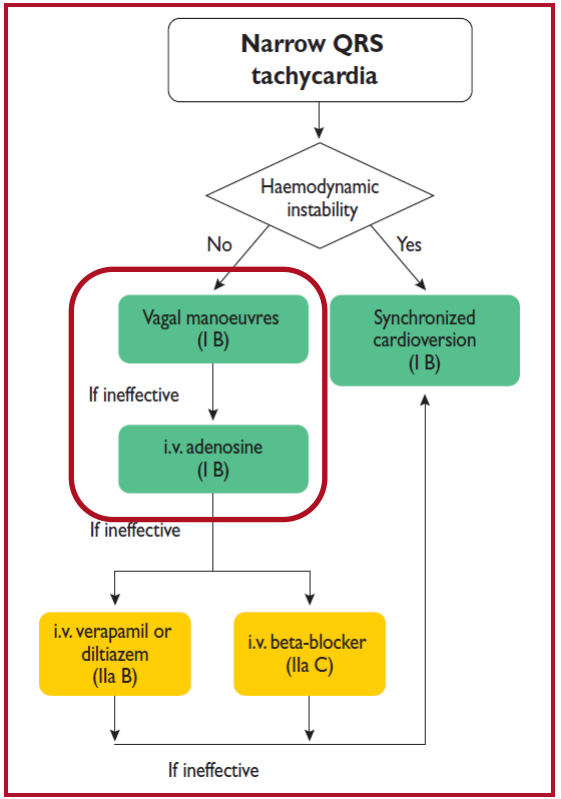
PSVT: Recommendations for Narrow Complex Tachycardia

Recommendation	Class[a]	Level[b]
Haemodynamically unstable patients		
Synchronized DC cardioversion is recommended for haemodynamically unstable patients.[86–88]	I	B
Haemodynamically stable patients		
A 12 lead ECG during tachycardia is recommended.	I	C
Vagal manoeuvres, preferably in the supine position with leg elevation, are recommended.[41,89–91]	I	B
Adenosine (6–18 mg i.v. bolus) is recommended if vagal manoeuvres fail.[92–94]	I	B
Verapamil or diltiazem (i.v.) should be considered, if vagal manoeuvres and adenosine fail.[92,94–98]	IIa	B
Beta-blockers (i.v. esmolol or metoprolol) should be considered if vagal manoeuvres and adenosine fail.[97,99,100]	IIa	C
Synchronized direct-current cardioversion is recommended when drug therapy fails to convert or control the tachycardia.[87,88]	I	B

ESC European Society of Cardiology

ESC Guidelines 25 YEARS

ESC GUIDELINES



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Brugada J, et al European Heart Journal 2019

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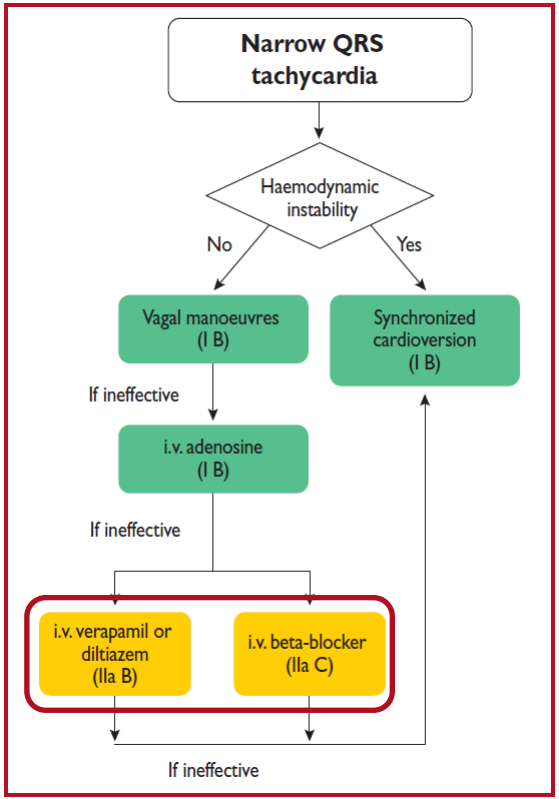

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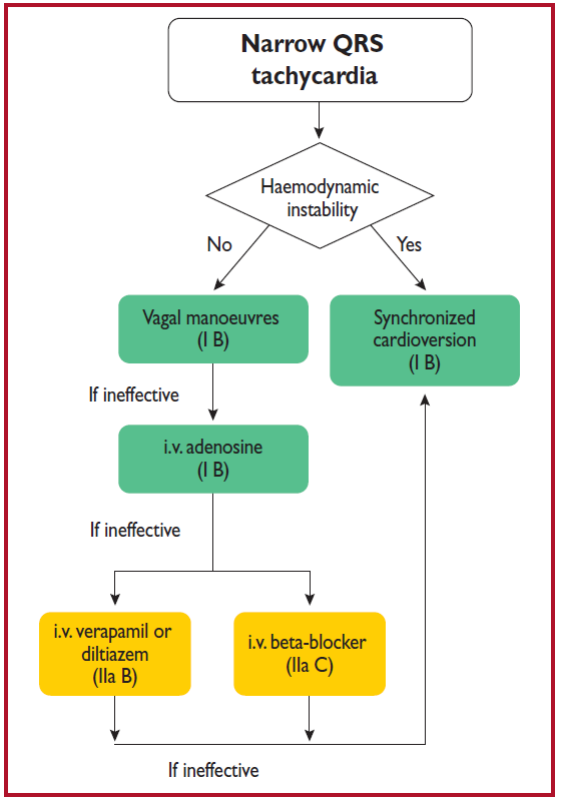
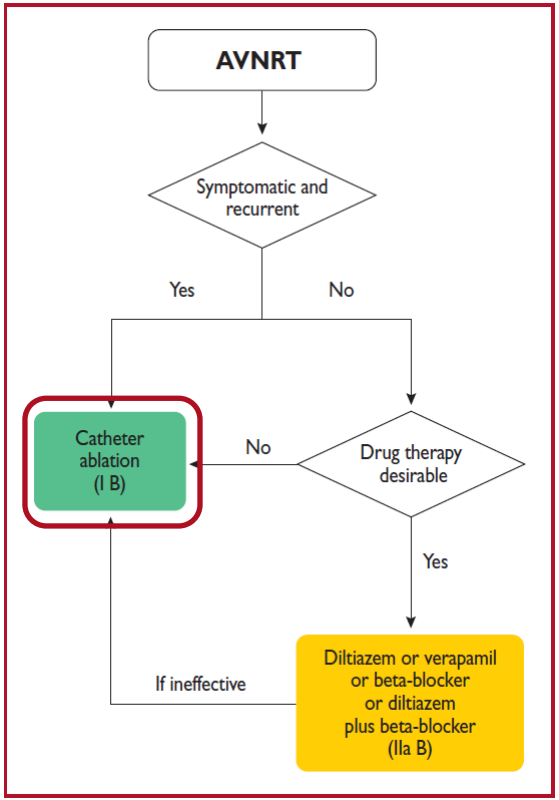


Brugada J, et al European Heart Journal 2019

PSVT Chronic Therapy



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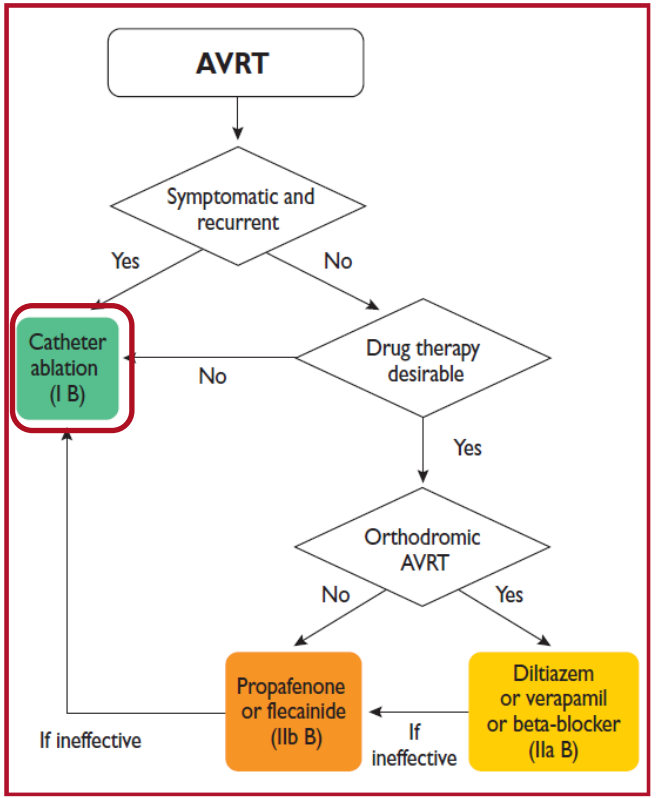

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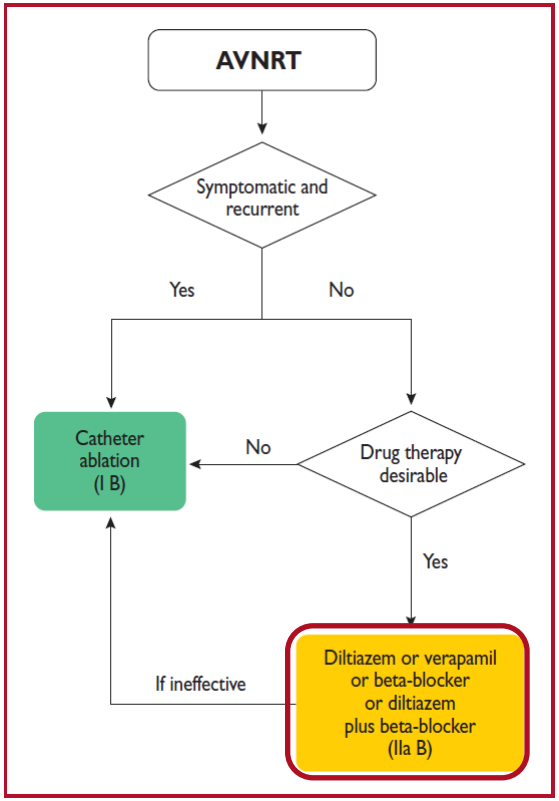

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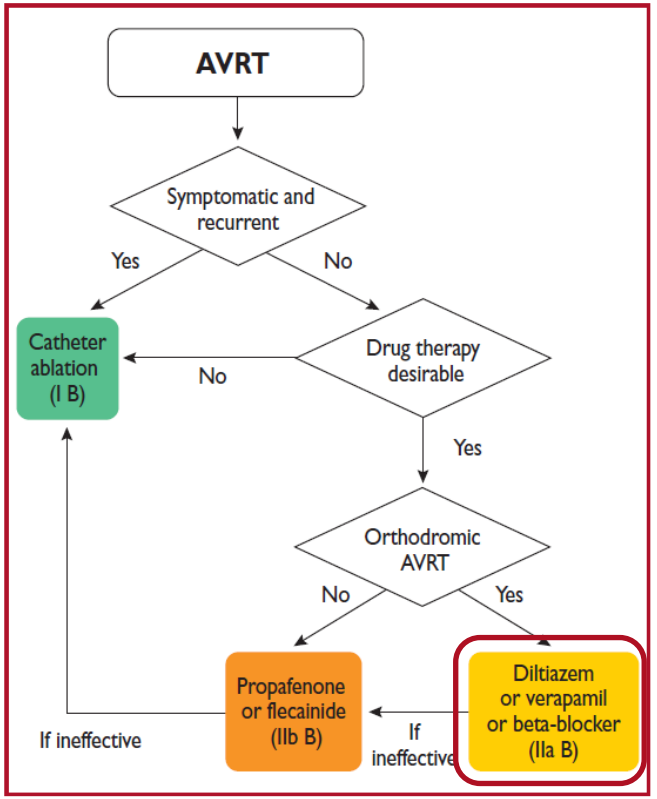


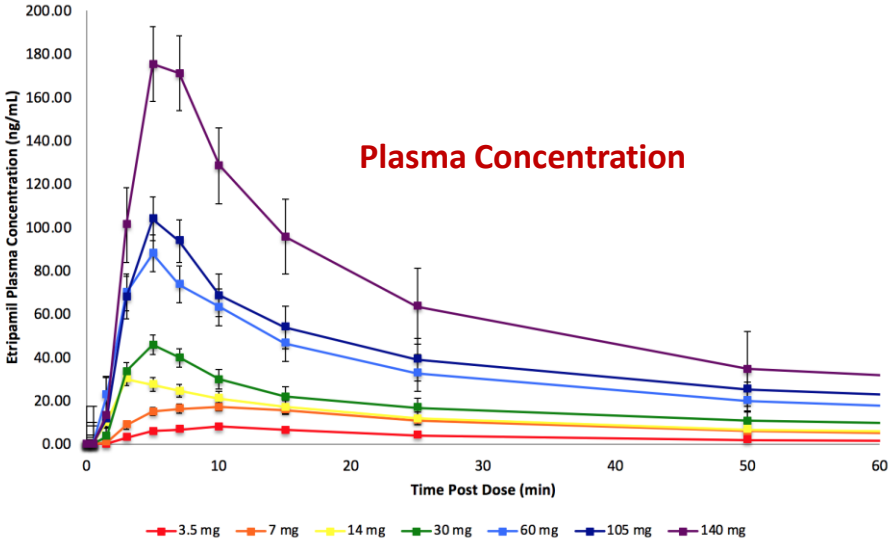
Brugada J, et al European Heart Journal 2019

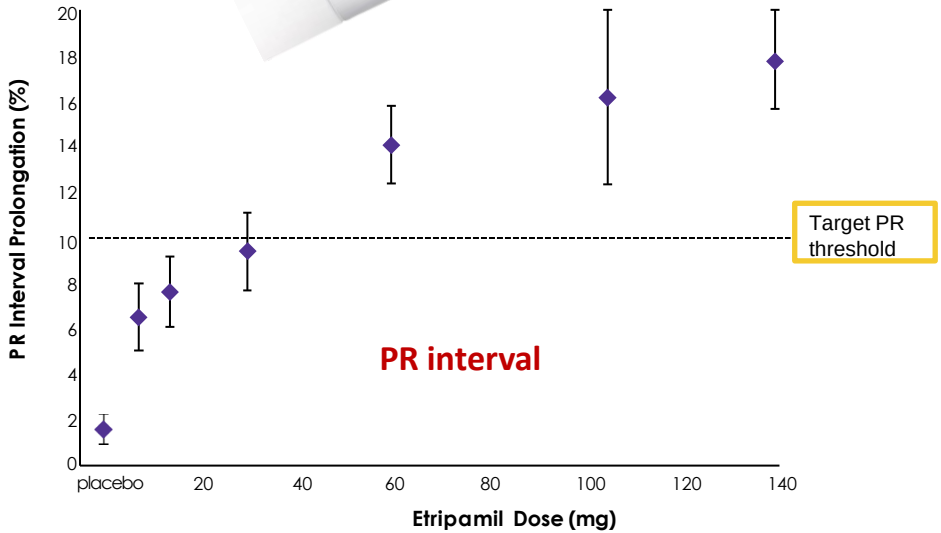
Etripamil: PK/PD

- Novel formulation of rapidly acting calcium channel antagonist
- Rapidly metabolized by blood esterases

- Known target: L-type calcium channels
- Mechanism of action on cardiac tissue very well understood

Administered by nasal insufflation



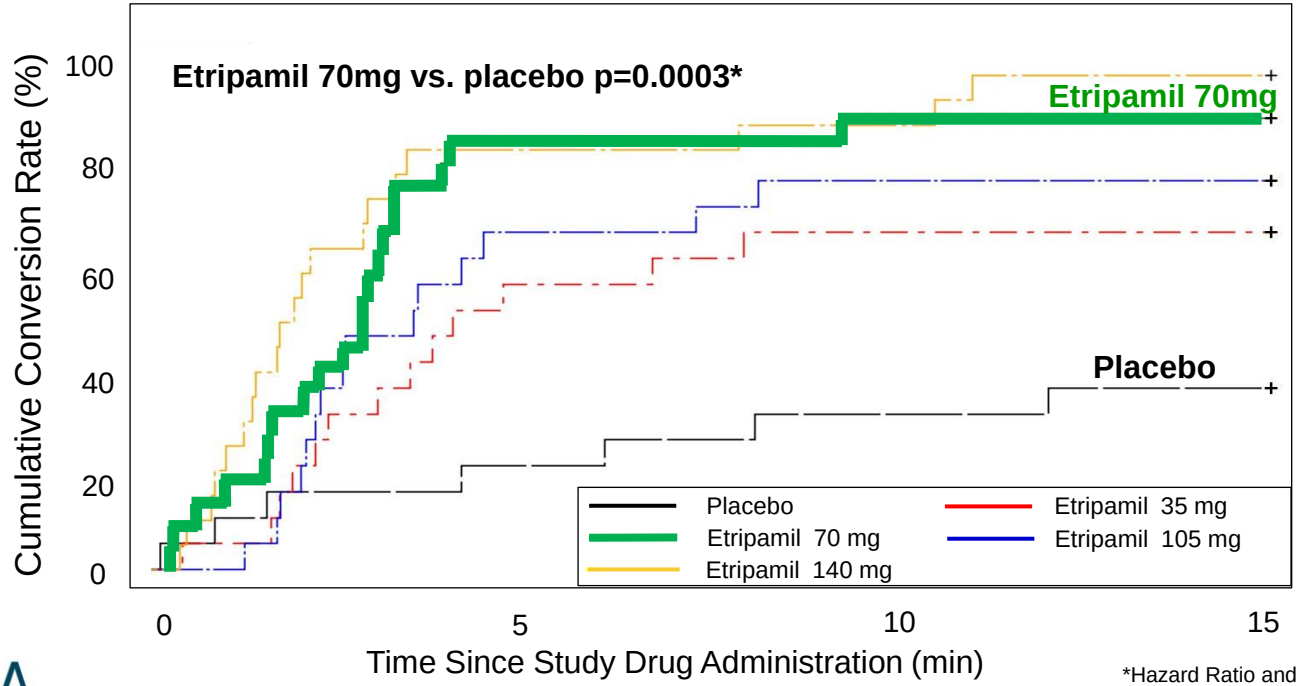


Error bars indicate standard error of the mean

Data on file Milestone Pharmaceuticals

Etripamil Phase 2 study: Electrophysiology Lab Setting Time to PSVT Conversion 15 min post-Dose – (NODE-1)

70mg etripamil dose showed rapid time to conversion (median < 3 min)

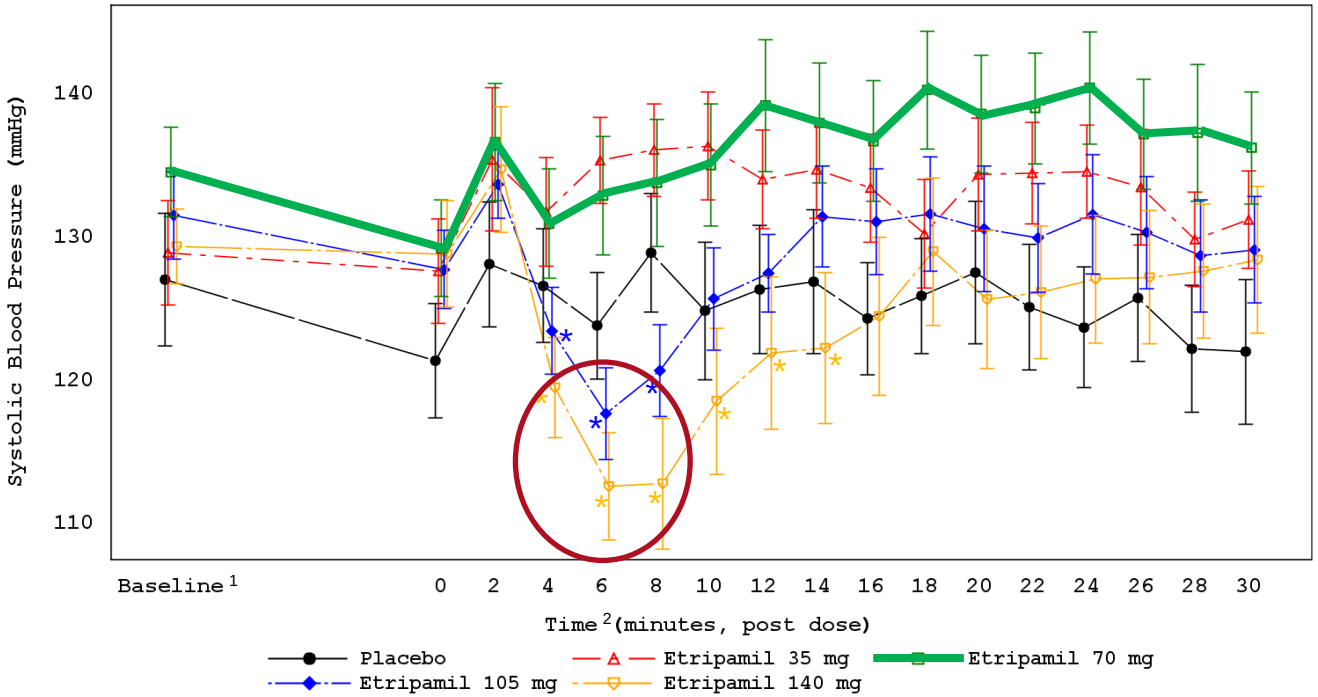


20-23 pts per group

*Hazard Ratio and 95% Confidence Intervals etripamil 70mg vs. placebo; 4.99 (2.09, 11.93)

Stambler, B.S. et al. J Am Coll Cardiol. 2018;72(5):489–97

Node-1: Mean Systolic Blood Pressure Effects



Etripamil 70 mg showed no drop in blood pressure

[1] Baseline is defined as the average of the 20-min and 10-min pre-dose measurements. [2] Time 0 is defined as the average of the measurements during supraventricular tachycardia between 5 and 0 min before study drug administration. *p < 0.05 versus baseline.

Stambler, BS. et al. J Am Coll Cardiol. 2018;72(5):489–97

Pivotal Phase 3 Study Design

NODE-301
Etripamil Clinical Research in PSVT

Objective: Superiority of single-dose etripamil over placebo in terminating SVT events in the outpatient setting

Randomized
Etr : Pbo (2:1)
(N=419, 97%)

Patient dosed for suspected episode
Safety Dataset
(N=198, Etr=138, Pbo=60)

Test Dose
Active drug while in SR
(N=431)

Adjudicated PSVT events
Efficacy Dataset
(N=156, 79%)
Etr=107, Pbo=49)

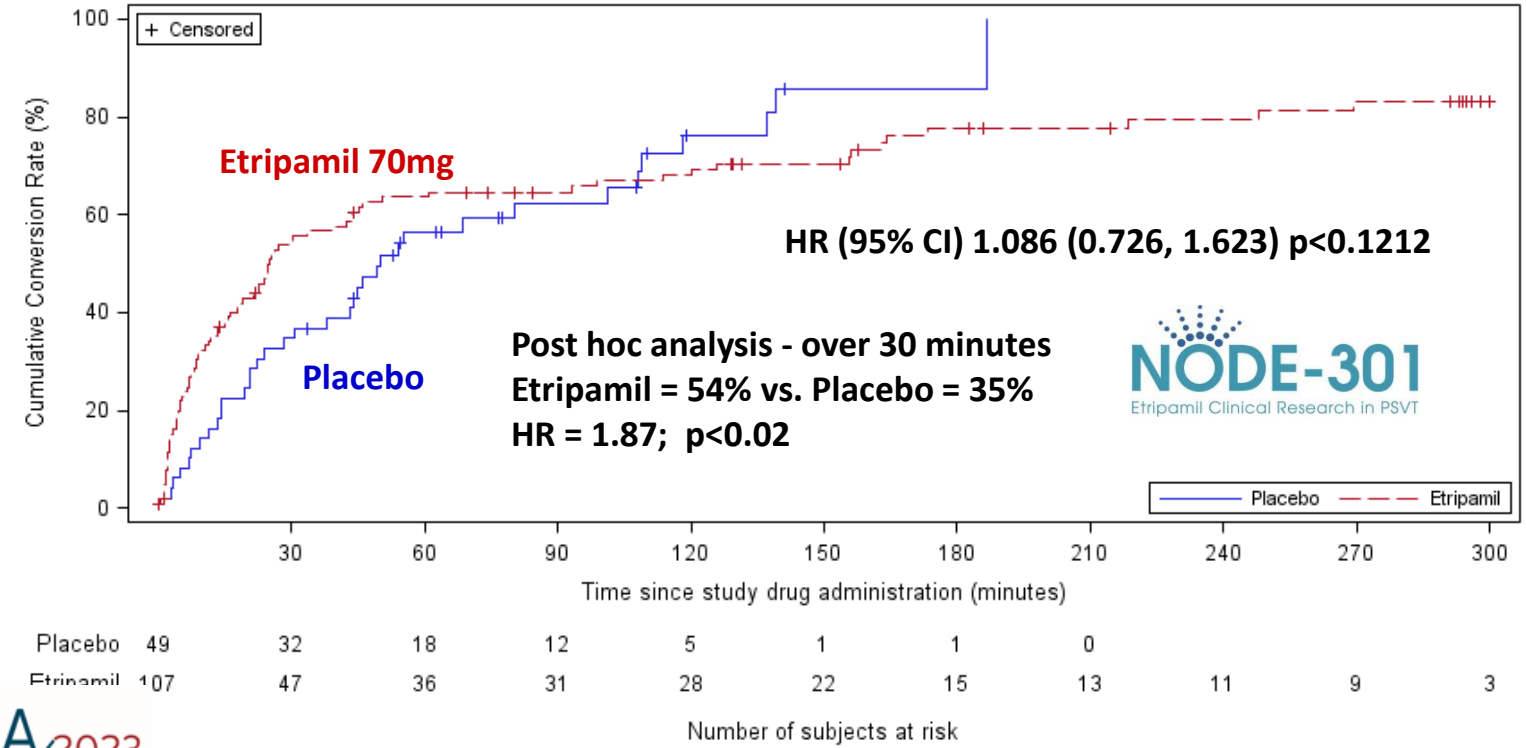
Documented diagnosis of PSVT
History of longer episodes

PSVT = Paroxysmal Supraventricular Tachycardia; SR = Sinus Rhythm; Etr = etripamil; Pbo = placebo

Stambler BS, et al. Circ Arrhythm Electrophysiol. 2022 Dec;15(12):e010915

NODE-301 Kaplan-Meier Plot of Conversion up to 5 Hours

Pre-specified Primary Endpoint



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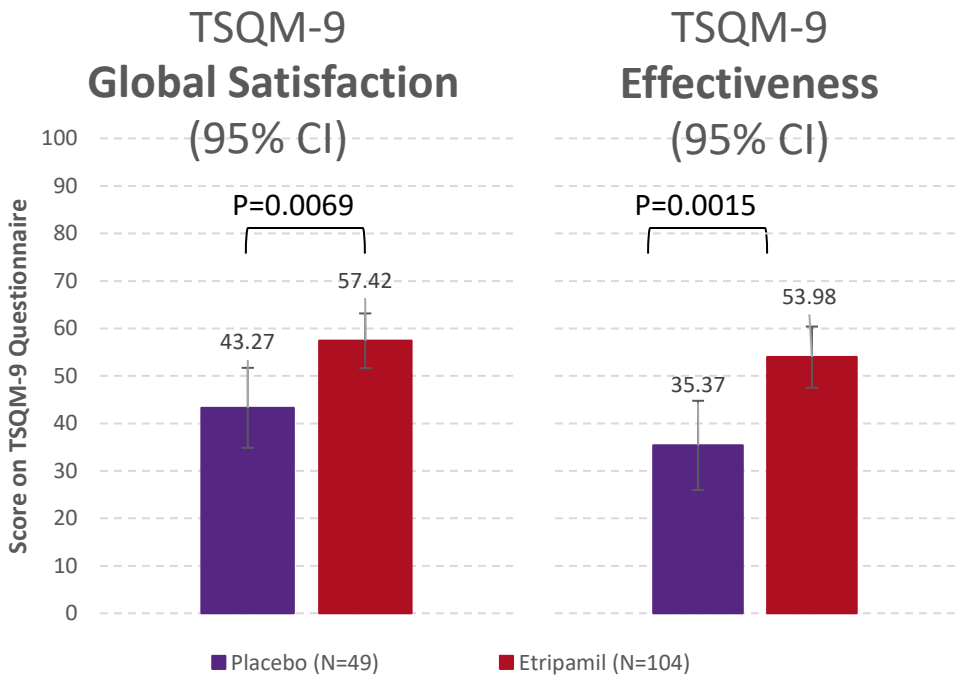
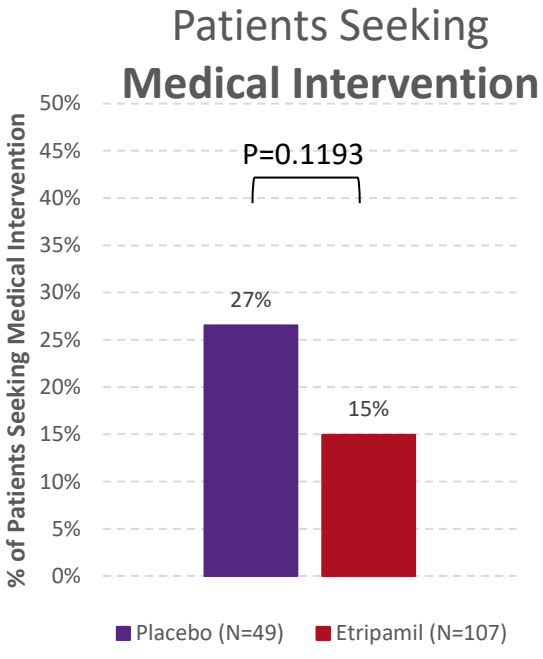
Stambler BS, et al. Circ Arrhythm Electrophysiol. 2022 Dec;15(12):e010915

NODE-301 Key Secondary Endpoints

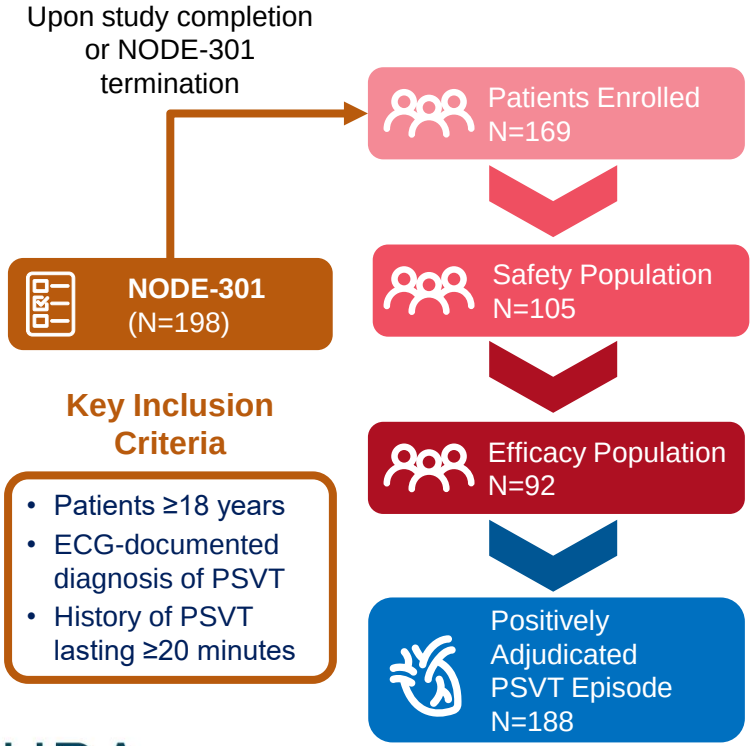
Key secondary endpoints from NODE-301 support potential benefit of etripamil to patients





Stambler BS, et al. Circ Arrhythm Electrophysiol. 2022 Dec;15(12):e010915

NODE-302 Study Design:
Single-arm, Open-label Extension Study From NODE-301



Study Procedures

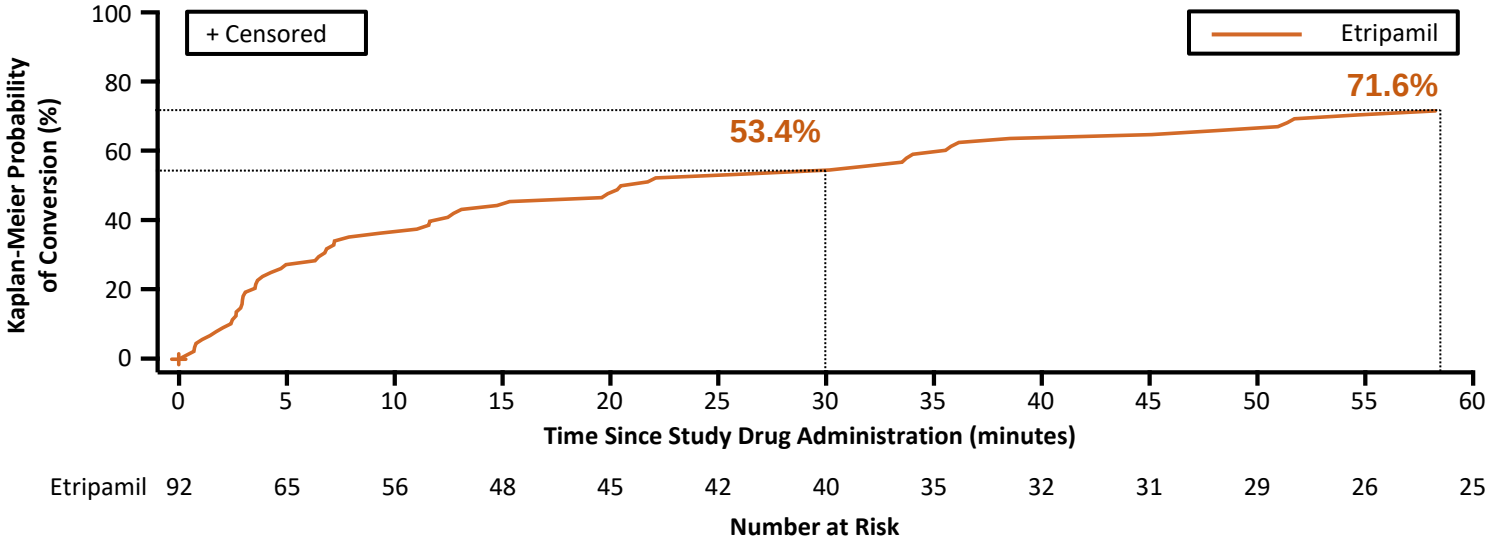
1. **Patient perceived PSVT episode**
2. **Patient applied CMS**
3. **Patient performed trained VM**
4. **If the episode persisted, the patient self-administered etripamil 70 mg IN (intra nasal)**
5. **CMS ECG monitoring continued for 5 hours**
6. **An independent adjudication committee used the complete CMS ECG recordings to confirm PSVT and conversion to sinus rhythm**

- Patients continued in the study for up to 11 treated episodes
- Median time in the study: 223 days[a] (range: 1−584)

[a]Includes patients with 0 episodes.
CMS, cardiac monitoring system; ECG, electrocardiogram; PSVT, paroxysmal supraventricular tachycardia; VM, vagal maneuver.

Ip J, et al. https://www.ahajournals.org/doi/10.1161/circ.144.suppl_1.11430

NODE 302: Conversion of Adjudicated PSVT to Sinus Rhythm – 1st Episode



- Data are from 1st confirmed PSVT episode (**n=92**)[a]
- Median time from NODE-302 enrollment to 1st treated episode**: 46.5 days** (3–518)[b]
- Median time to conversion: **21.1 minutes** (95% CI, 11.6–35.5)

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Ip J, et al. https://www.ahajournals.org/doi/10.1161/circ.144.suppl_1.11430

Consistency of Conversion at 30 Minutes Between the 1st and 2nd Adjudicated PSVT Episodes

	No Conversion on 1st Episode	Conversion on 1st Episode
No conversion on 2nd episode	9	5
Conversion on 2nd episode	5	21

75% of patients (30/40) had a consistent response between the 1st and 2nd episode (Chi-square=8.09; *P*=0.0045)

- **21/26 patients (81%) who converted on their 1st episode also successfully converted during their 2nd episode**

PSVT, paroxysmal supraventricular tachycardia.

Ip J, et al. https://www.ahajournals.org/doi/10.1161/circ.144.suppl_1.11430

Most Frequent Etripamil-related TEAEs

Etripamil-related TEAEs Occurring in >1%,[a] n (%)	Safety Population (N=105)
Patients with any TEAE	34 (32.4)
TEAEs by preferred term	
Nasal discomfort	15 (14.3)
Nasal congestion	15 (14.3)
Rhinorrhea	13 (12.4)
Epistaxis	5 (4.8)
Sneezing	4 (3.8)
Cough	2 (1.9)
Throat irritation	2 (1.9)
Headache	2 (1.9)
Lacrimation increased	2 (1.9)

- **Majority of TEAEs were nasal/local, mild, and brief**
- **No reported cases of syncope or symptoms of hypotension**
- **No episodes of AV block or pauses after PSVT conversion with etripamil**

[a]Etripamil-related TEAEs are defined as AEs with a start date occurring 0 to 24 hours after etripamil dose that were considered related to etripamil by investigator; patients could have more than one TEAE.-AE, adverse event; AV, atrioventricular; PSVT, paroxysmal supraventricular tachycardia; TEAE, treatment-emergent adverse event.

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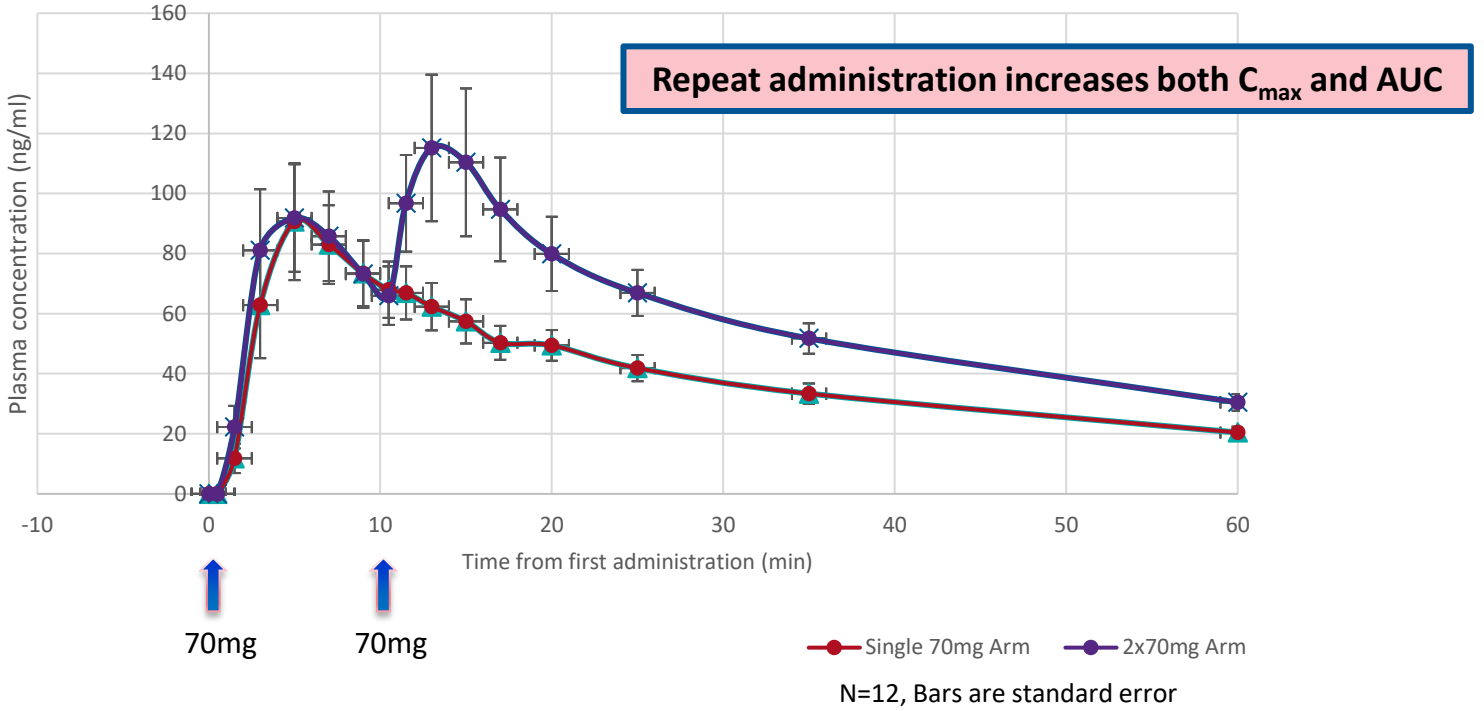
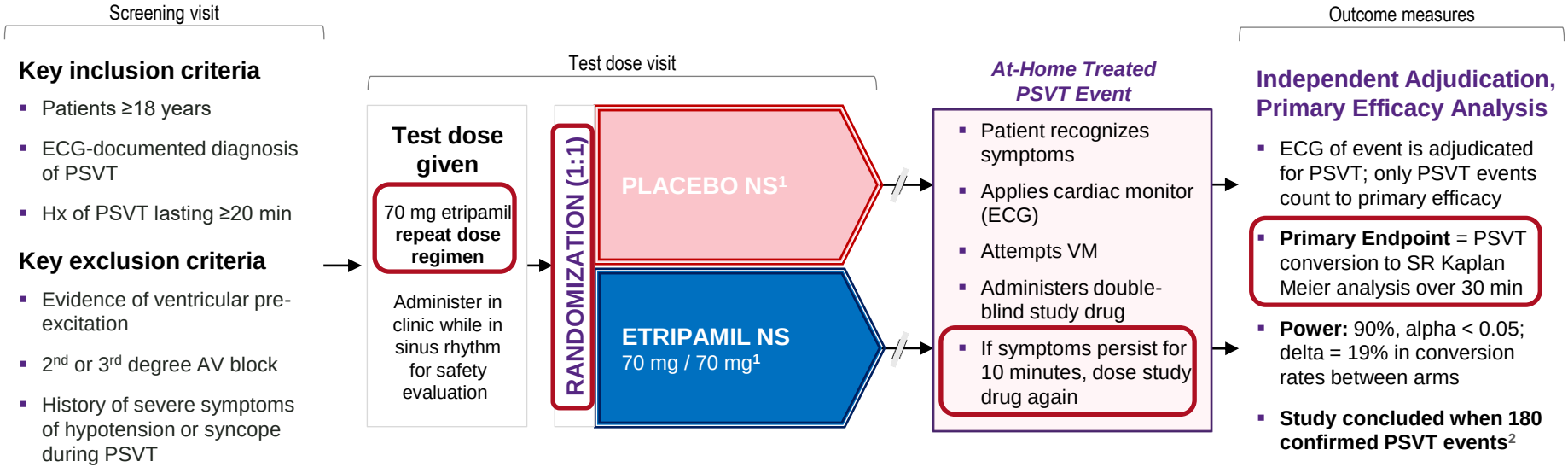
Etripamil 70 mg Repeated at T=10 min (Phase 1, NODE-103)



Data on file Milestone Pharmaceuticals

RAPID Phase 3 Clinical Study Design

Objective: Evaluate the efficacy and safety of etripamil nasal spray in patients experiencing a PSVT episode in an at-home setting



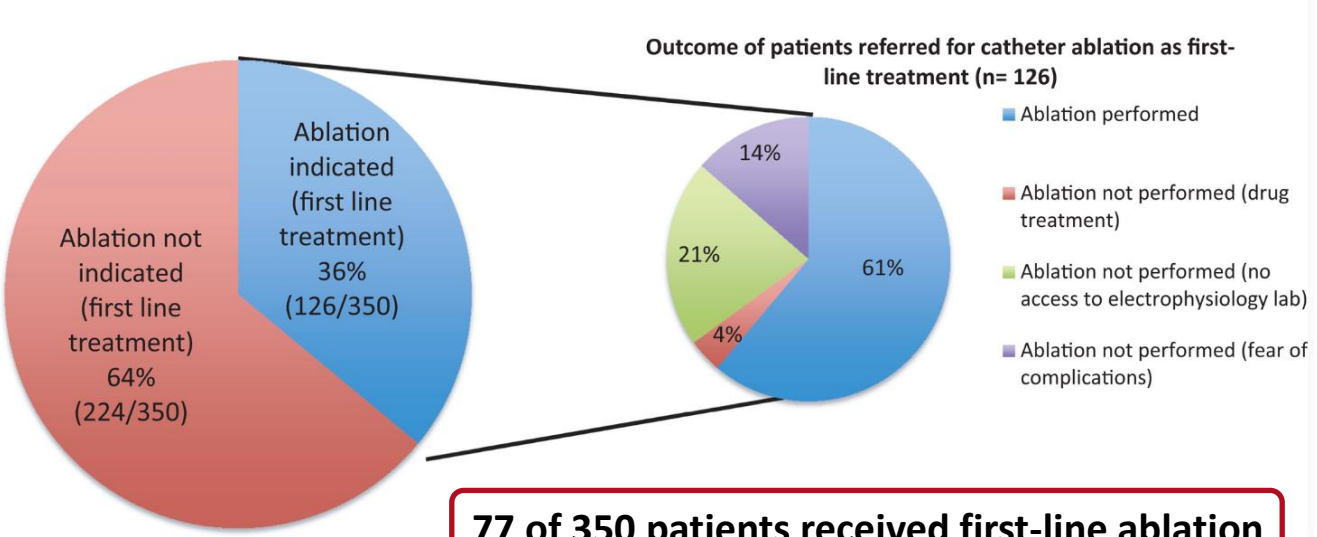
1. Second dose of study drug self-administered if SVT episode does not resolve within 10 minutes after first dose
2. Includes 29 events of single-dose double-blind study drug administration from NODE-301 Part 1 patients who experienced an event after event lock in that study; all blinds maintained.

ECG = electrocardiogram; AV = atrioventricular; PSVT = paroxysmal supraventricular tachycardia; Hx = history; SR = sinus rhythm; VM = vagal maneuver; NS = nasal spray.

Stambler BS, Camm AJ, et al. Amer Heart Assoc 2022

Paroxysmal Supraventricular Tachycardia
Referral for Catheter Ablation as First-line Therapy

Catheter ablation is a safe, effective, cost-effective technique and is considered a first-line strategy for the treatment of symptomatic SVT



77 of 350 patients received first-line ablation

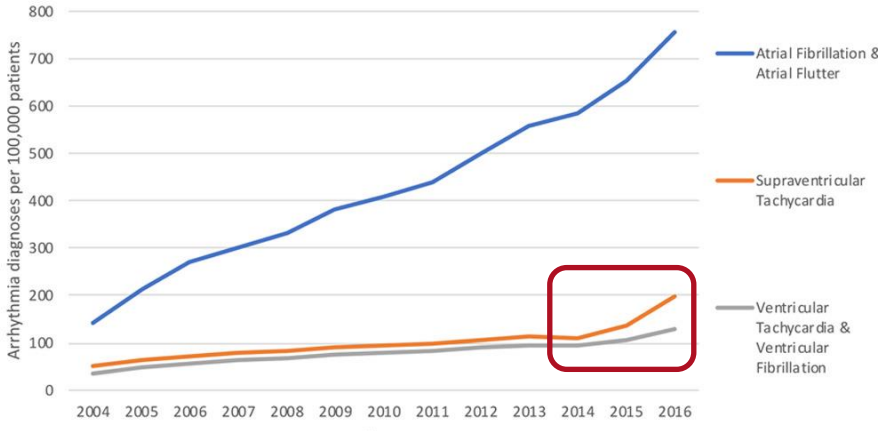
Multivariable analysis: **age** OR, 1.2; 95% CI 1.01–1.32; *P*=0.04), **chest discomfort during SVT** (OR, 2.7; CI 1.6–4.7; *P*<0.001) and **number of antiarrhythmic drugs** before ablation (OR, 1.8; CI 1.4–2.3; *P*<0.001) showed a positive independent association for non-referral for CA as SVT first-line treatment.

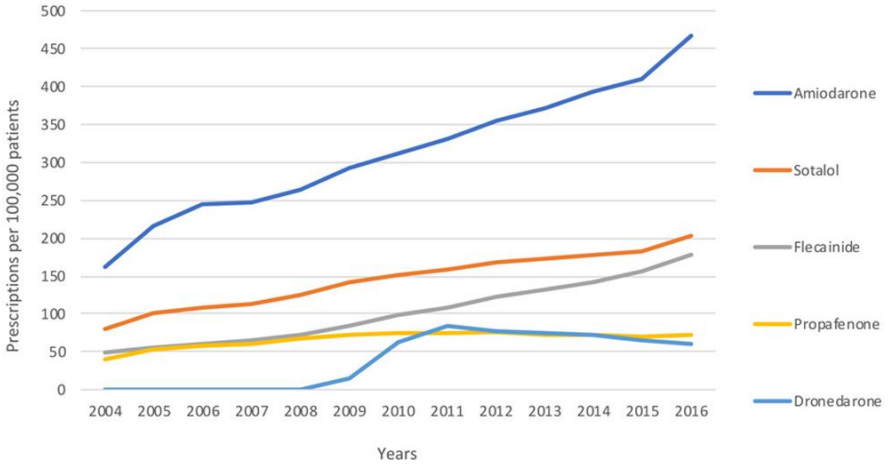
Hollanda Oliveira L et al. . J Am Heart Assoc. 2022 Jun 7;11(11):e022648

Trends in Antiarrhythmic Drug Use United States Between 2004 and 2016

- Optum Clinformatics Data Mart, a de-identified database of commercial and Medicare claims
- 406,181 patients were prescribed 1 or more AADs between 2004 and 2016
- An ICD 10.2% or permanent pacemaker 10.5%.
- Atrial fibrillation or flutter (82.2%), ventricular tachycardia or fibrillation (17.8%) and SVT (16.2%)

4-fold increase in drug treatment of SVT between 2004 and 2016





EHRA 2023

Markman TM, et al. Circulation. 2020;141:937–939

Etripamil Nasal Spray is a Newly Formulated, Intranasal L-type Investigational Calcium Channel Blocker Designed to Treat Quickly

Fast onset of action
(T_{max} ≤ 7 min)

Patient
self-administered

Small enough to
fit in your pocket

Conclusions

- There is little progress in the medical management of PSVT
- Acute management of AV nodal-dependent PSVT could potentially be rapidly, safely and effectively achieved by patient-initiated nasal insufflation of etripamil
- Although catheter ablation is a safe, effective and cost-effective method of long-term management of PSVT it is significantly underused, leaving large numbers of patients dependent on antiarrhythmic drug approaches
- Repeated use of nasal insufflation of etripamil may be used as a long-term strategy for those who are not offered or refuse catheter ablation, or as a bridge between referral and receiving catheter ablation treatment
- This represents a potential, new treatment paradigm – with pivotal trials completed and now pending regulatory review for potential drug approval
- The RAPID study is in press with a refereed journal, to be published shortly

Thank you for your attention…

John Camm

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https://www.stgeorges.nhs.uk/people/professor-john-camm

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