



CardiaCareTM

Non-invasive personalized neuromodulation therapy for Atrial Fibrillation

Clinical Overview

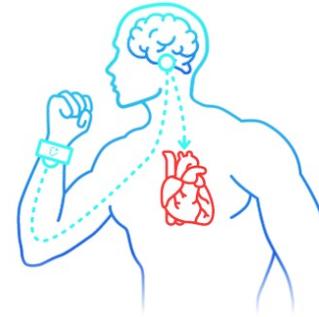
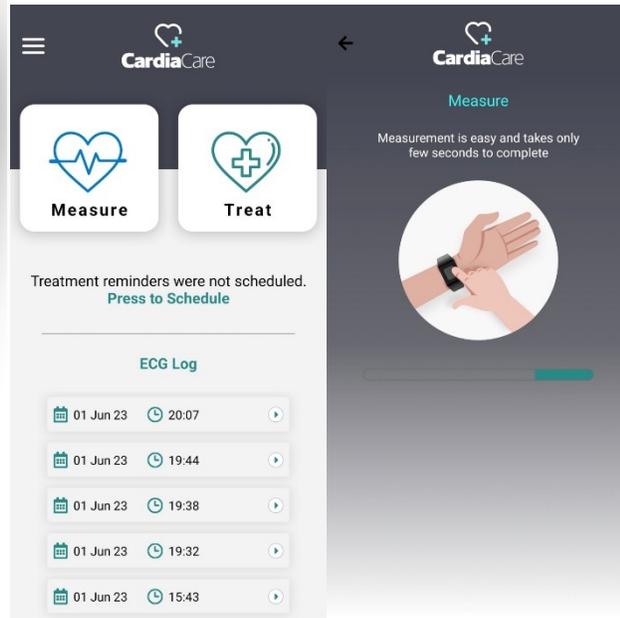
June 2023



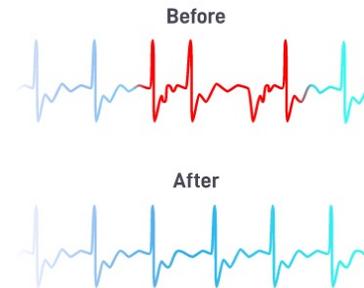
MEDTECH
INNOVATOR
ACCELERATOR

CardiaCare overview

A new approach in atrial fibrillation aimed at reducing AF burden, symptoms and recurrence by non-invasive electrical neuro modulation applied at the wrist



Neuro modulation of the Median and ulnar nerves of the wrist (via CardiaCare) stimulates the stellate ganglion Vagus nerve, which balances sympathetic and vagal nerve control over heart rate and rhythm

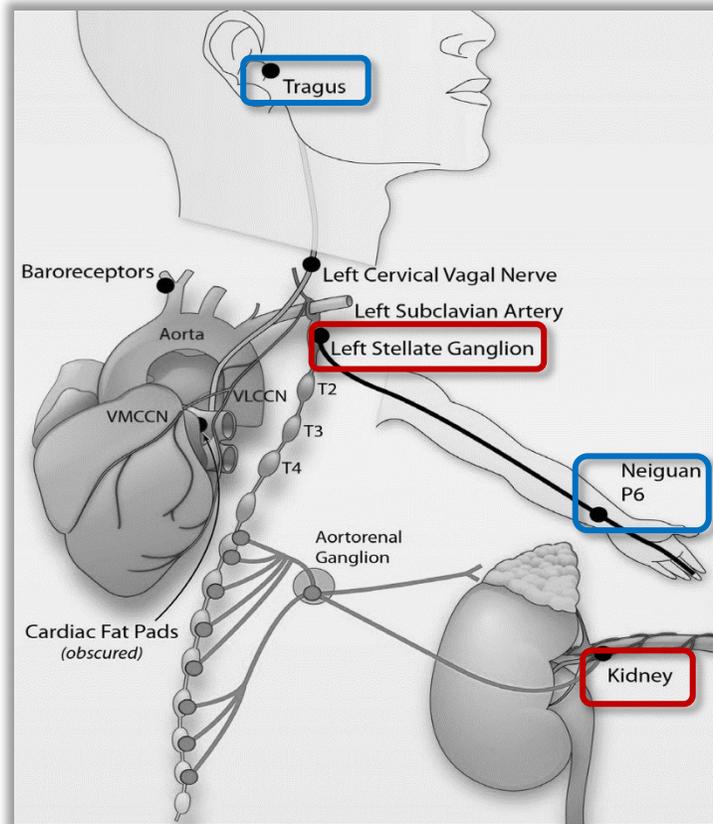


The therapy augments central nervous system balance, reduces precursors of AF like premature atrial contractions (PAC's) resulting in fast clinical and symptomatic relief

Current clinical evidence with Neuro modulation in treatment of AF

Autonomic Modulation for Cardiac Arrhythmias

Invasive Approaches → Transcutaneous Approaches



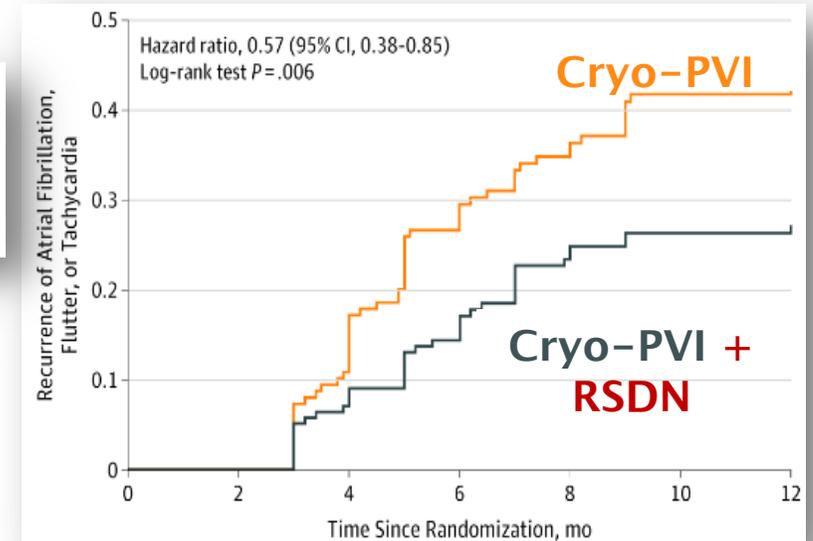
- Autonomic Modulation has a profound effect on cardiac arrhythmias
- **Invasive Approaches (Largely Efferent Pathway Modification)**
 - ✓ Renal Denervation
 - ✓ Stellate Ganglion Resection
- **Non-invasive Approaches (Largely Afferent Nerve Stimulation)**
 - ✓ Tragus Nerve Stimulation
 - ✓ Median Nerve Stimulation

JAMA | Original Investigation

Effect of Renal Denervation and Catheter Ablation vs Catheter Ablation Alone on Atrial Fibrillation Recurrence Among Patients With Paroxysmal Atrial Fibrillation and Hypertension The ERADICATE-AF Randomized Clinical Trial

Jonathan S. Steinberg, MD; Vitaliy Shabanov, MD; Dmitry Ponomarev, MD; Denis Losik, MD; Eduard Ivanicky, MD; Evgeny Kropotkin, MD; Konstantin Polyakov, MD; Pawel Ptaszynski, MD; Boris Keweloh, MD; Christopher J. Yao, MPH; Evgeny A. Pokushalov, MD, PhD; Alexander B. Romanov, MD

J Steinberg, V.Shabanov, D.Ponomarev, et al, JAMA 323 (3):248-55 (2020)



Transcutaneous stimulation (tragus nerve) for the *treatment of AF*



ELSEVIER

Journal of the American College of
Cardiology

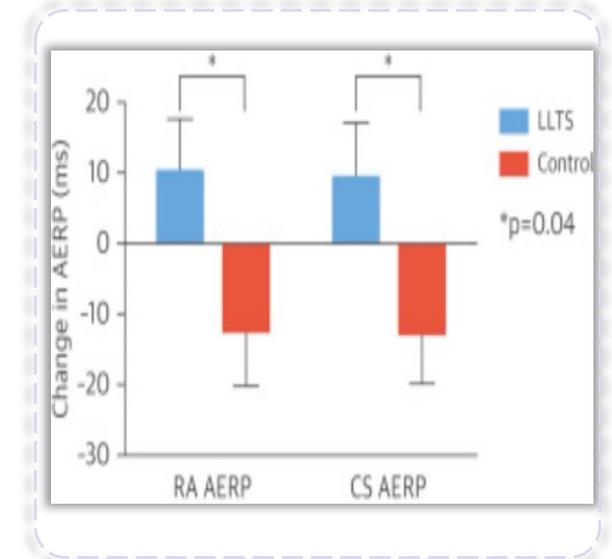
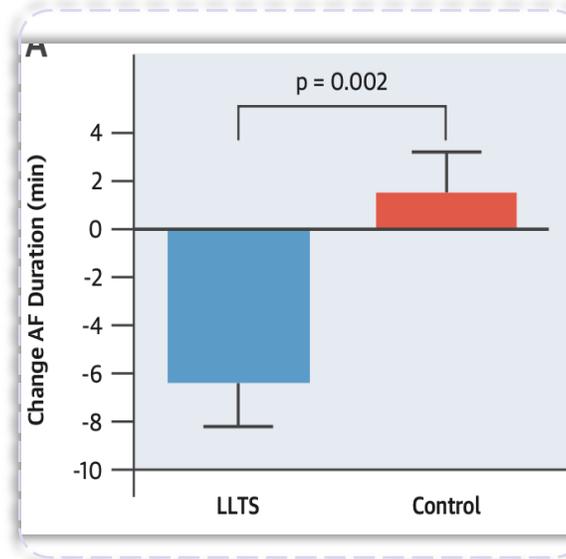
Volume 65, Issue 9, 10 March 2015, Pages 867-875



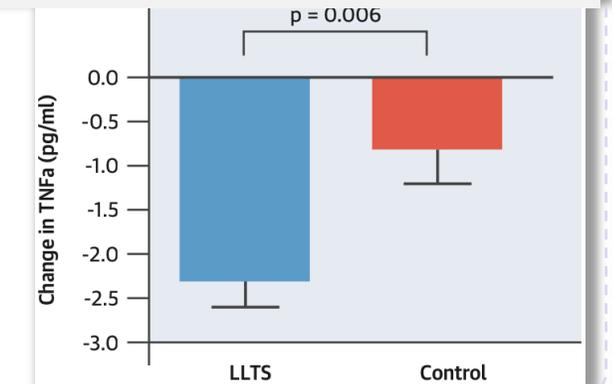
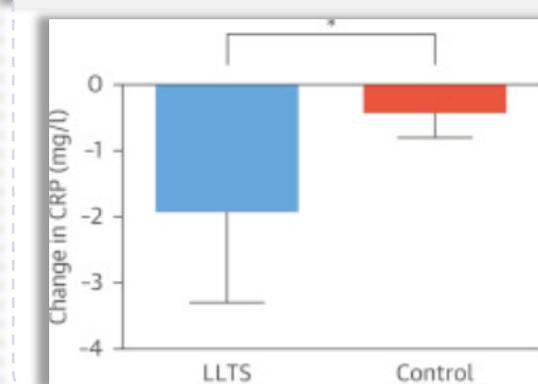
Original Investigation

Low-Level Transcutaneous Electrical Vagus Nerve Stimulation Suppresses Atrial Fibrillation

The study examined antiarrhythmic and anti-inflammatory
effects of LLVNS in humans via tragus nerve stimulation



LLTS significantly resulted in reduction of CRP and TNF-alpha levels



Sources: Stavrakis et al. J Am Coll Cardiol. 2015 Mar 10;65(9):867-75

- Confidential -



Transcutaneous stimulation (tragus nerve) for the *treatment of AF*



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JACC: Clinical Electrophysiology

Volume 3, Issue 9, September 2017, Pages 929-938

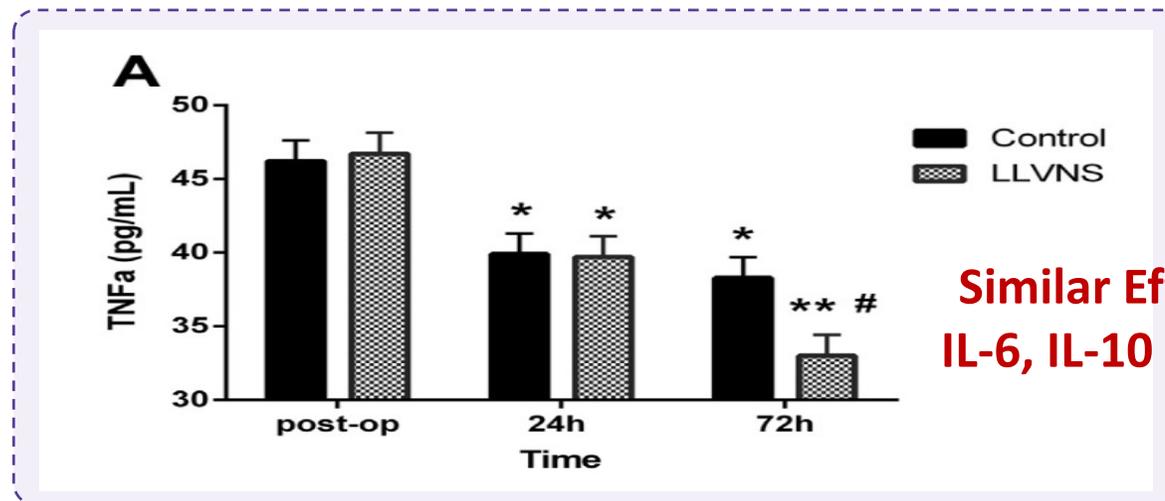
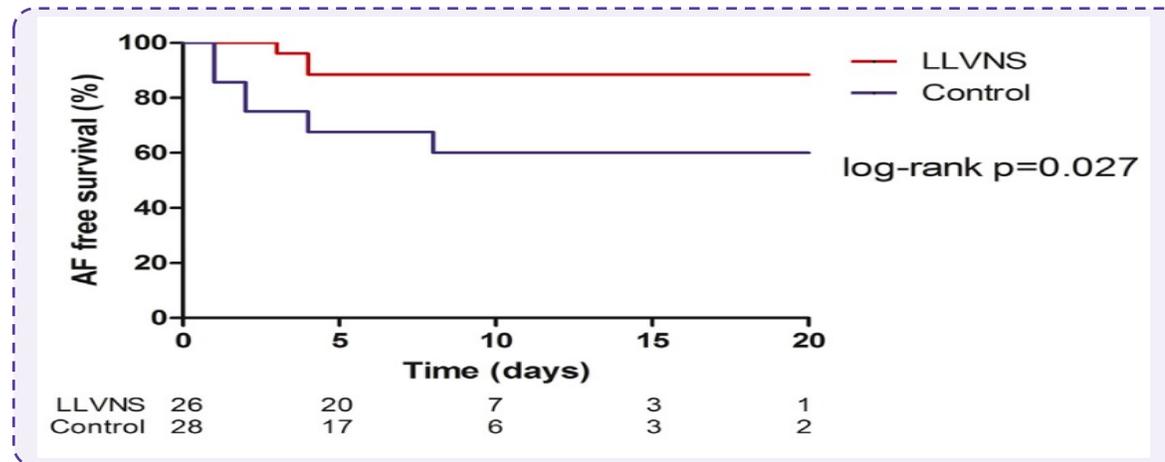


Focus on Neuromodulation of Cardiac Arrhythmias

Low-Level Vagus Nerve Stimulation Suppresses Post-Operative Atrial Fibrillation and Inflammation: A Randomized Study

The study examined antiarrhythmic and anti-inflammatory effects of LLTS suppressing post-operative atrial fibrillation (POAF) and inflammatory cytokines in patients undergoing cardiac surgery

Source: Stavrakis et al. JACC Clin Electrophysiol. 2017 Sep;3(9):929-938

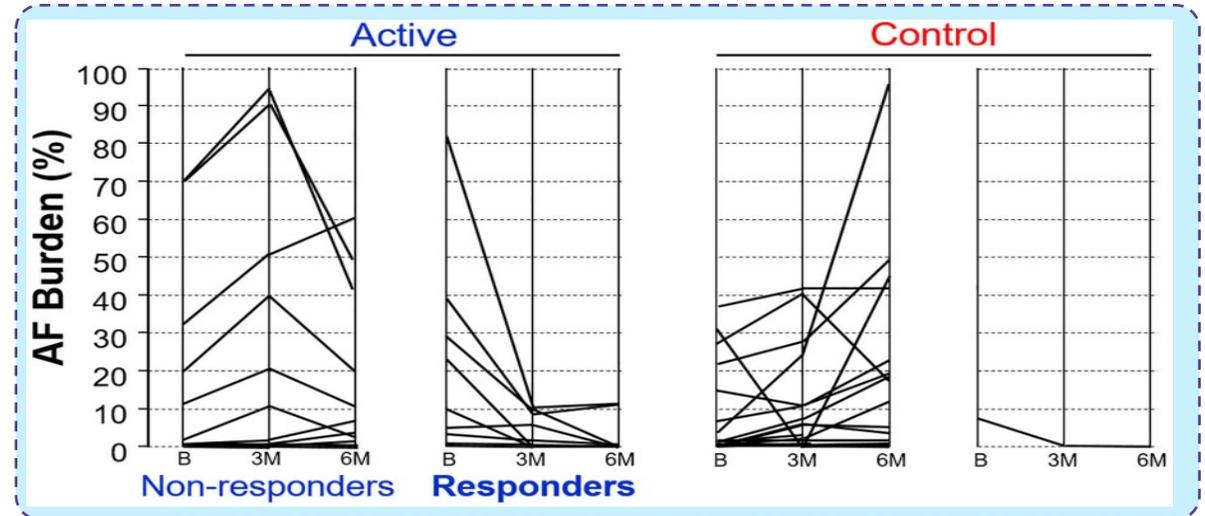
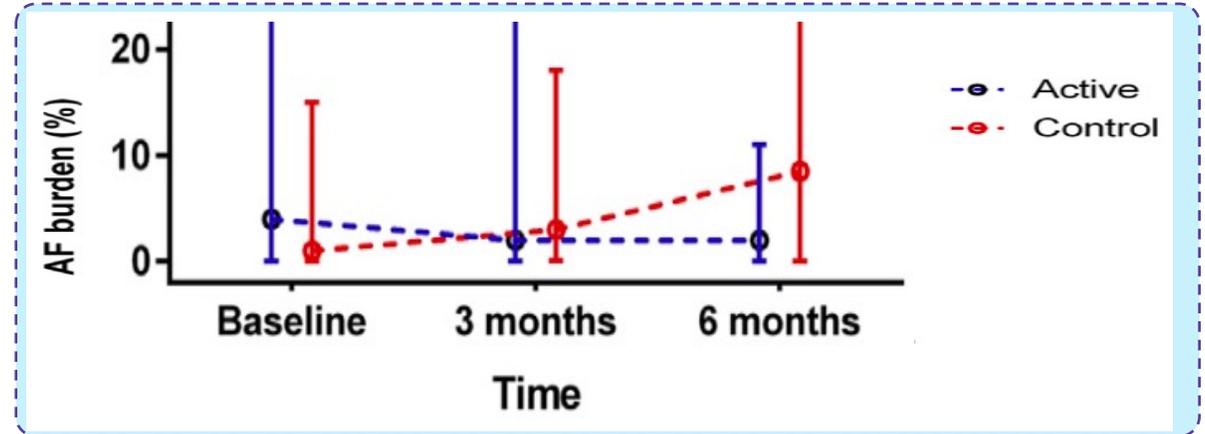


Transcutaneous stimulation (tragus nerve) for the *treatment of AF*

 **JACC: Clinical Electrophysiology**
Volume 6, Issue 3, March 2020, Pages 282-291

Atrial Fibrillation
TREAT AF (Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation): A Randomized Clinical Trial

To examine the effect of chronic low level tragus stimulation (LLTS) in patients with paroxysmal AF



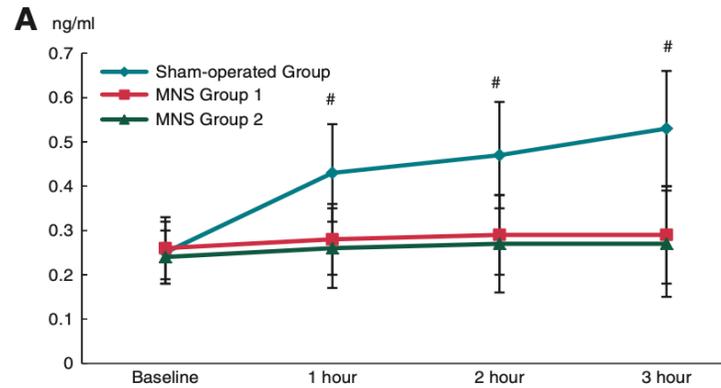
Source: Stavrakis et al. Jacc: clinical electrophysiology vol. 6, no. 3, 2020

Responder rates: 47% (Active) vs 5% (Sham)

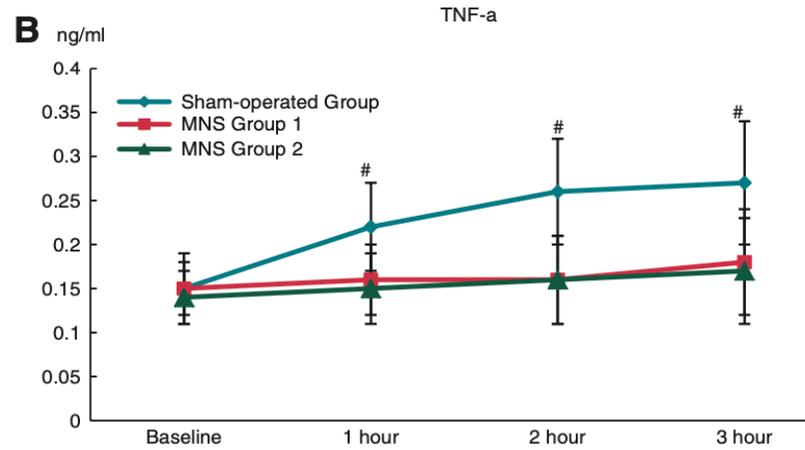
- Confidential -

Transcutaneous stimulation (median nerve) for the *treatment of AF*

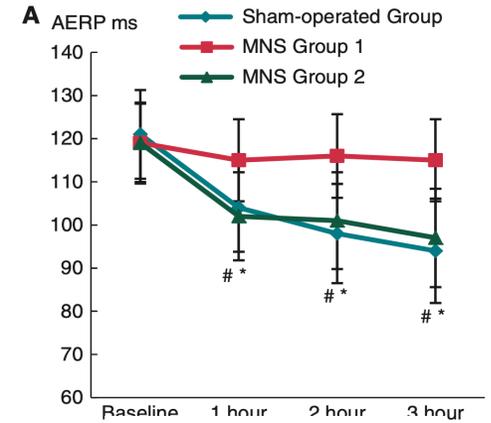
Changes in the plasma levels of TNF-a, IL-6 and acetylcholine (Ach) during 3 h of pacing in the sham-operated group (n = 6), MNS Group 1 (n = 7), and MNS Group 2 (n = 7)



TNF- α



IL-6



AERP

P < 0.05 compared with the baseline condition in the sham-operated group. *P < 0.05 compared with the MNS Group 1 and MNS Group 2 at the same time point

Transcutaneous stimulation (median nerve) for the *treatment of AF*

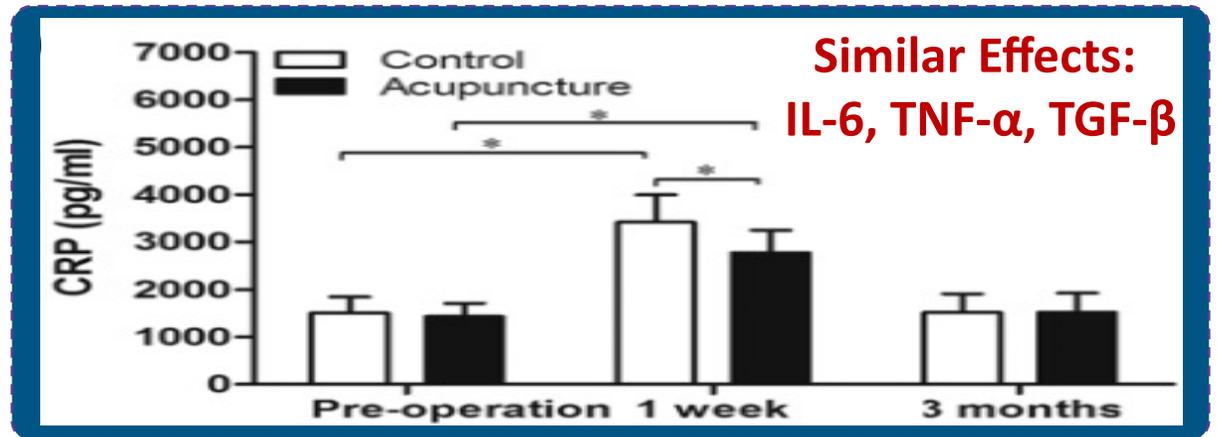
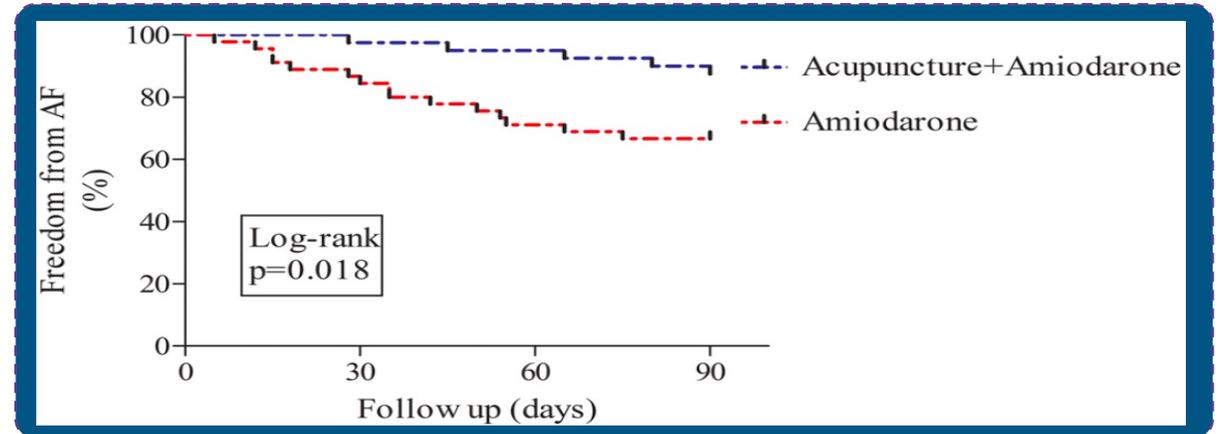
Journal of Cardiovascular Electrophysiology
THE OFFICIAL JOURNAL OF THE WORLD SOCIETY OF ARRHYTHMIAS

World Society of Arrhythmias
Editor-in-Chief
Bradley P. Knight

ORIGINAL ARTICLE

Effect of acupuncture at Neiguan point combined with amiodarone therapy on early recurrence after pulmonary vein electrical isolation in patients with persistent atrial fibrillation

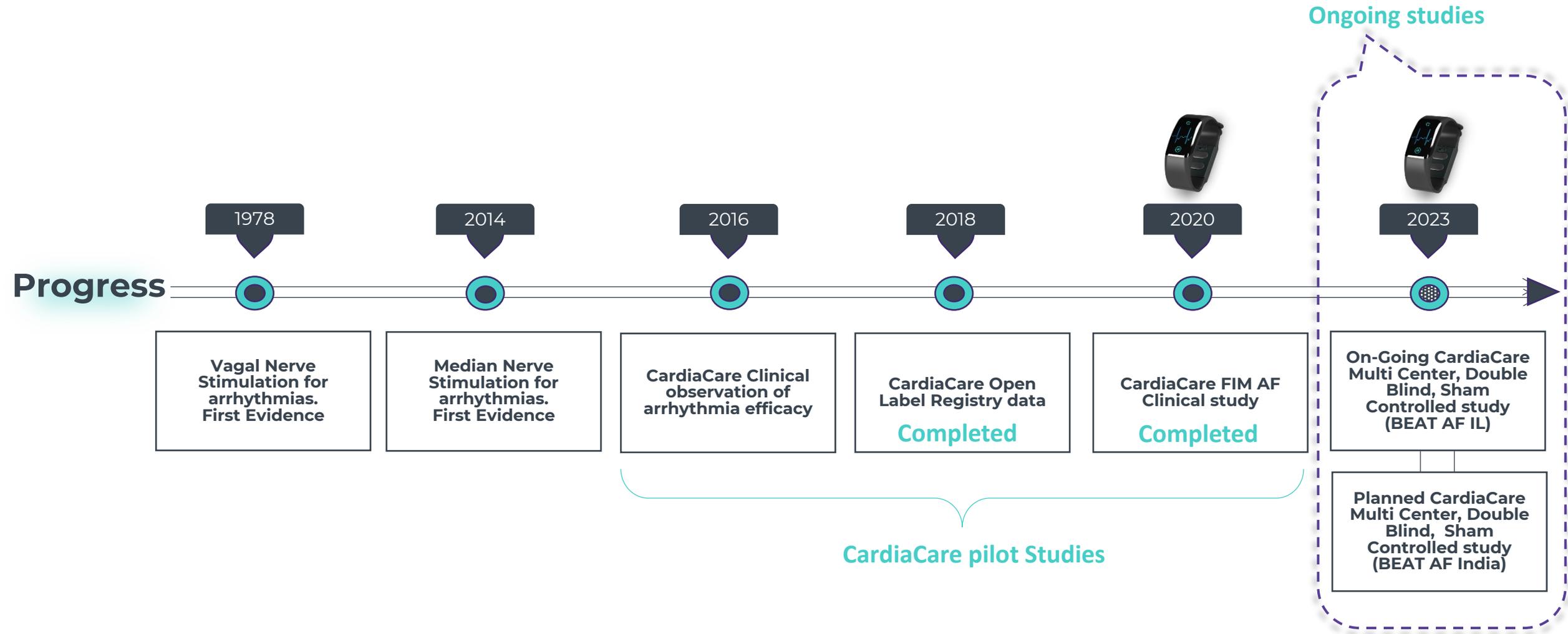
To examine the effect of Neiguan point acupuncture in treatment of persistent AF



Source: Junkui yin et al. J cardiovasc electrophysiol. 2019;30:910-917

CardiaCare Clinical Overview, PoC and FIH evaluations

Development journey of CardiaCare



Pre Clinical study

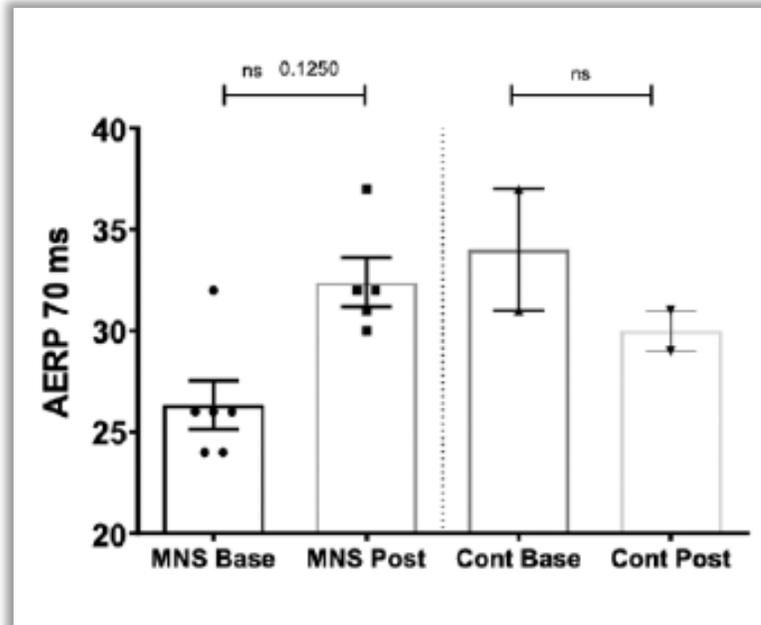
Animal Safety, Mechanism of Action validation and screening of optimal treatment parameters



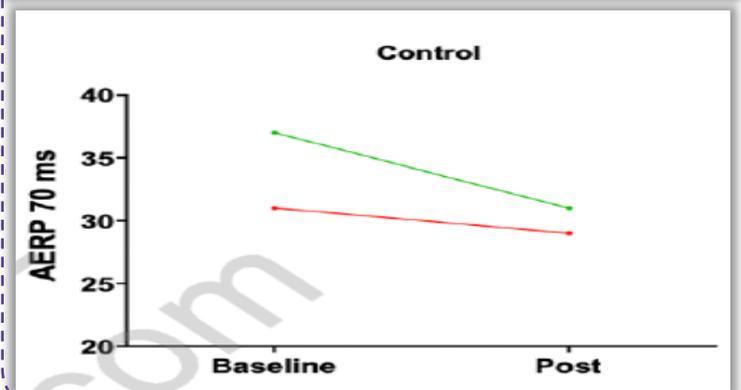
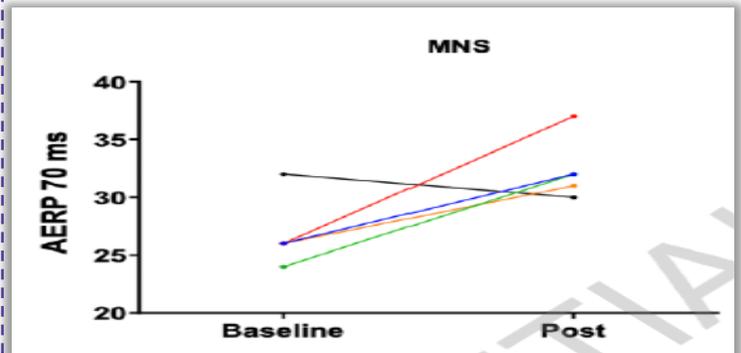
The study examined antiarrhythmic effects of CardiaCare stimulation protocols in a rapid atrial pacing AF induction conscious rat model

- Atrial Fibrillation Rat Model of rapid atrial pacing was used
- Prior to rapid atrial pacing, rats were stimulated with the CardiaCare electrode or with mock sham stimulation for control

Mean AERP was increased after stimulation (MNS post) compared to before stimulation (MNS pre) and decreased in the control rat group



The increase was observed in 4 out of 5 rats in the stimulation treatment arm and was decreased in the control rat arm (2 rats)



FIH Clinical study with CardiaCare in AF patients (n=10)

Journal of Cardiovascular Electrophysiology - January 13-15, 2022 DOI: 10.22541/au.164382361.16457613/v1 ; AFS2022-05. Safety and Feasibility of Home-Care Neuromodulation and Monitoring Wearable Device for Treatment of Atrial Fibrillation. 27th Annual International Atrial Fibrillation Symposium January 13-15, 2022 ([Abstracts from the 27th Annual International Atrial Fibrillation Symposium January 13-15, 2022 \(authorea.com\)](#))

First In Human Safety, Usability and Early Clinical Evidence of CardiaCare Device – A Home-Care 8 Week Study

➤ Patients arriving to the ER with symptomatic AF were recruited, underwent pharmacological or electrical cardioversion, received standard of care medication, and received a 24-hour ECG Holter monitor

➤ They returned the next day for a supervised in-hospital first neuro modulation session and received the device and phone app for 8 weeks of home use

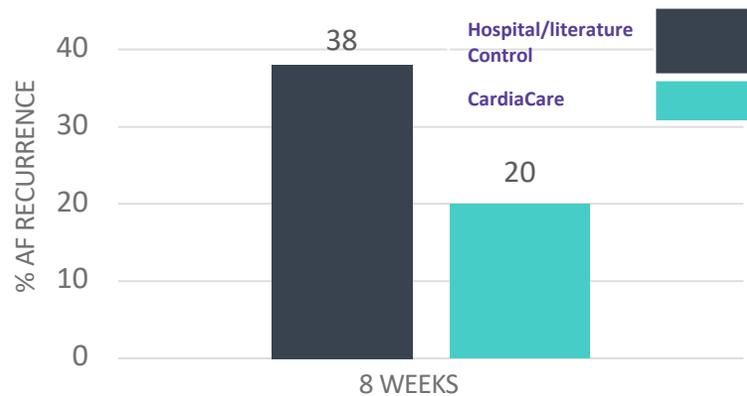
➤ Patients were asked to conduct two neuro modulation sessions a week and three 30 sec ECG monitoring sessions daily

✓ N=10 (mean age 66±12 years, 64% male)

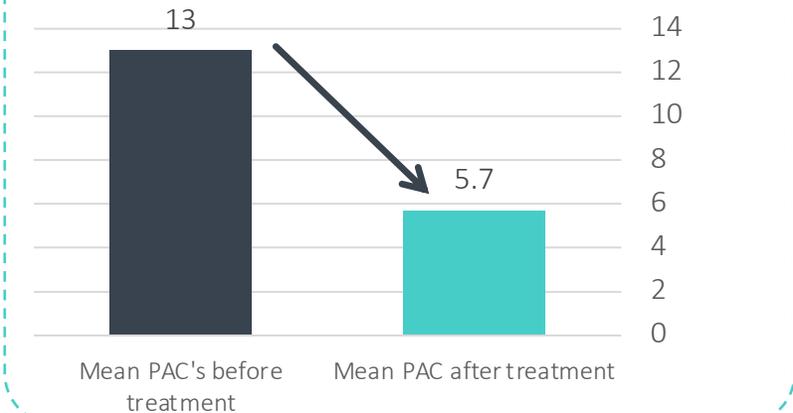
✓ Usability rates were

- 94.7% for ECG monitoring (1675 recorded and analysed)
- 96.8% for neuro modulation (155 treatments, Avg 15.5 per patient)

~50% reduction in AF recurrence after 8 weeks of therapy



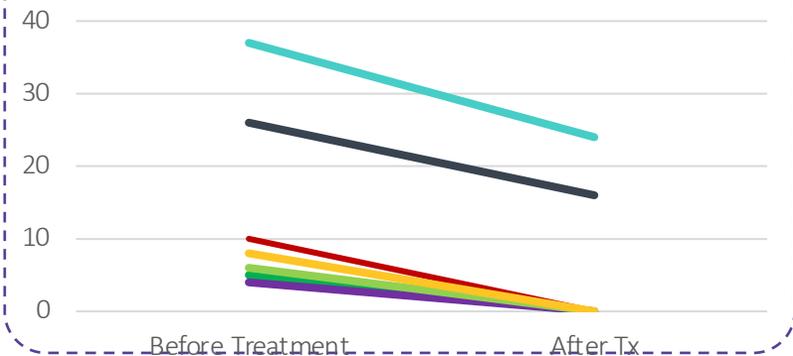
~60% reduction in PACs after 8 weeks of therapy



Safety

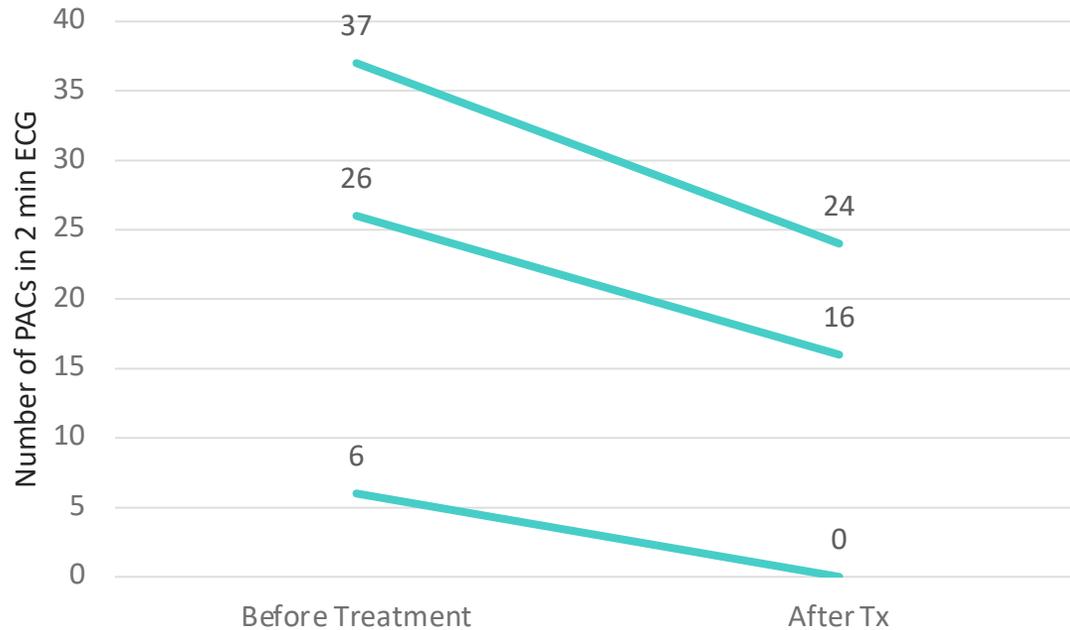
- No unscheduled emergency department re-visits
- No serious Adverse Events were observed
 - One patient reported minimal itching during use of the device,
 - One patient reported feeling more tired
 - One patient had non-device related bradycardia
 - One patient with high AF burden and received an ablation at week 6

PAC'S reduction in individual patients

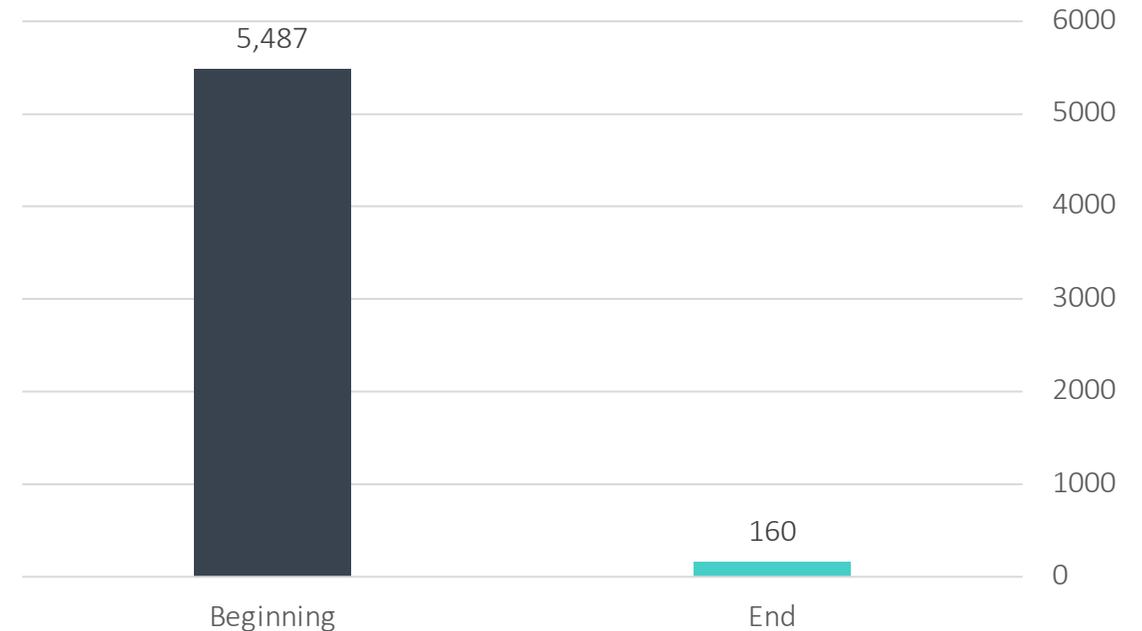


Reduction of PACs- single patient observation

Acute and sustained PAC reduction (single patient)



PAC's significant reduction following 8 weeks' treatment in a single patient (24hr Holter)



Source: *Journal of Cardiovascular Electrophysiology* - January 13-15, 2022 DOI: 10.22541/au.164382361.16457613/v1 ; AFS2022-05. Safety and Feasibility of Home-Care Neuromodulation and Monitoring Wearable Device for Treatment of Atrial Fibrillation. 27th Annual International Atrial Fibrillation Symposium January 13-15, 2022 ([Abstracts from the 27th Annual International Atrial Fibrillation Symposium January 13-15, 2022 \(authorea.com\)](#))

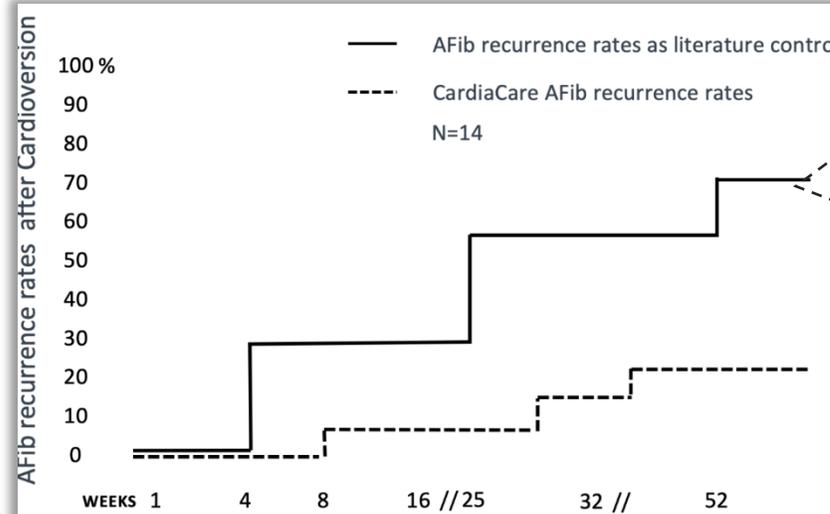
PoC study : retrospective case series with CardiaCare in treatment of AF ; n= 14 (2/3)

Data was collected from June 2018 to September 2020 from two private clinics in Israel and was analysed as a retrospective, open label case registry

- 14 Men and women aged ≥ 18 with symptomatic and ECG documented recent onset atrial fibrillation (AF), lasting less than 48 hours, that have undergone recent (less than 72 hours) electrical cardioversion or spontaneous conversion to normal sinus rhythm (NSR) as evident by an additional documented electrocardiogram (ECG)
- Neuromodulation treatments were delivered weekly, for 10 weeks
 - Each session was conducted for 20 minutes. Following the 10-week period, treatment frequency was reduced to one session every two weeks and then to once a month for the rest of the follow up period (Mean group follow-up was 59 weeks (range 12 - 123))

✓ *No serious adverse events were reported*

Total reoccurrence rates were 7.1% (1 of 14) at 6 months and 21.4% (3 of 14) at 1 year follow up



Despite pharmacological follow-on care, AF recurrence rates after cardioversion are as high as 30% 57% and 71% within 4 weeks, 6 months and 1 year, respectively.

		n	Before	After	% Change	p
AFEQT Score	Total	13	65.5	85.49	23.38	<0.001
	Symptom		66.24	89.67	26.13	<0.001
	Daily Activities		75.82	88.95	14.75	0.057
	Concern		50.58	80.23	36.996	<0.001

Sources: Hindricks G et al. Eur Heart J. 2021;42(5):373-498; Glotzer TV et al. Circulation 2003;107(12):1614-1619; Shanmugam N et al. Europace. 2012;14(2):230-237

PoC study : retrospective case series with CardiaCare in treatment of AF ; n=28 (3/3)

- A retrospective case analysis (ECG data obtained between November 2015 and December 2016) in a mixed population of 28 patients with arrhythmia (AF, PVC, APC, SVT), post MI, hypertension and heart failure, treated with CardiaCare + SoC
- A 2-minute, 1-lead ECG was performed using a strip was performed at baseline and at the end of treatment to compare the effect on arrhythmia burden
- Treatments were administered for 15-25 minutes, once every 7 days, for a total duration of 3-5 weeks

A specific analysis of arrhythmic events and device acute effect was conducted on 28 patients who presented with arrhythmias during their visits

Heart rate & Arrhythmic events before and after treatments (n=28)				
Parameter	Before (mean)	After 3-5 weeks of treatment (mean)	%age change	p Value
Mean HR	73.4	67.49	8.05	<0.001
Mean PACs	15.64	5.97	61.82	0.023
Mean PVCs	10.13	6.56	35.19	0.014
Total PAC	516	197	61.82	n/a
Total PVC	810	525	35.19	n/a

Group mean scores of numbers of arrhythmic beats before and after treatment as recorded by 2 minute ECG in 28 patients that received 140 treatments.
HR: heart rate; PAC: premature atrial complexes; PVC: premature ventricular complexes

Sources: Hindricks G et al. Eur Heart J. 2021;42(5):373-498; Glotzer TV et al. Circulation 2003;107(12):1614-1619; Shanmugam N et al. Europace. 2012;14(2):230-237



MedTech Innovator 2022 Value Award Finalists



THANK YOU!



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