Ivabradine in Management of Pediatric Arrhythmias

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COI Disclosure

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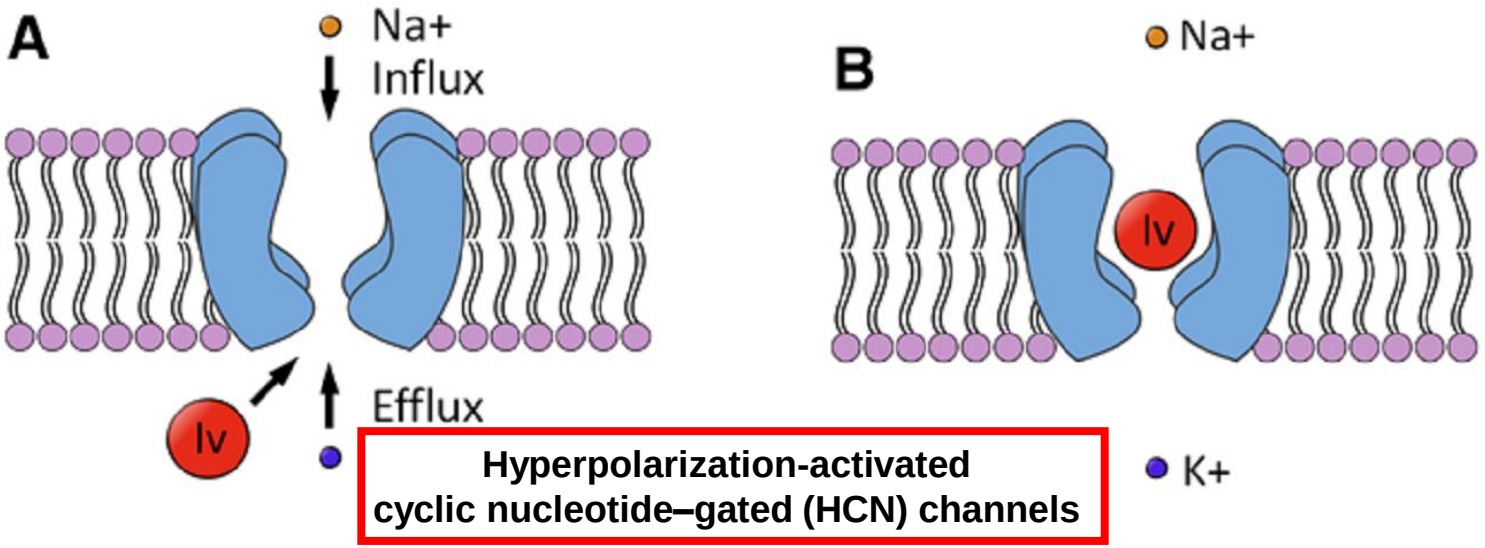
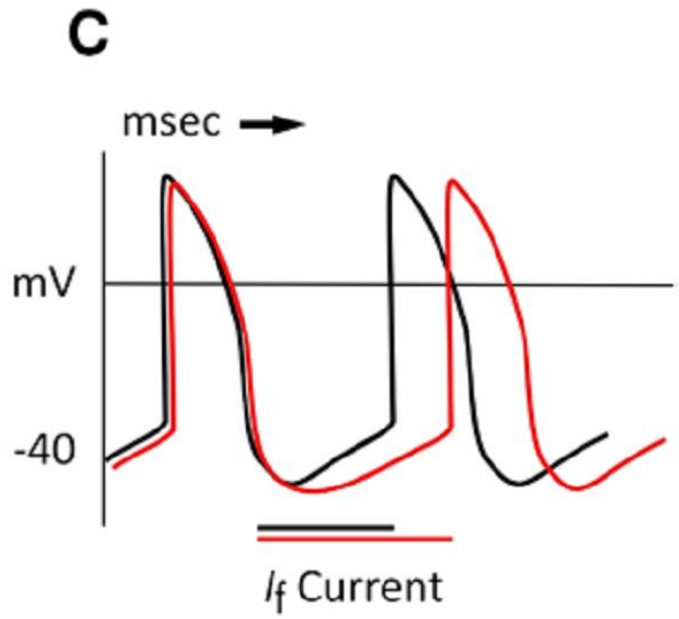
The authors have no financial conflicts of interest to disclose concerning the presentation

Ivabradine

- **Selective inhibitor** of the HCN channels
- No change in inotropy, diastolic function, cardiac output, or vascular resistance



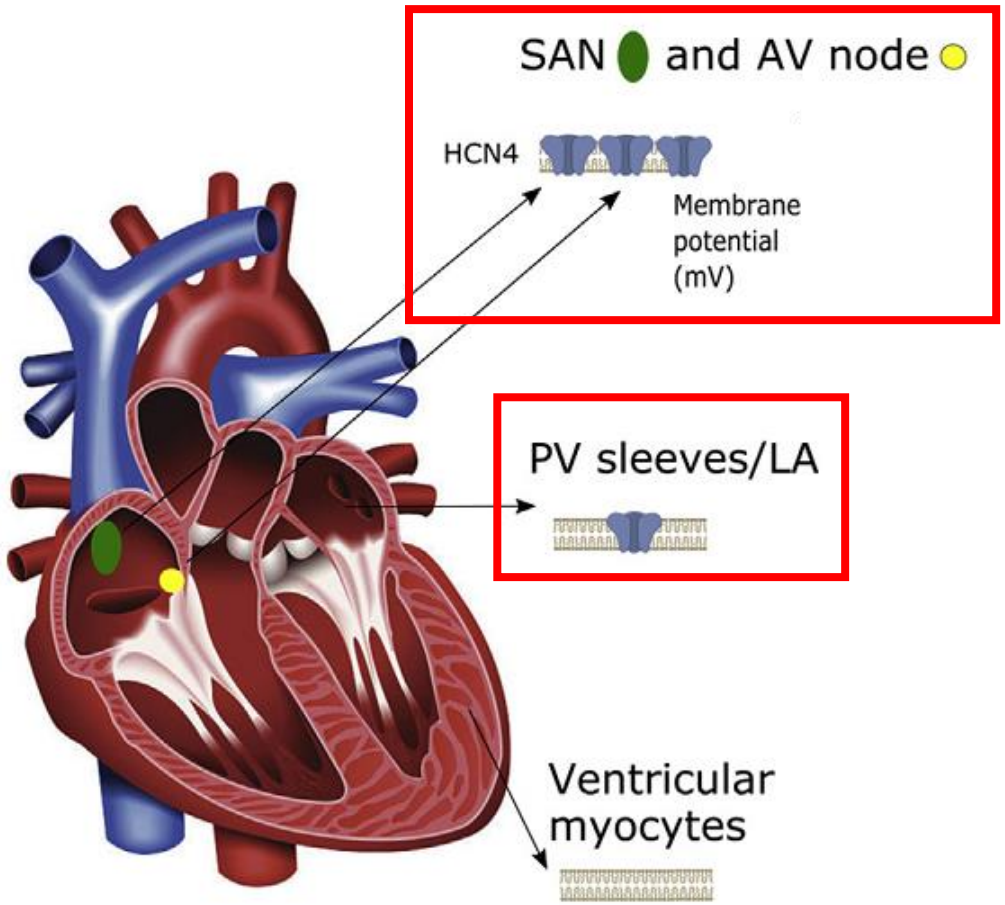
“Funny” pacemaker current (I_f)
of the sinoatrial node



Slow diastolic depolarization & heart rate

Psotka MA et al. *Circulation* 2016

Hyperpolarization-activated cyclic nucleotide–gated (HCN) channels

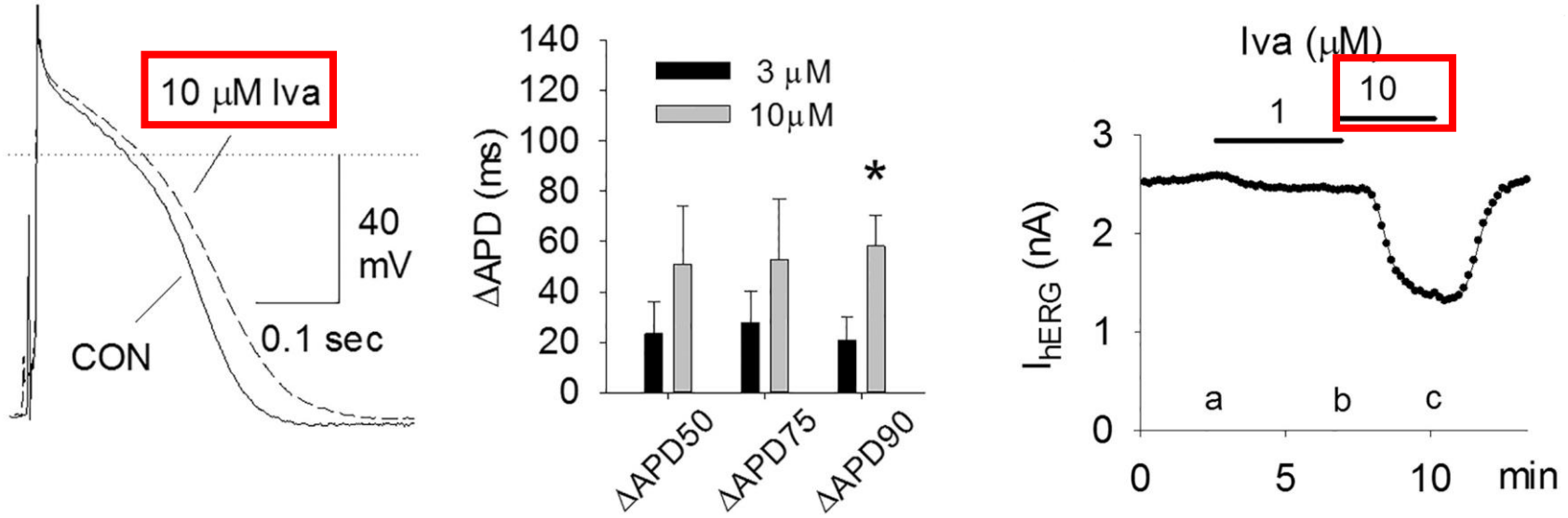


Psotka MA et al. *Circulation* 2016

- Voltage-dependent channels **activated at negative potentials**
- Slowly **depolarize** the membrane toward **the threshold required to activate calcium channels** and generate a spontaneous action potential
- Expression of HCN channels is largest in the **SA node** and in the conduction system (**AV node and Purkinje fibers**), whereas their expression in the atria and ventricles is low

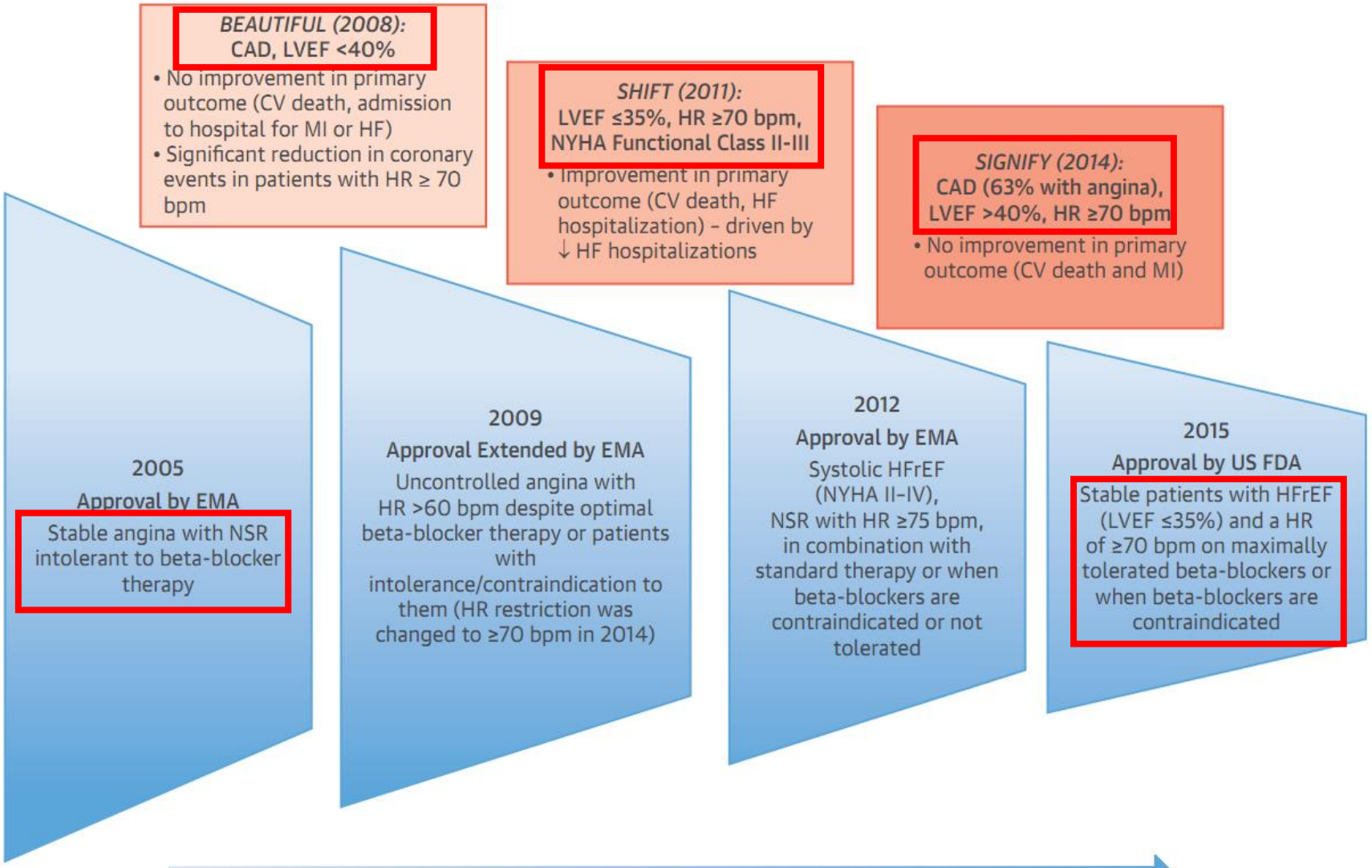
Prolongation phase III repolarization by Ivabradine

- Prolongs **action potential duration** and blocks **the hERG (KCNH2) current**



Lees-Miller JP et al. *J Mol Cell Cardiol* 2015

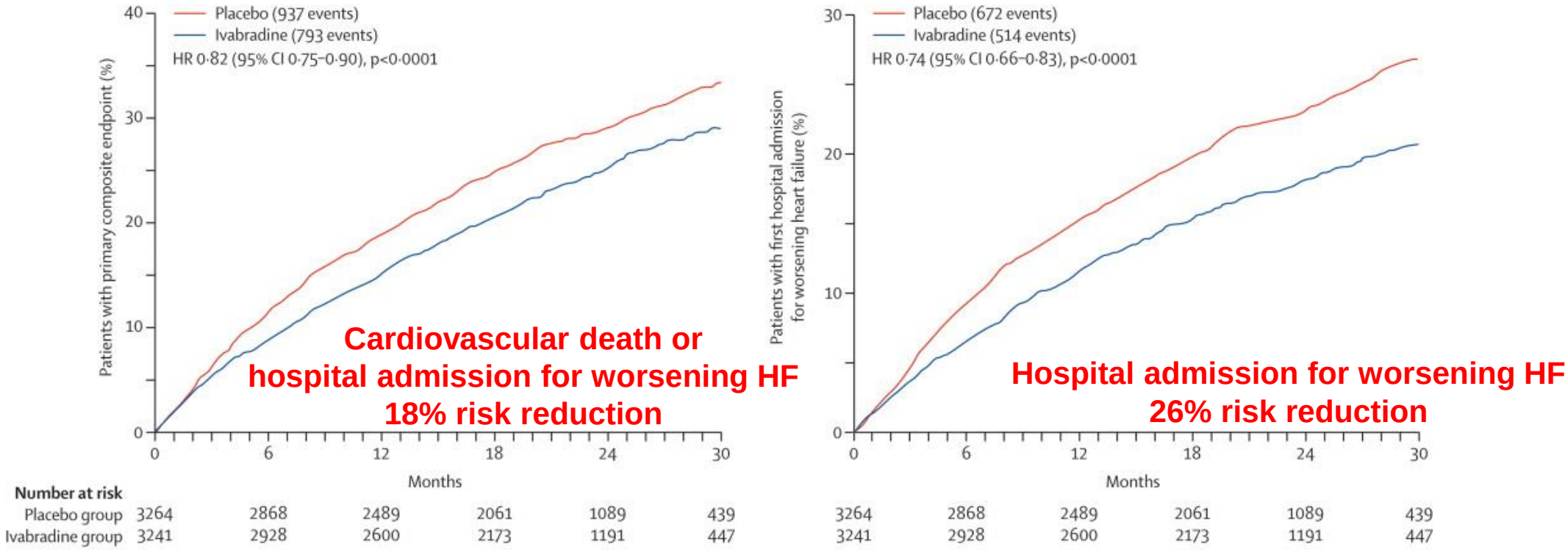
Use of Ivabradine



Koruth JS, et al. *JACC* 2017

SHIFT trial

- **Symptomatic heart failure** and a **left-ventricular ejection fraction of 35% or lower**, were in **sinus rhythm with heart rate 70 beats per min or higher** **Class IIa (ESC 2021, AHA 2022)**



Swedberg K, et al. *Lancet* 2010

Ivabradine for children with chronic HF

- Randomized, double-blind, placebo-controlled, phase II/III study with 12 months of follow-up
- Children with **DCM**, **class II-IV**, **LVEF ≤ 45%** on stable treatment for chronic HF

Primary Endpoint at End of Titration	Ivabradine (n = 73)	Placebo (n = 41)	Odds Ratio (95% CI)	p Value*
All children	51/73 (70)	5/41 (12)	17.24 (5.91 to 50.30)	<0.0001
6–12 months	6/10 (60)	1/6 (17)	7.50 (0.62 to 90.63)	0.113
1–3 yrs	17/24 (71)	0/12 (0)	NA†	
3–18 yrs	28/39 (72)	4/23 (17)	12.09 (3.35 to 43.66)	0.0001
Change in LVEF from Baseline, %				
To 6 months				
All children	11.4 ± 11.6 (n = 72)	5.3 ± 10.3 (n = 39)	5.11 (0.87 to 9.35)	0.0186
To 12 months				
All children	13.5 ± 13.1 (n = 72)	6.9 ± 11.4 (n = 39)	5.57 (0.75 to 10.40)	0.024
Change in Total PedQL‡ Score From Baseline				
To 6 months				
All children	9.1 ± 17.3 (n = 36)	−1.5 ± 13.6 (n = 19)	9.64 (1.83 to 17.46)	0.0166
To 12 months				
All children	9.1 ± 14.2 (n = 36)	1.3 ± 15.3 (n = 19)	6.92 (−0.08 to 13.93)	0.0527

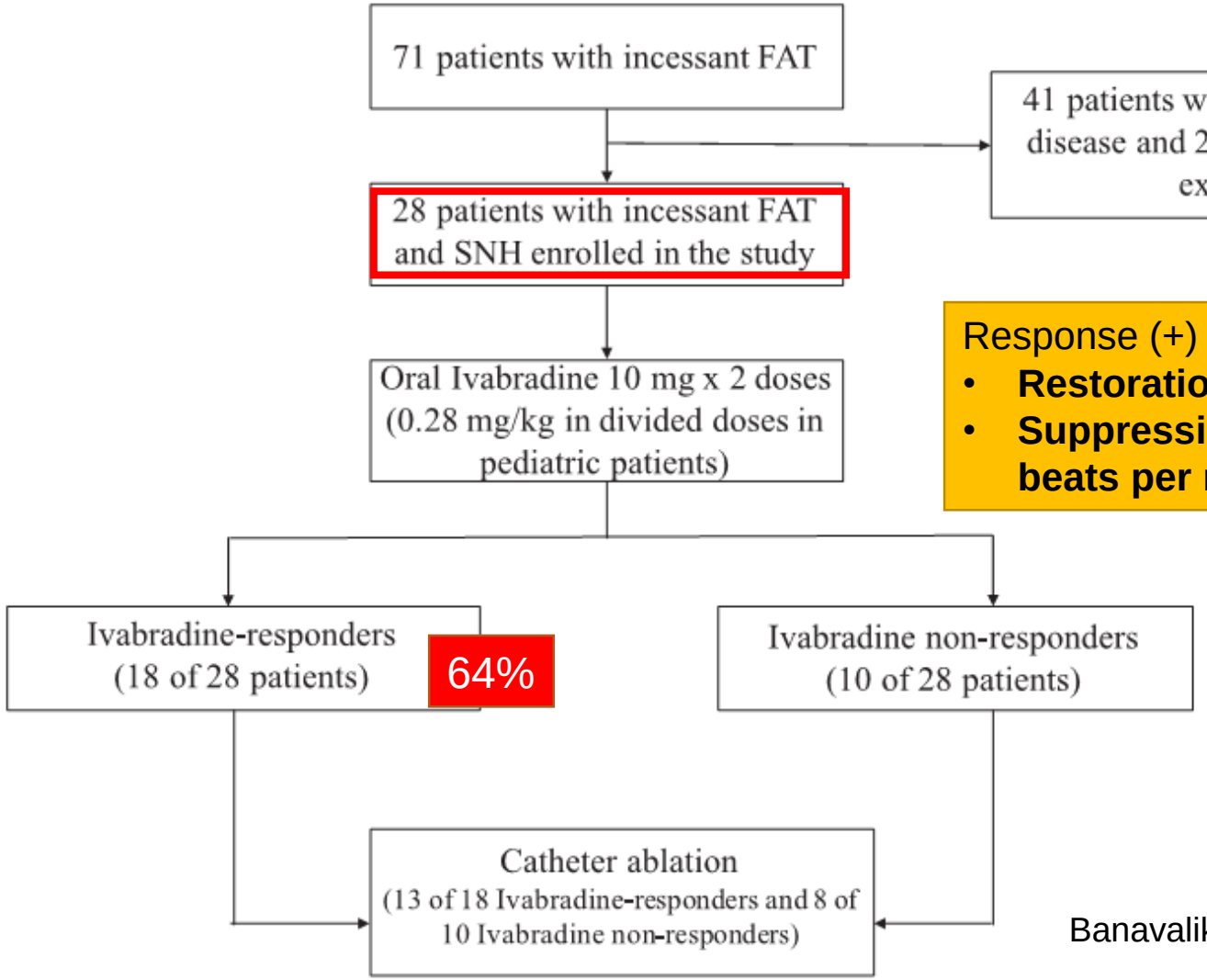
≥20% reduction in heart rate without bradycardia or symptoms of bradycardia

Bonnet D, et al. *JACC* 2017

Ivabradine in management of arrhythmia

- Atrial ectopic tachycardia
- Junctional ectopic tachycardia
  - Congenital
  - Postoperative
- Catecholaminergic polymorphic ventricular tachycardia
- Inappropriate sinus tachycardia in adult patients
- Atrial fibrillation in adult patients

Incessant Ivabradine-sensitive atrial tachycardia



Response (+) within 12 h after ivabradine

- **Restoration of sinus rhythm**
- **Suppression of the tachycardia to <100 beats per minute** without termination

Banavalikar B et al. *Cir Arrhythm Electrophysiol* 2019

Table 2. Comparison Between Ivabradine Responders and Nonresponders

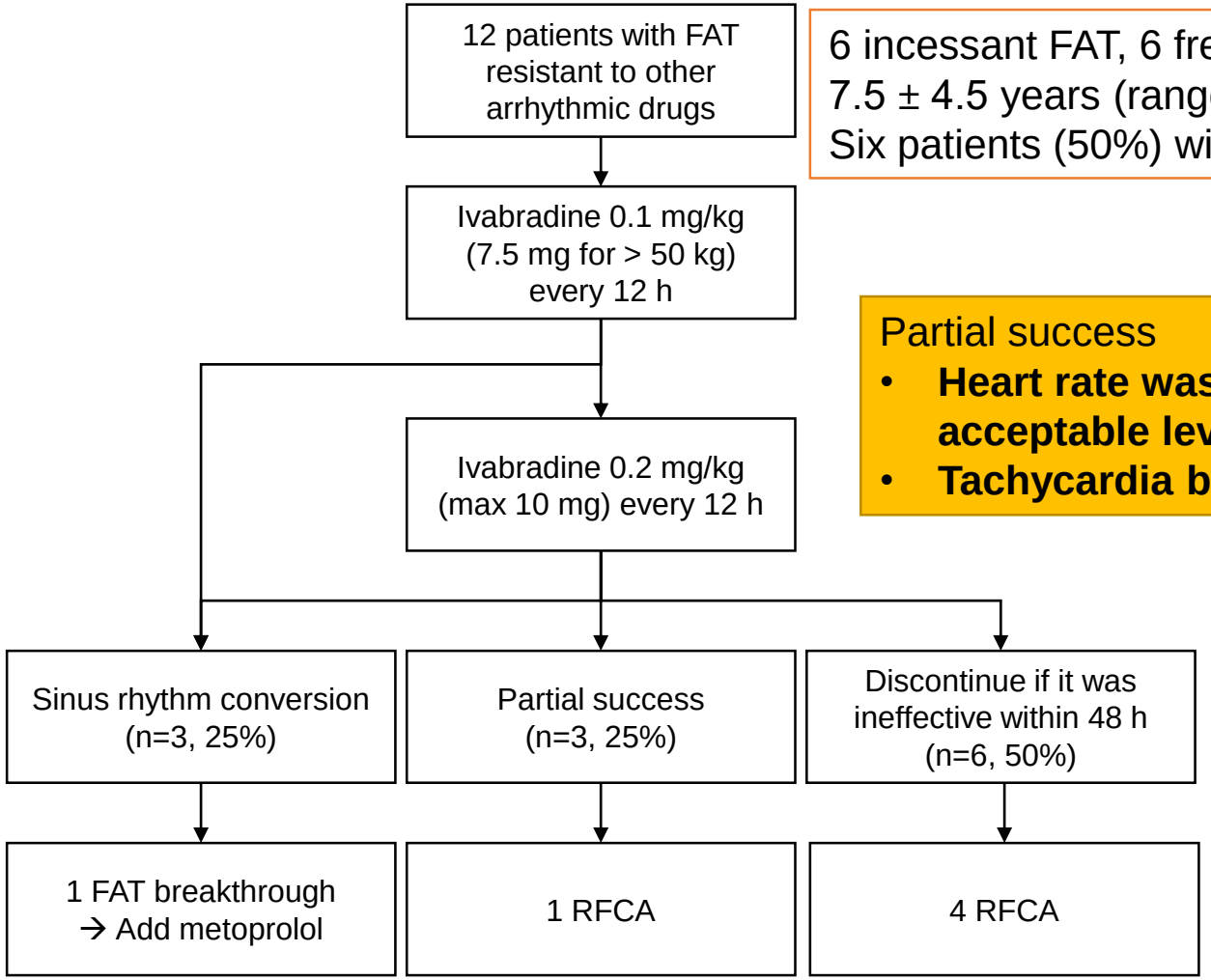
	Ivabradine Responders (n=18)	Ivabradine Nonresponders (n=10)	*P* Value
Age, y	35.7±22.5	32.2±19.1	0.68
Female sex, n (%)	11 (61.1%)	7 (70%)	0.7
LVEF, %	55.7±15.1	52.8±12.8	0.61
TIC (%)	4/18 (22.2%)	3/10 (30%)	0.67
FAT rate, bpm*	166.7±20.6	175.5±22.5	0.3
Tachycardia cycle length, ms†	361.8±39.9	352.9±44.5	0.64
Local activation time, ms‡	41.8±6.2	42.6±5	0.75
Adenosine response			
Transient suppression	10/15 (66.6%)	7/9 (77.8%)	0.67
No effect (persistence of FAT)	5/15 (33.3%)	2/9 (22.2%)	0.67
Tachycardia focus, n (%)			
RA	10/13 (76.9%)	5/8 (62.5%)	0.63
Left atrium	3/13 (23.1%)	3/8 (37.5%)	0.63
Atrial appendages (right or left)	6/13 (46.2%)	0/8	0.046

Table 3. Clinical and Electrophysiological Characteristics of Patients With Ivabradine-Sensitive Atrial Tachycardia

Sl. No.	Age, y	Sex	FAT Rate, bpm	LVEF, %	Adenosine Response*	Ivabradine Maintenance Dose, mg/d	Tachycardia Focus
1	14	F	170	25	1	10	RAA
2	52	M	145	65	2	15	Upper CT
3	61	F	165	62	2	15	RA free wall
4	16	F	166	65	2	10	CS ostium
5	17	M	154	68	1	15	RAA
6	37	F	210	68	2	15	TA
7	57	M	185	60	1	15	TA
8	70	M	150	30	1	15	RAA
9	45	F	152	65	2	15	CS ostium
10	35	F	160	26	3	15	Upper CT
11	07	F	160	35	1	10	LAA
12	60	M	185	61	2	15	LAA
13	53	F	146	58	3	15	LAA
14	1 mo	M	200	65	2	2.5	…
15	9	M	200	64	2	10	…
16	16	F	150	62	2	12.5	…
17	62	F	146	58	2	15	…
18	32	F	152	64	3	15	…

Banavalikar B et al. *Cir Arrhythm Electrophysiol* 2019

Prospective study of Ivabradine for FAT



6 incessant FAT, 6 frequent short runs of FAT
7.5 ± 4.5 years (range, 5 months to 15 years)
Six patients (50%) with tachycardia induced cardiomyopathy

Partial success
- **Heart rate was reduced to an age-acceptable level**
- **Tachycardia burden was reduced to < 10%**

Xu X et al. *Eur J Pediatr* 2023

Shanghai Children's Medical Center (June 2021 to July 2022)

Table 2 Clinical characteristics of patients with FAT who achieved rhythm or heart rate control with ivabradine

	Patient number					
	1	2	3	4	5	6
Age (yrs)	10	5 months	9	3	6	13
Sex	F	M	F	F	F	M
LVEF (%)	28	73	64	45	68	31
Mitral insufficiency	severe	none	none	mild	none	Moderate
LVDD (mm)	52.4	25.1	38.9	37.8	36.3	56.5
Prior antiarrhythmic medications	Digoxin, metoprolol, amiodarone	Metoprolol	Metoprolol	Propafenone, sotalol	Metoprolol/propafenone	Digoxin, metoprolol, amiodarone
FAT rate (bpm) before ivabradine	200	272	204	146	157	145
FAT burden (%) before ivabradine*	> 90%	75%	44%	> 90%	25%	> 90%
Mean HR (bpm) after ivabradine*	80	110	71	96	79	86
FAT burden (%) after ivabradine*	< 1%	< 1%	< 1%	> 90%	2.5%	> 90%
Ivabradine efficacy	Success[a]	Success	Success	Partial success	Partial success	Partial success
Ivabradine dose (mg/kg, every 12 h)	0.2	0.2	0.1	0.2	0.2	0.2
Follow-up (months)	12	5	3	15	3	One week

Xu X et al. *Eur J Pediatr* 2023

FAT in children with congenital heart disease

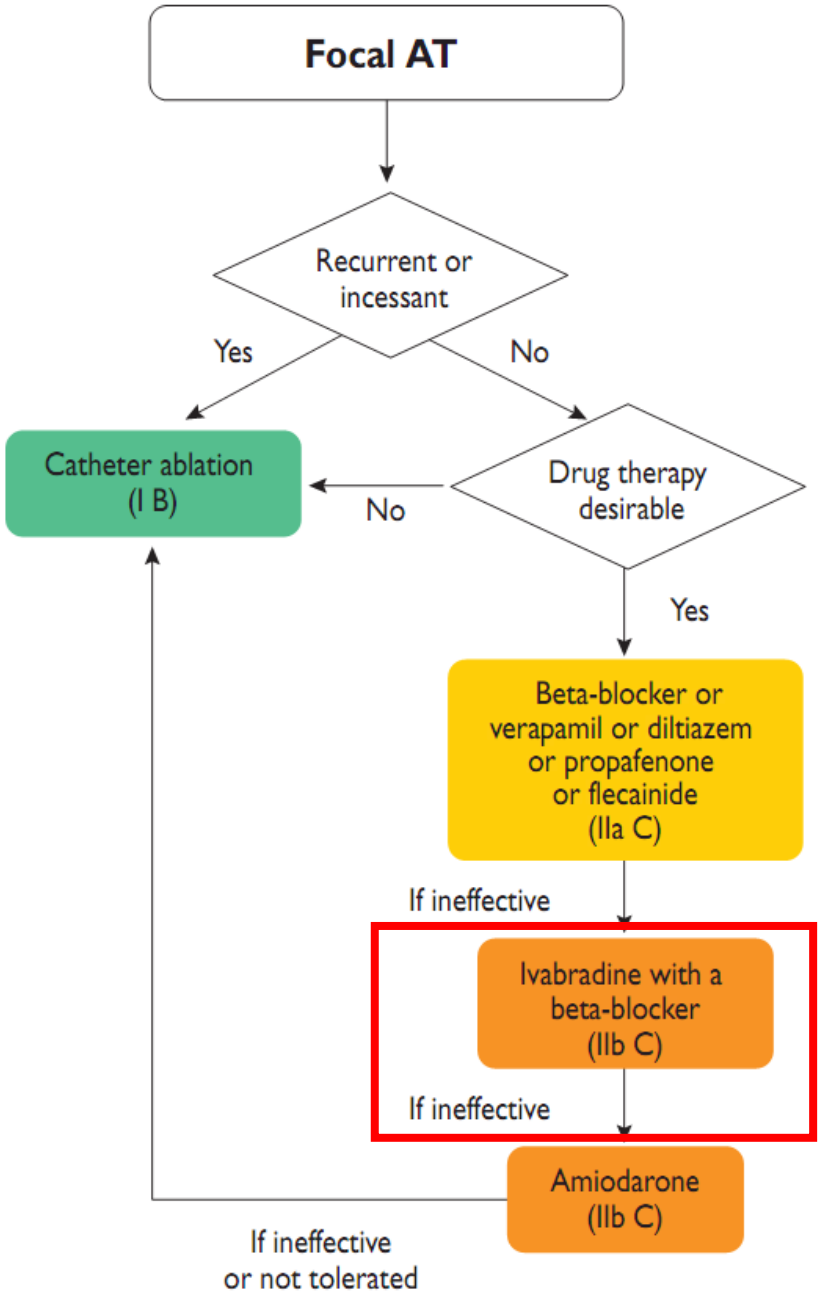
	Study population (n=15)
Age (months)	**7 [1-18]**
Weight (kg)	6.7 [3.9-8.5]
Gender (kg)	9/15 (60%)
Complex congenital heart disease	**12/15 (80%)**
Single ventricle physiology	**8/15 (54%)**
Diminished systolic ventricular function	**4/15 (27%)**
FAT after cardiac surgery or intervention	**6/15 (40%)**
Therapy indication:	
1st line	4/15 (27%)
2nd line	6/15 (40%)
3rd line	1/15 (7%)
Breakthrough	4/15 (27%)

Response (+)
- Complete rhythm control within 24 hours of initiation of ivabradine

Maximum ivabradine dose (mg/kg/dose)	0.07 [0.05-0.10]
Monotherapy	**2/15 (13%)**
Concurrent anti-arrhythmic medication	
Flecainide	4/15 (27%)
Amiodarone	4/15 (27%)
Beta blocker	4/15 (27%)
Digoxin	3/15 (20%)
Dexmedetomidine	2/15 (13%)
Acute success	**12/15 (80%)**
Adverse events	
Sinus bradycardia	5/15 (33%)
Functional bradycardia (blocked PACs)	2/15 (13%)

Children's Health of Dallas (August 2020 until May 2023)

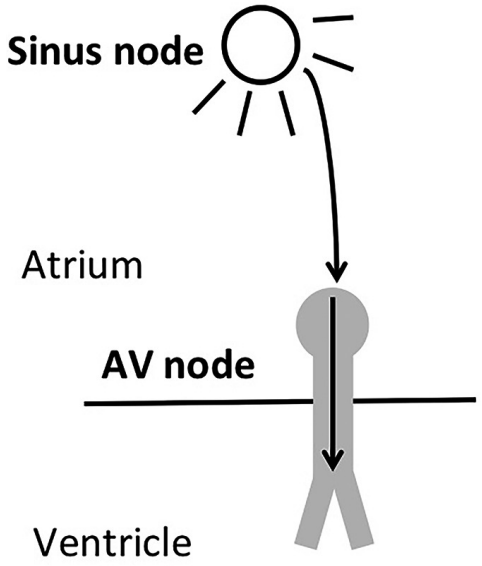
Drishti T et al. *medRxiv* 2023



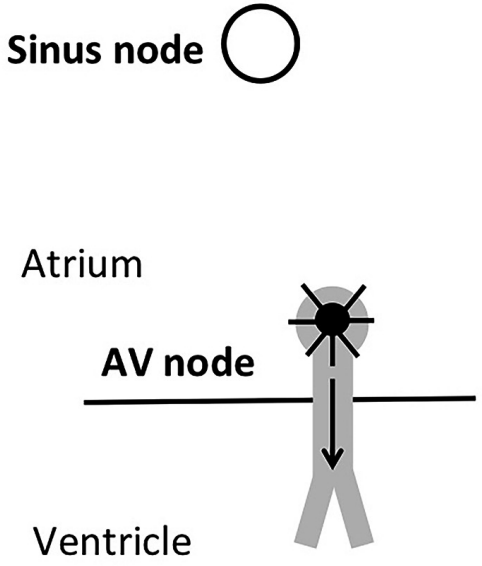
Brugada J et al. *Eur Heart J* 2019

Junctional ectopic tachycardia (JET)

- Tachyarrhythmias originating in the AV node and AV junction including the bundle of His complex



Normal sinus rhythm



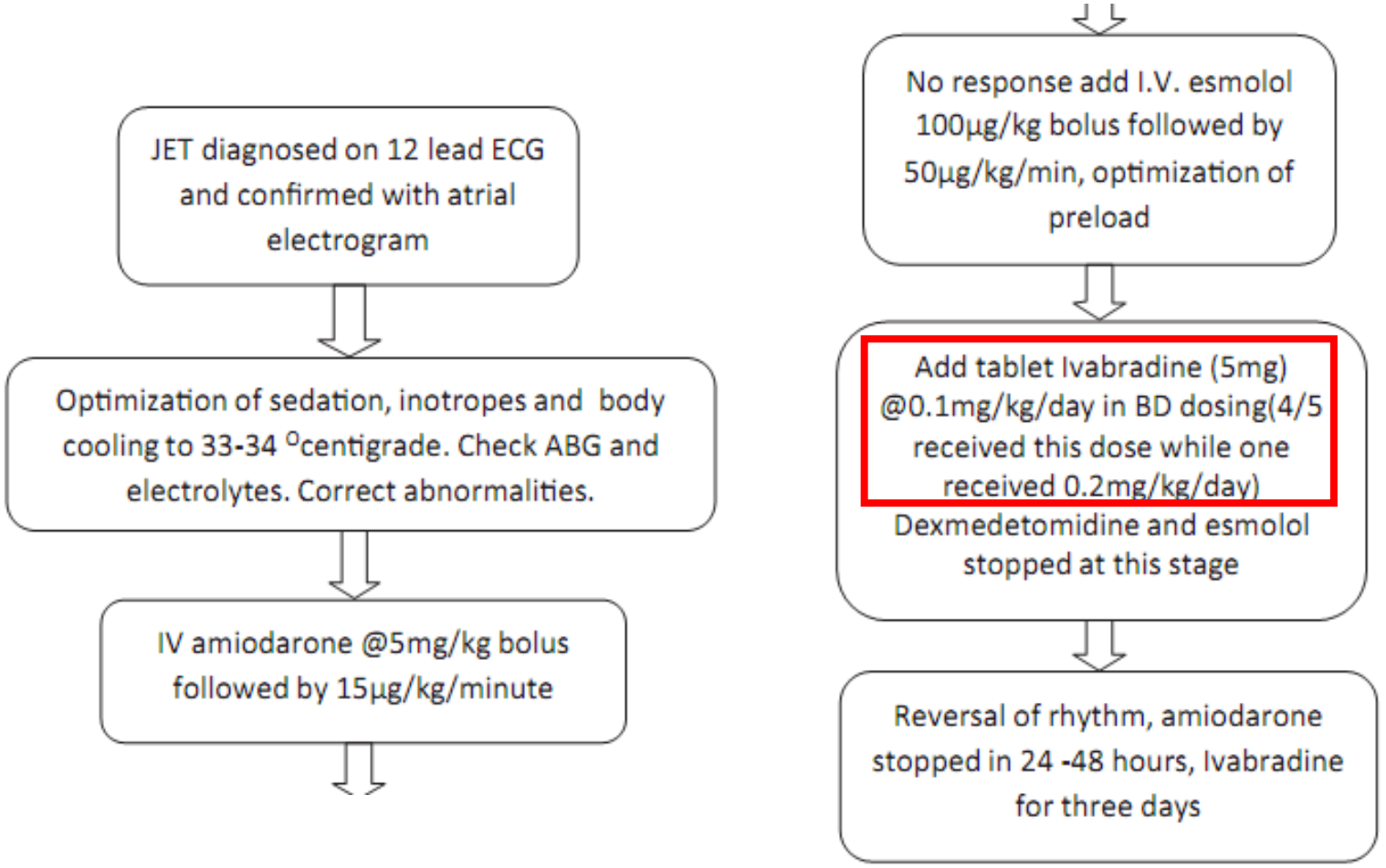
Junctional ectopic tachycardia

- **Congenital JET**
: increased automaticity

- **Postoperative JET**
: fluid and electrolyte shifts, trauma, stretch, local edema, or ischemia in the region of the AV node or bundle of His complex

Kylat RI et al. *J Arrhythmia* 2019

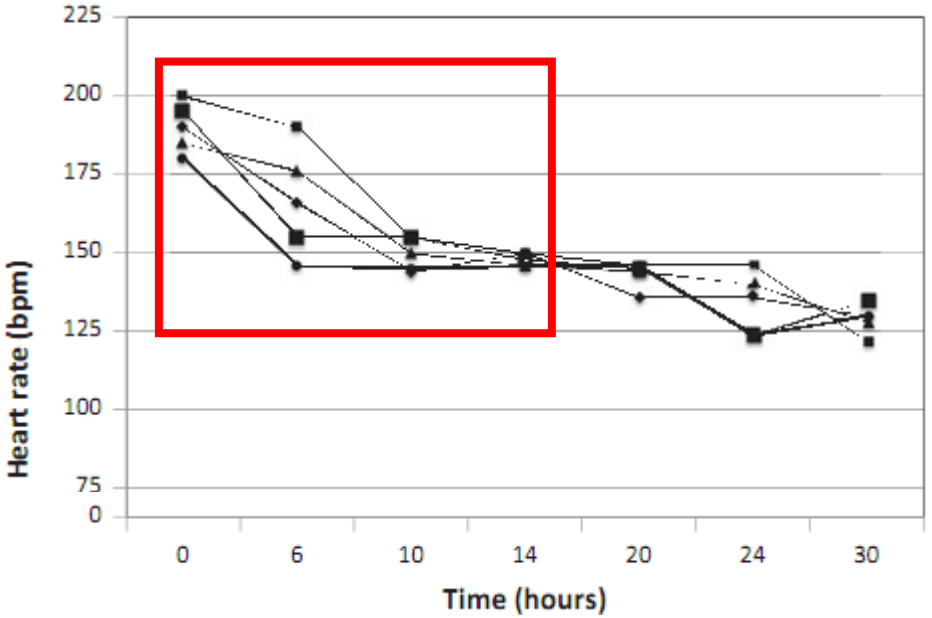
Ivabradine for refractory postoperative JET



5 children in Army Hospital Research and Referral, India (Jan 2017-Dec 2017)

Ivabradine for refractory postoperative JET

S No	Diagnosis	Age	Sex	Time to Onset	Dose of Oral Ivabradine	CPB	ACC	VIS
1	TOF repair	8 m	M	2 hours	0.1 mg/kg/d	75	48	8.75
2	TOF repair	7 m	M	2.5 hours	0.1 mg/kg/d	82	40	8.75
3	TOF repair	12 m	F	1.5 hour	0.1 mg/kg/d	67	38	13.75
4	VSD closure	7 m	M	1 hour	0.1 mg/kg/d	50	32	10
5	CAVSD repair	8 m	F	6 hours	0.2 mg/kg/d	116	88	20



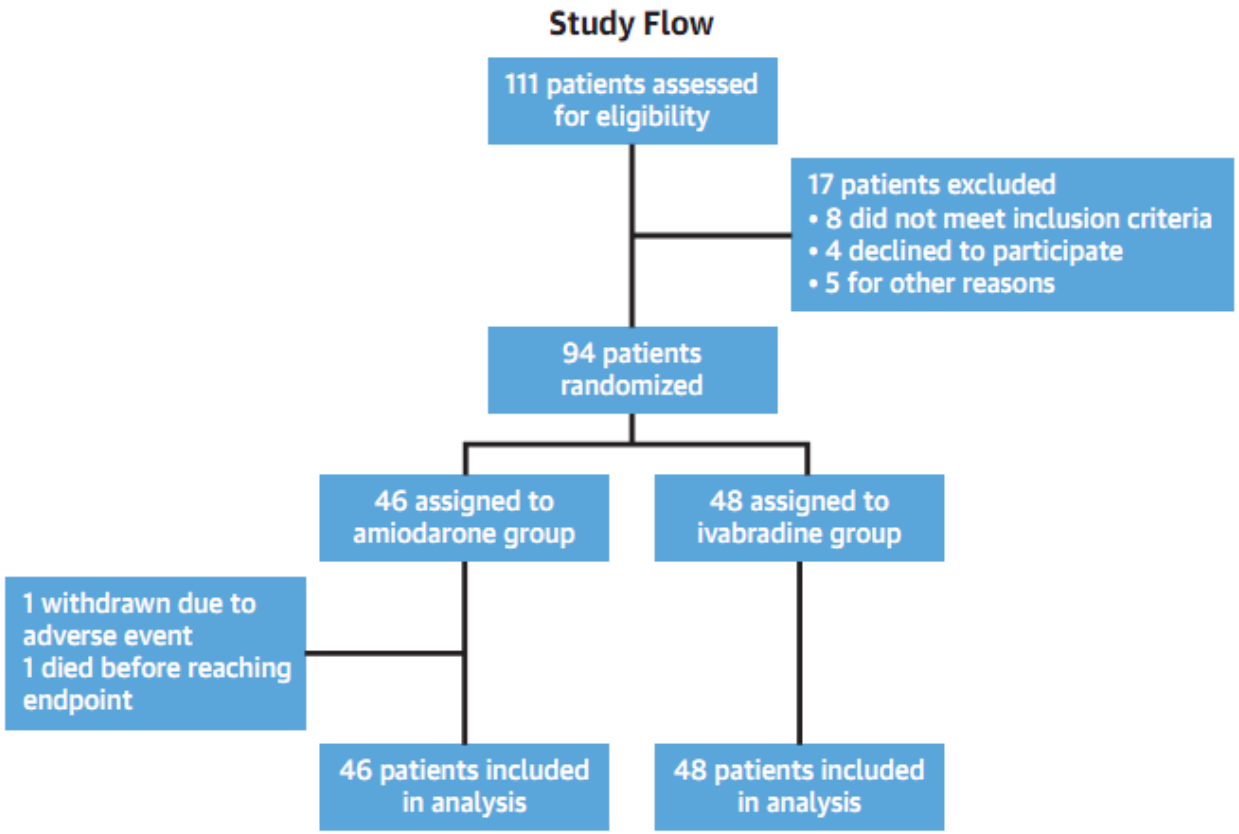
Mean duration to achieve sinus rhythm
31.6 ± 13.6 hours

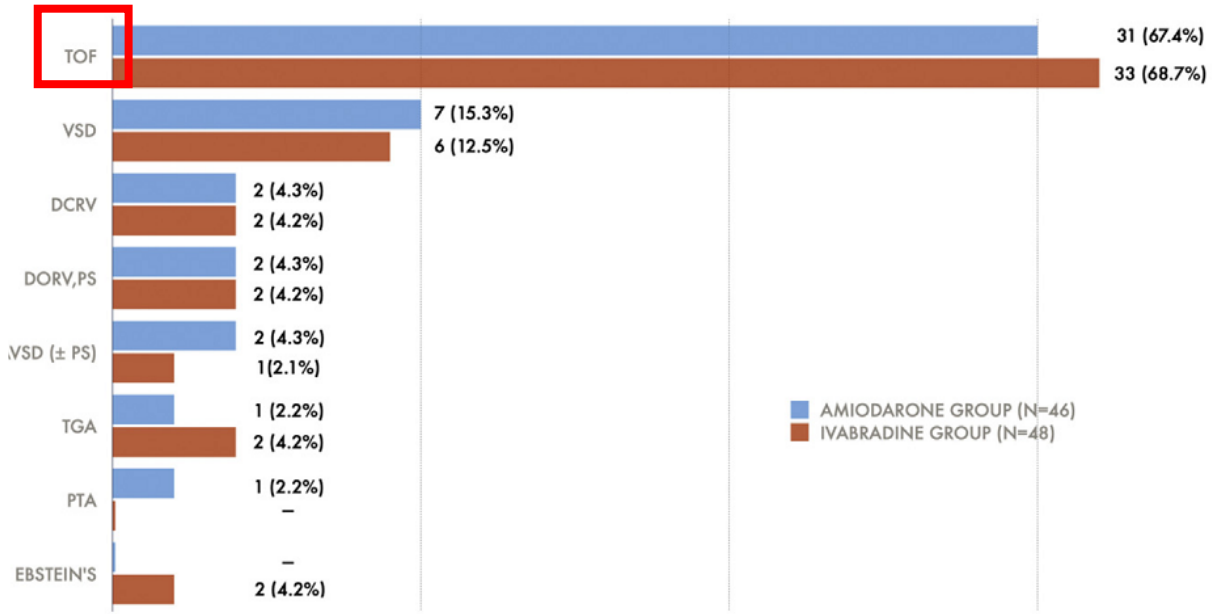
Kumar V et al. *World J Pediatr Congenit Heart Surg* 2019

5 children in Army Hospital Research and Referral, India (Jan 2017-Dec 2017)

Ivabradine vs. Amiodraone for postoperative JET

- Randomized, parallel-design, open-label noninferiority study





Arvind B et al. *JACC EP* 2021

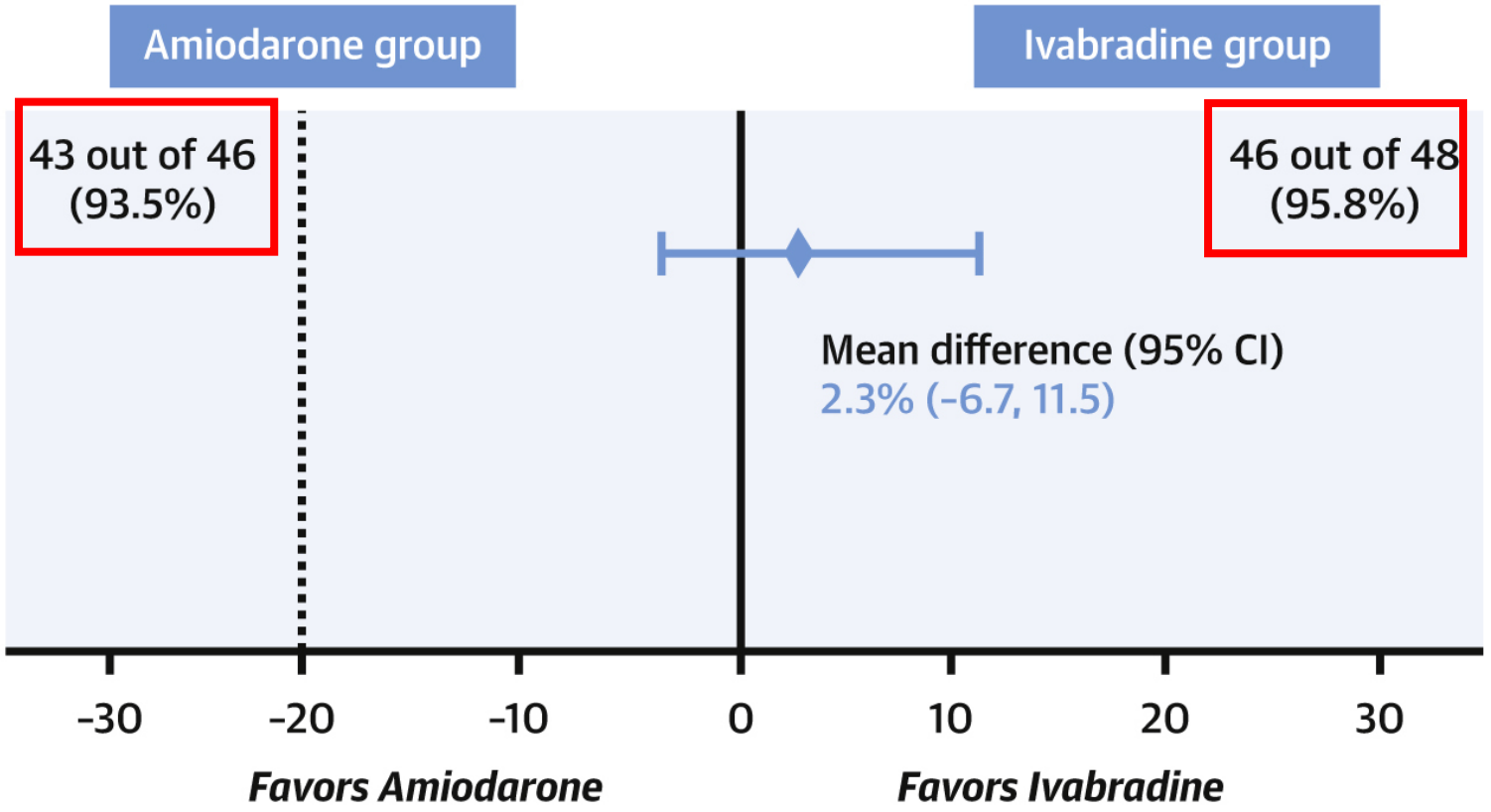
94 children in New Delhi, India (age <18 years) (Aug 2018 – Feb 2020)

TABLE 1 Baseline Characteristics of Patients in the Treatment Groups

	Amiodarone Group (n = 46)	Ivabradine Group (n = 48)	p Value
Male	26 (56.5)	36 (75)	0.08
Age, mo	39.5 (26-99)	33.5 (22.5-71)	0.09
Weight, kg	12.2 (10-20)	11.5 (8-14.5)	0.20
Height, cm	101.5 (88-129)	95 (80.5-116)	0.11
Cardiopulmonary bypass time, min	107 (90-153)	117.5 (95.5-139.5)	0.90
Aortic cross-clamp time, min	66 (53-98)	72.5 (56.5-95.5)	0.74
Right ventriculotomy performed	26 (56.5)	28 (58.3)	0.51
Duration from surgery to onset of JET, h	40.4 (10.1-68.3)	39.9 (19.5-82.5)	0.25
Maximum heart rate during the arrhythmia, beats/min	185 (178-194)	185 (175.5-194.5)	0.74

Arvind B et al. *JACC EP* 2021

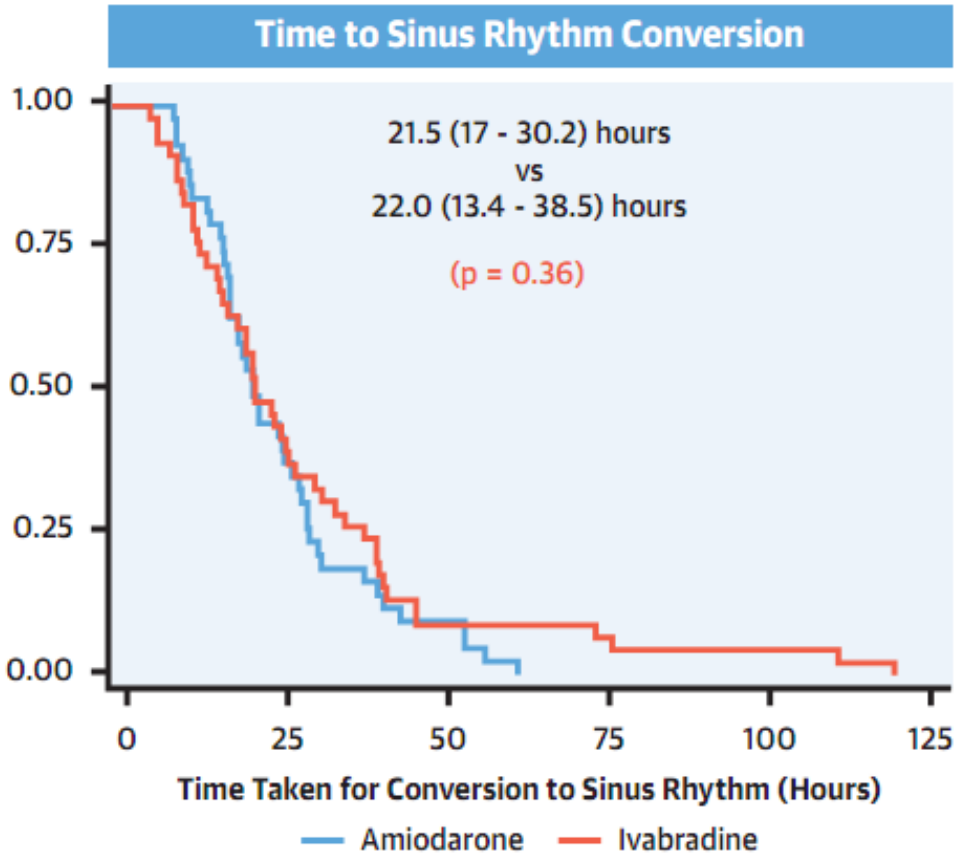
Conversion to Sinus Rhythm

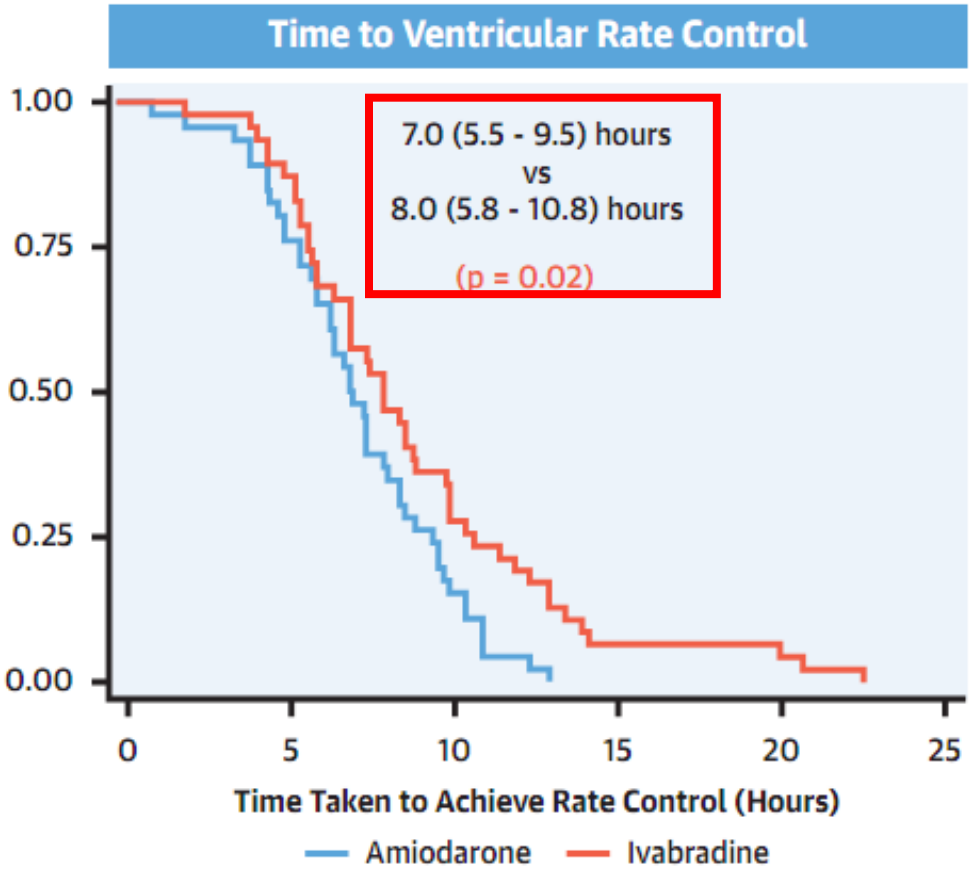


Recurrence **1 patients** **6 patients**

Arvind B et al. *JACC EP* 2021

Rate control was earlier in patients with amiodarone





Arvind B et al. *JACC EP* 2021

Adjunctive ivabradine for congenital JET

Table 1 Patient characteristics

	Patient no.				
	1	2	3	4	5
Sex	Female	Male	Female	Male	Female
Age at diagnosis (weeks)	8	14	14	0	0
Age at start with ivabradine	8 weeks	3 years 6 months	2 years 1 month	10 days	17 days
Weight (kg)	4.2	14.5	9.8	2.17	3.5
Length (cm)	51	94	75	48	52
Antiarrhythmic medication before ivabradine (mg/kg/d)	Amiodarone (10)	Amiodarone (10) Digoxin (0.002)	Amiodarone (5) Digoxin (0.004) Flecainide (2.5)	Amiodarone (10)	Amiodarone (10)
Antiarrhythmic medication with ivabradine (mg/kg/d)	Ivabradine (0.24) Amiodarone (10)	Ivabradine (0.22) Amiodarone (5)	Ivabradine (0.2) Amiodarone (5) Digoxin (0.004) Flecainide (2.5)	Ivabradine (0.12) Amiodarone (7) Propranolol (3)	Ivabradine (0.28) Amiodarone (10) Propranolol (4)
Inotropic support	No	No	No	Yes	Yes
Mean HR before ivabradine (Holter; bpm)	171	105	137	143	NE
Mean HR with ivabradine (Holter; bpm)	96	82	97	110	137
HR on surface ECG before ivabradine (bpm)	210	118	117	210	210
HR on surface ECG with ivabradine (bpm)	118	77	132	119	136
FS before ivabradine (%)	17	39*	38*	25	11
FS with ivabradine (%)	32	39	33	46	25
Heart rhythm at discharge from hospital	SR	SR	JR/JET	SR	JR/SR
Success of ivabradine treatment at last follow-up	Total	Total	Partial	Total	Total

5 patients in Georg-Agust-University Hospital, Germany

Dieks JK et al. *Heart Rhythm* 2016

Ivabradine for catecholaminergic polymorphic VT

- 20-year-old female, RyR2 hetero mutation, exertional syncope

→ Complete suppression of ventricular arrhythmia with nadolol & ivabradine

- 16-year-old boy, RyR2 hetero mutation, asymptomatic, Family Hx of SCD

→ Marked reduction in ventricular arrhythmia with nadolol, flecainide, ivabradine

Before treatment

Nadolol (2.7 mg/kg/d)

Nadolol + Ivabradine 5mg/d

Vaksmann G et al. *PACE* 2018

Caution for Ivabradine use

- Substrate of **cytochrome p450 (CYP) 3A4**
  - Use cautiously with **concomitant administration of cytochrome p450 3A4 inhibitors** (ketoconazole, verapamil, diltiazem, clarithromycin, and grapefruit juice) or **inducers** (rifampin and carbamazepine)

- **Phosphenes**
  - Sensations of increased brightness not mediated by retinal stimuli
  - Inhibition of similar hyperpolarization-activated channels in the retina
  - In SHIFT trial, **Ivabradine 89/3232 (3%)** vs. placebo 17/3260 (1%) (p<0.0001)

Swedberg K et al. *Lancet* 2010

Atrial fibrillation & QT prolongation after Ivabradine use

Table 1 Arrhythmic outcomes: Large clinical trials of ivabradine

Study (year)	Study population	No. of patients	Mean/median follow-up	Study design	Result		
					VA	Supraventricular arrhythmias other than AF	AF
Coronary artery disease							
BEAUTIFUL[34] (2008)	CAD + LV systolic dysfunction, sinus rhythm ≥70 bpm	10,917	1.6 years	RCT			IVA: 7.2% PLA: 5.5% (P <.001)
BEAUTIFUL Holter Substudy[35] (2011)		840	2 × 24 h 1 and 6 mo	RCT substudy	VT: IVA: 24%–26% PLA: 26%–24% (P = NS)	SVT: IVA: 44%–45% PLA: 40%–38% (P = NS)	
SIGNIFY[36] (2014)	CAD without CHF, sinus rhythm ≥70 bpm	19,107	2.3 yr	RCT	Severe VA: IVA: 0.8% PLA: 0.7% (P = NS) QT prolongation: IVA: 1.8% PLA: 0.7% (P <.001)	SVT: IVA: 44%–45% PLA: 40%–38% (P = NS)	IVA: 5.3% PLA: 3.8% (P <.001)
Heart failure							
SHIFT[37] (2010)	CHF, LVEF ≤35%, sinus rhythm ≥70 bpm	6558	1.9 yr	RCT			IVA: 9% PLA: 8% (P = .012)
SHIFT Holter Substudy[38] (2015)		602	24 h at 8 mo	RCT substudy	nsVT: IVA: 28% PLA: 33% (P = NS) PVC: IVA: 78/h PLA: 69/h (P = NS)	nsSVT: IVA: 44% PLA: 41% (P = NS) PSVC: IVA: 37/h PLA: 15/h (P = NS)	IVA: 2.4% PLA: 2.0% (P = NS)

Marciszek M et al. *Heart Rhythm* 2021

Take home message

- **Ivabradine** is being used **off-label** for the treatment of arrhythmias characterized by **enhanced automaticity**, and it has demonstrated promising results in **a small pediatric population**

- **A prospective, well-designed study is required** to assess the effectiveness of ivabradine in managing pediatric arrhythmias. This study should include a large number of pediatric patients to provide more conclusive evidence on its efficacy.

Thank you for your attention