HFA Heart Failure Association
European Society of Cardiology
САНУ СРПСКА АКАДЕМИЈА НАУКА И УМЕТНОСТИ
УНИВЕРЗИТЕТ У БЕОГРАДУ МЕДИЦИНСКИ ФАКУЛТЕТ
KLINIČKI CENTAR SRBIJE
Heart failure Society of Serbia

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Vice-president, European Society of Cardiology

President, Heart Failure Association of the ESC (2018-2020)

Emerging alternatives for decongesting HF

Academician, Serbian Academy of Sciences and Arts

Professor of Cardiology, Belgrade University School of Medicine

President, Heart failure Society of Serbia

ESC European Society of Cardiology
European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1369
POSITION PAPE
Check for updates
HFA Heart Failure Association

The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology

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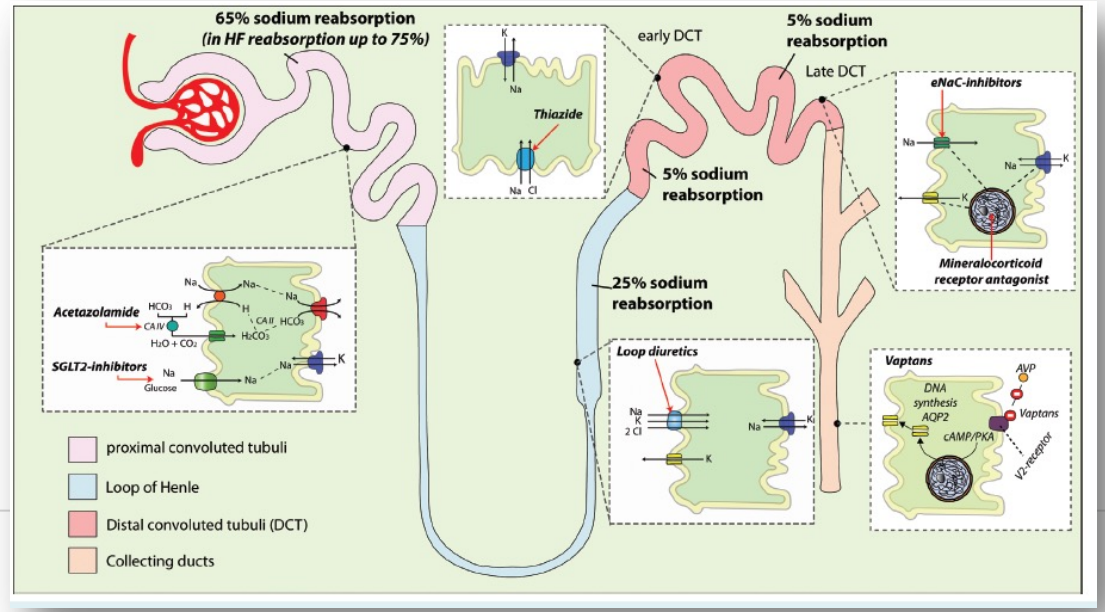
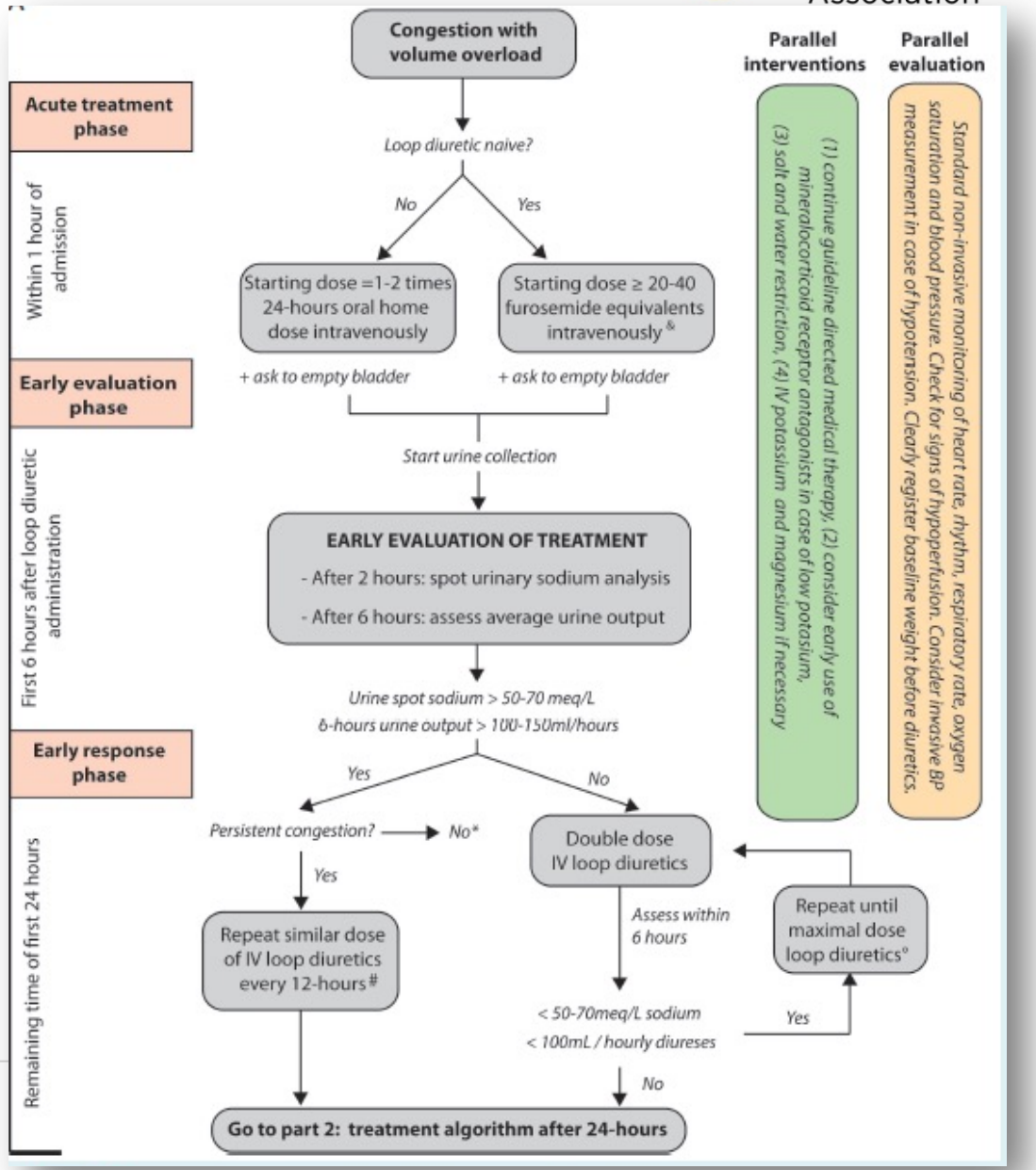
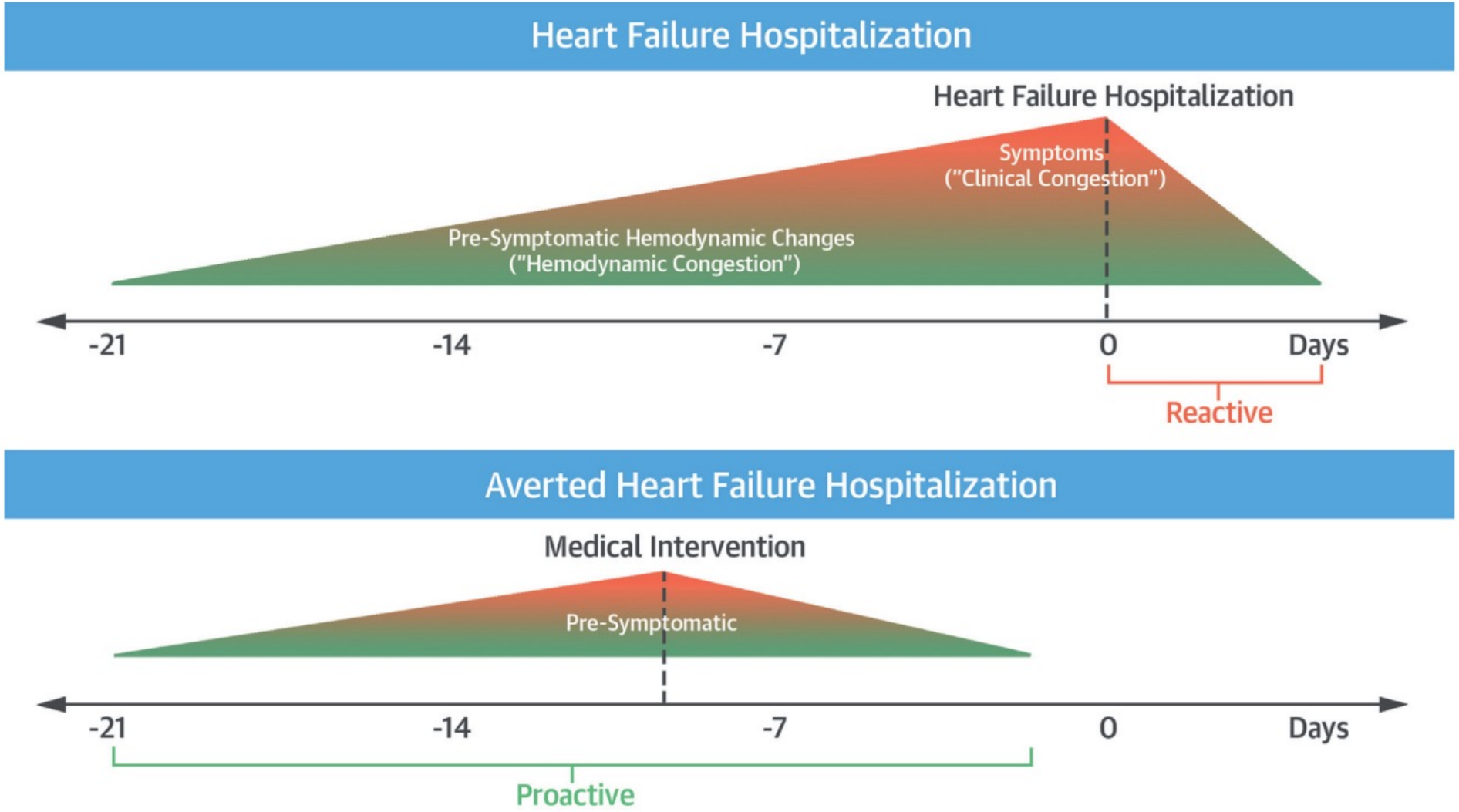




The Concept of Pressure-Guided HF Therapy

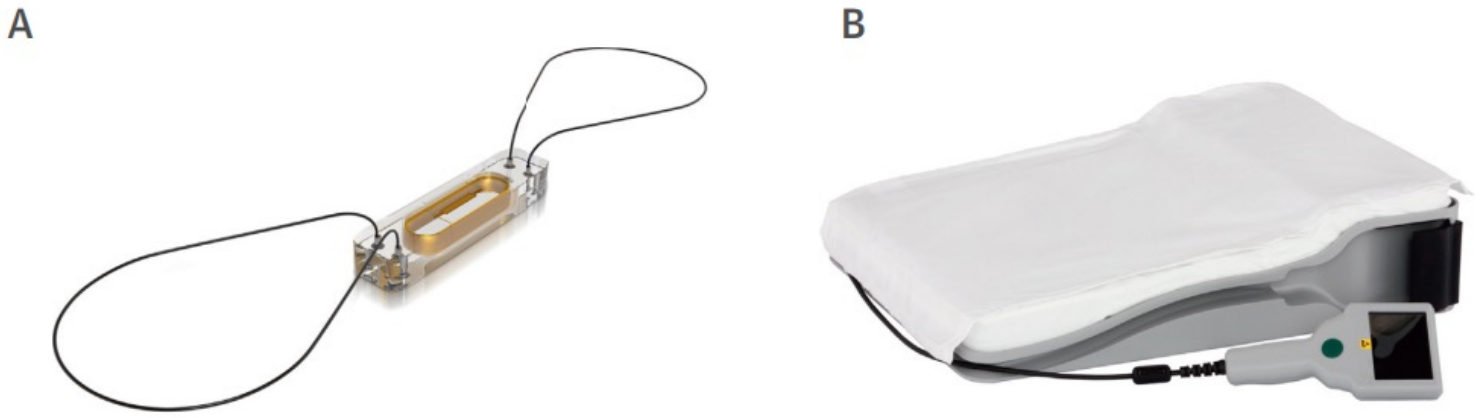


•Signs, symptoms, and weight change poor surrogates for ventricular filling pressures, and unreliable predictors of HF hospitalization

• Proactive approach to HF management: treating hemodynamic congestion during the pre-symptomatic phase of WHF

Abraham, W.T. et al. J Am Coll Cardiol. 2017;70(3):389–98

Components of the CardioMEMS HF System



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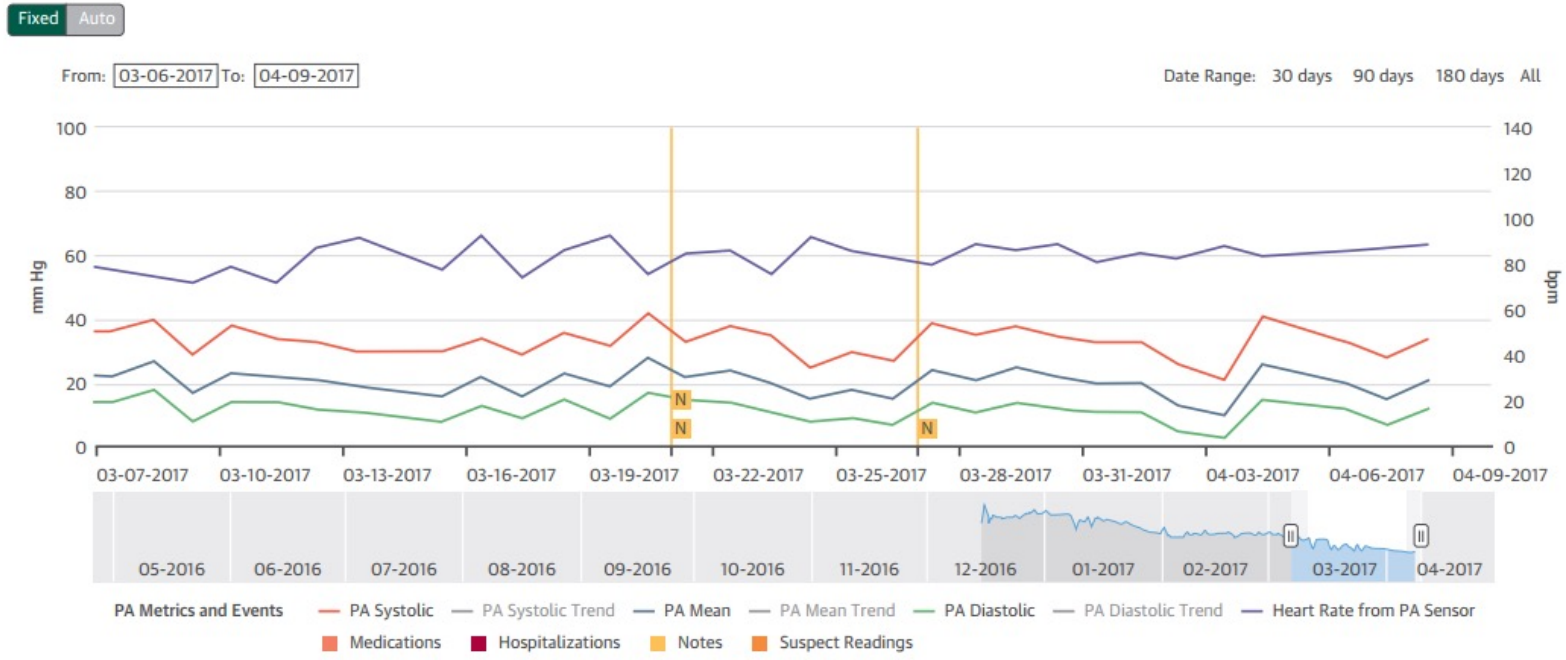


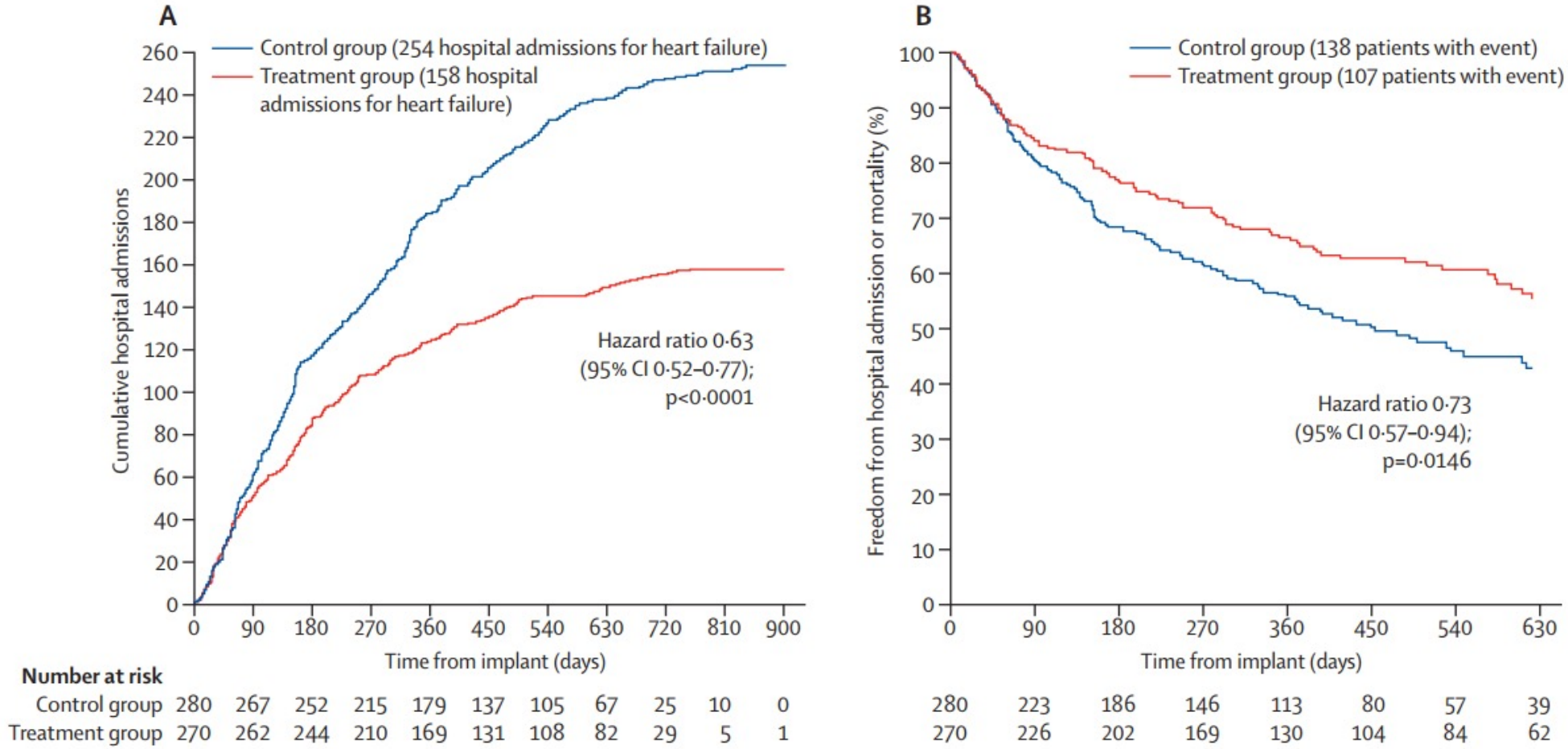
- **Implanted into a branch of the PA during right heart catheterization**
- **Requires no leads or batteries**
- **Concurrently powered and interrogated via an external antenna.**
- **Pressure applied to the sensor causes deflections of the pressure-sensitive surface, resulting in a characteristic shift in the resonant frequency**
- **Electromagnetic coupling achieved by an external antenna held against the patient's body or embedded in a pillow**

Abraham, W.T. et al. J Am Coll Cardiol. 2017;70(3):389–98

CHAMPION Trial

Endpoints

***Incluson criteria: NYHA III, irrespective of LVEF, previos HF hospitalization**



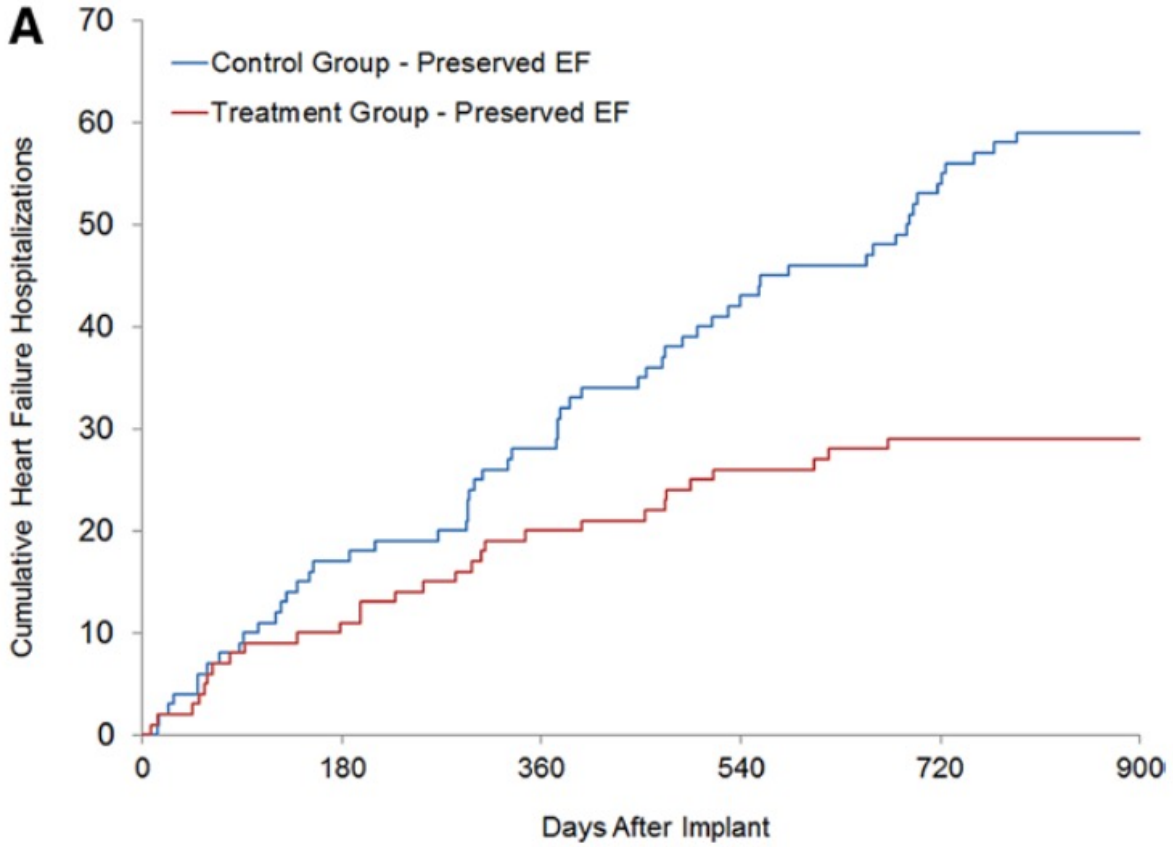
- 6-month risk of **HF hospital admission 30% lower** in the W-IHM group (managed with daily measurement of PAP plus SoC
- **Generalisability to most patients with NYHA class III HF**
- **Major restriction:** exclusion stage IV or V chronic kidney disease (patients might be difficult to treat (ie, diurese)

- **Freedom from device- or system-related complications-98.6%**
- **Overall freedom from pressure-sensor failures-100%**

CHAMPION Trial Study Group. Lancet 2011;377:658–66

CHAMPION Trial

HFpEF subgroup



Heart Failure Hospitalization Rates by Baseline Ejection Fraction Subgroup: Full Duration of Randomized Follow-Up (17.6 Months)

Ejection Fraction	Randomization Group	No. of Heart Failure Hospitalizations	Annualized Rate of Hospitalization for Heart Failure	Incidence Rate Ratio (95% CI; *P* Value)
≥40%	Treatment group (n=62)	29	0.43	0.50 (0.35–0.70; <0.0001)
	Control group (n=57)	59	0.86	
≥50%	Treatment group (n=35)	13	0.41	0.30 (0.18–0.48; <0.0001)
	Control group (n=31)	31	1.39	
<40%	Treatment group (n=208)	153	0.67	0.74 (0.63–0.89; 0.0010)
	Control group (n=222)	220	0.90	

- The primary endpoint of HF hospitalization at **6m 46% lower in the treatment group ($p < 0.0001$)**.
- After average of 17.6 months of blinded follow-up**, hospitalization rate was 50% lower ($p < 0.0001$)**

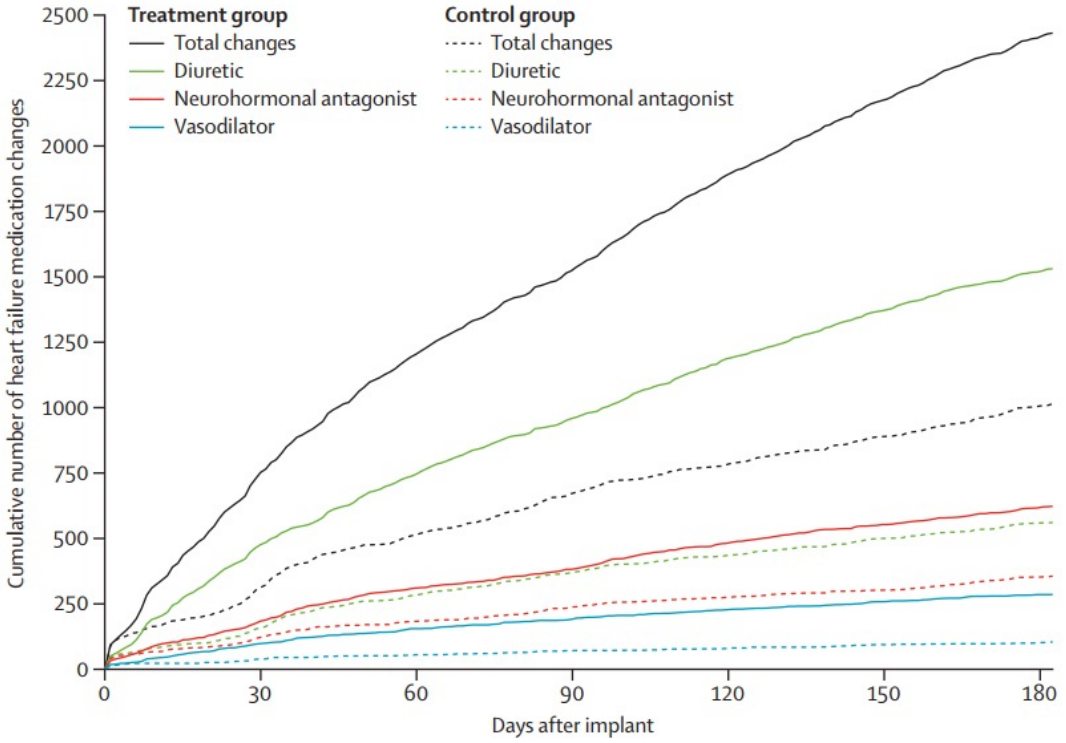
Circ Heart Fail. 2014;7:935-944.

CHAMPION Trial

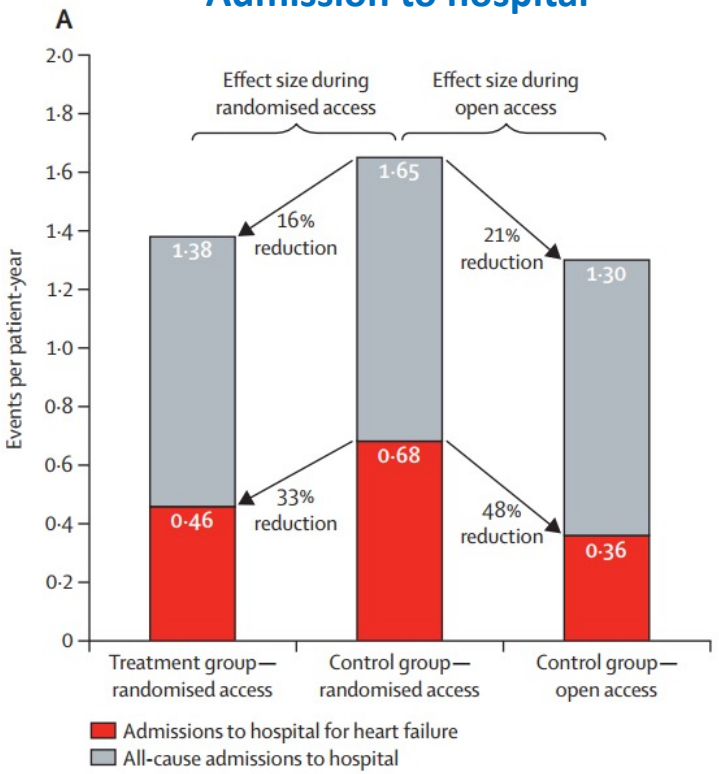
Complete follow-up results

*extended efficacy of this strategy over 18 months of randomised follow-up

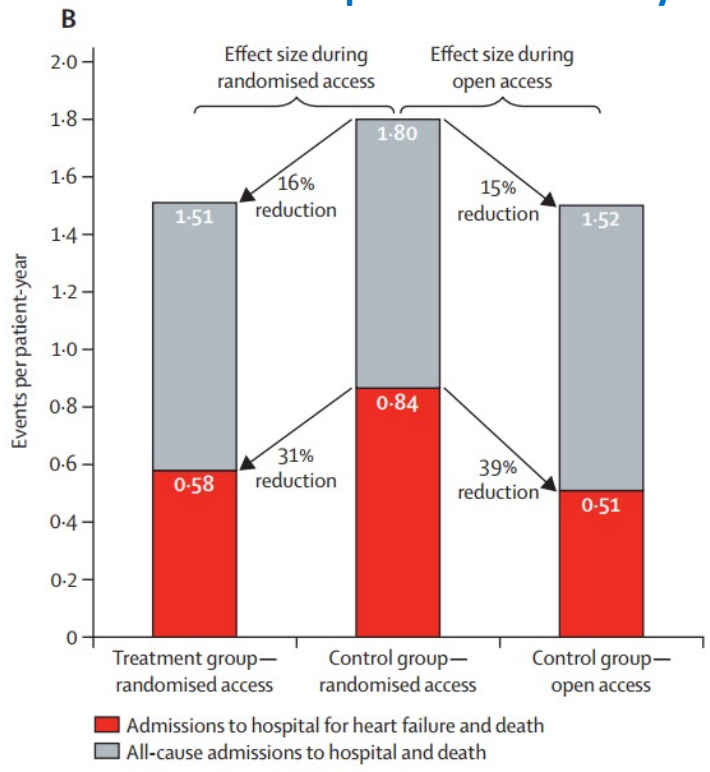
*clinical effect of open access to pressure information for an additional 13 months in patients formerly in the control group



Admission to hospital



Admission to hospital and mortality



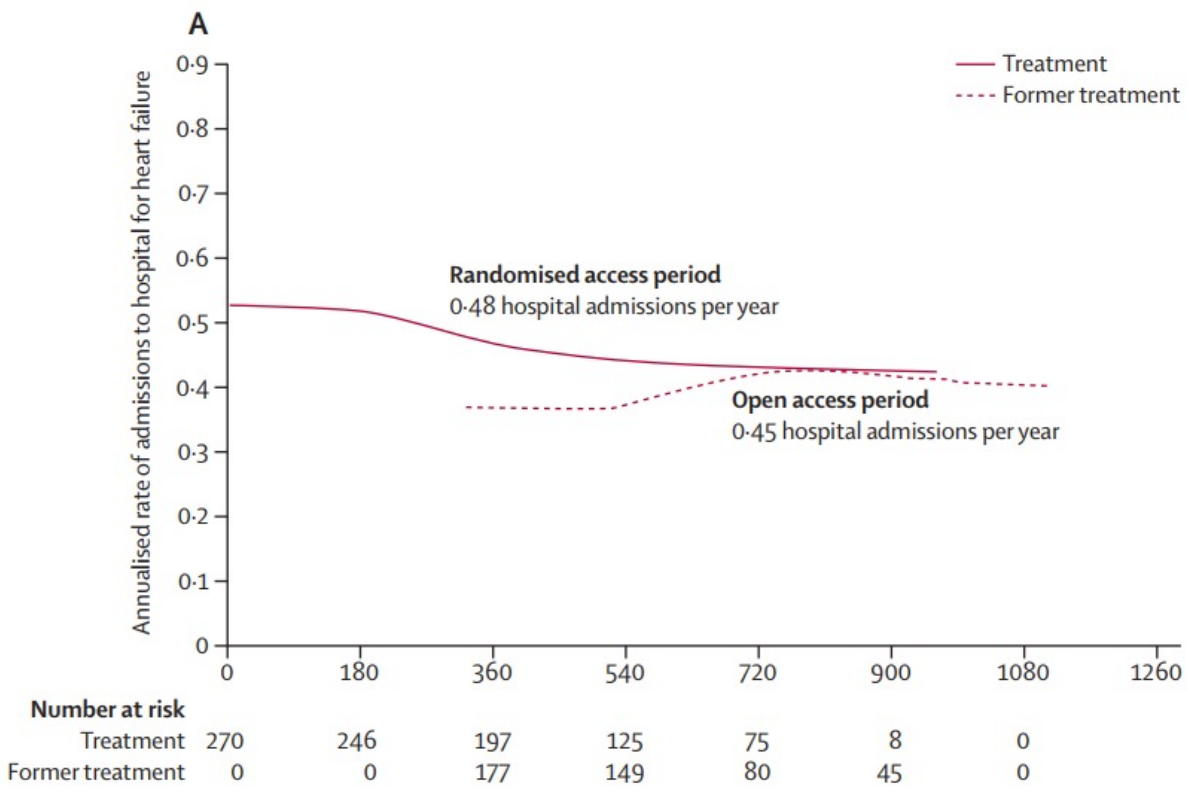
•Patients with CHF managed with PAP information transmitted from an implantable device **have better short-term and long-term clinical outcomes than patients receiving guideline-directed SoC**

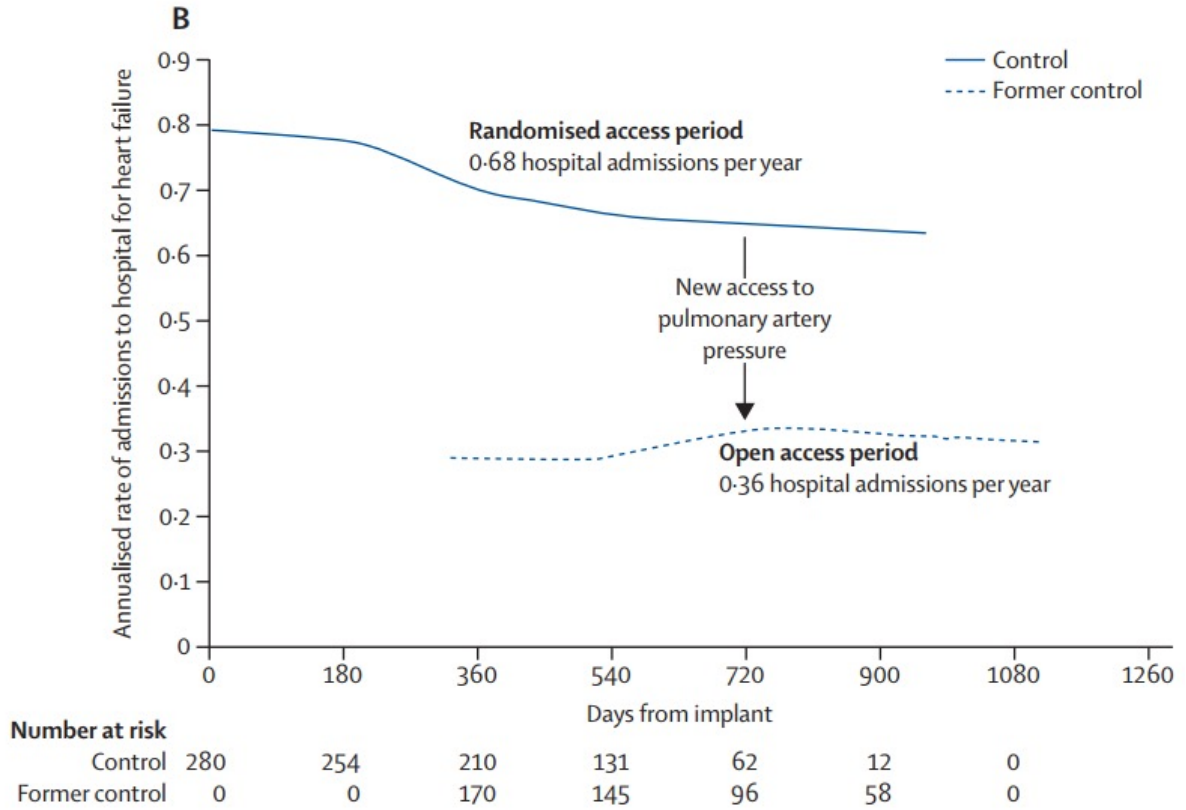
Lancet. 2016 Jan 30;387(10017):453-61

CHAMPION Trial

Complete follow-up results

***extended efficacy of this strategy over 18 months of andomised follow-up and the clinical effect of open access to pressure information for an additional 13 months in patients formerly in the control group**





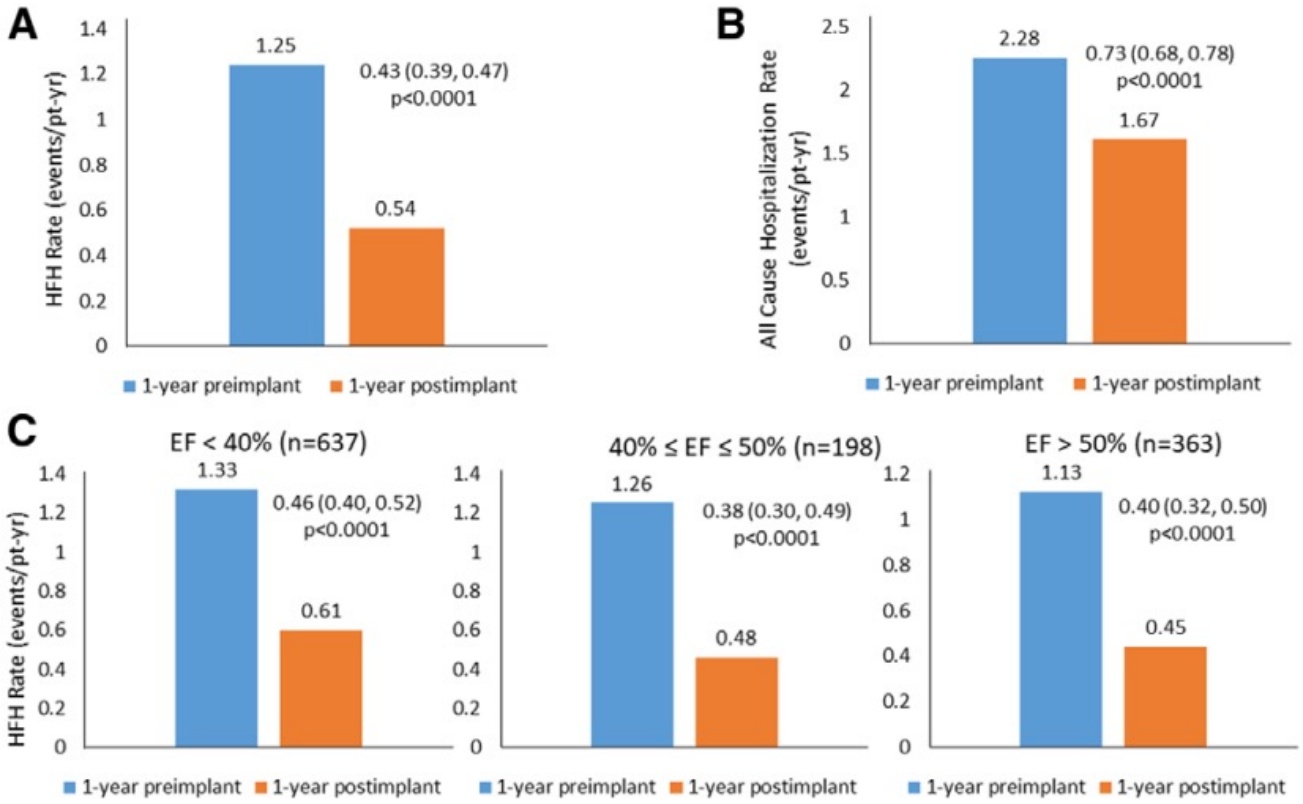
•Patients with CHF managed with PAP information transmitted from an implantable device have **better short-term and long-term clinical outcomes than patients receiving guideline-directed SoC**

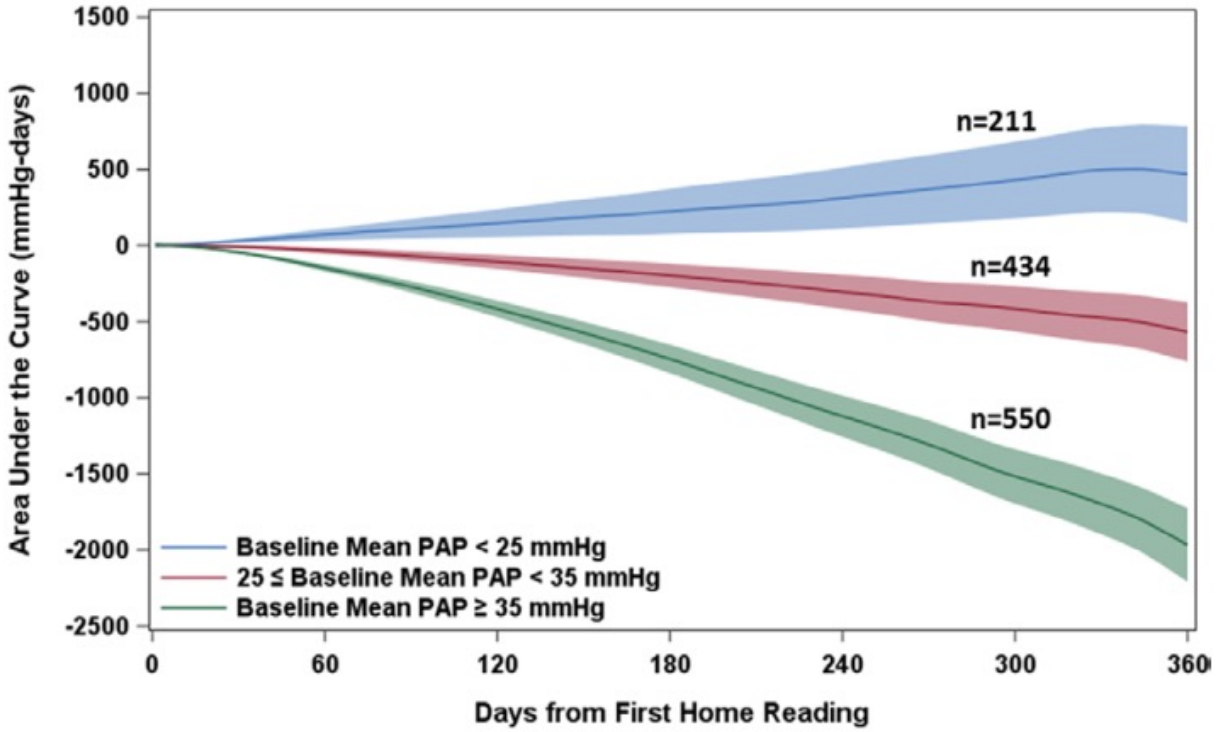
Lancet. 2016 Jan 30;387(10017):453-61

Pulmonary Artery Pressure-Guided Therapy

CardioMEMS Post-Approval Study

***1200 patients, 104 centers, USA**

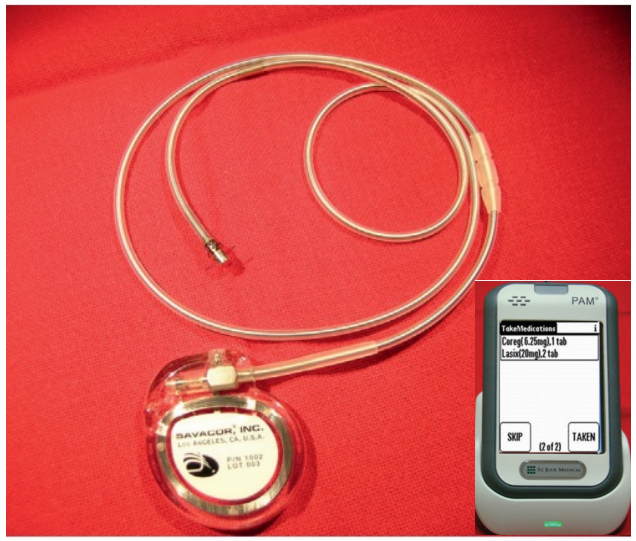




•In routine practice as in clinical trials, PA pressure-guided therapy for HF associated **with lower PA pressures, lower rates of HF** and **all-cause hospitalization, and low rates of adverse events** across a broad range of symptomatic HF and prior HF hosp.

Circ Heart Fail. 2014;7:935-944.

First- and Second-Generation LAP Sensors



HeartPOD left atrial pressure monitoring system

V-LAP left atrial pressure sensor

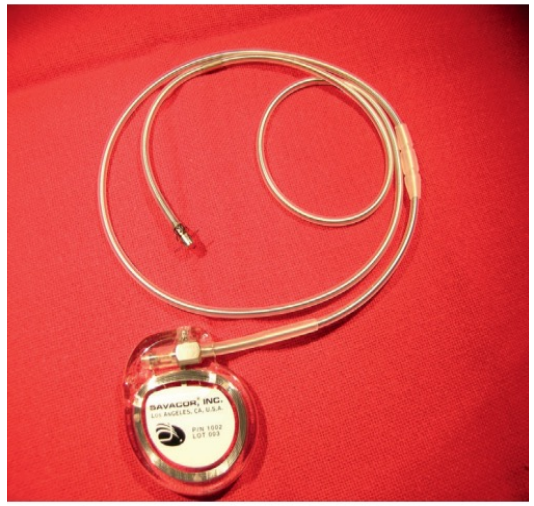
- PAP measurement alone may be an **inaccurate indicator of LVEDP** for many patients with HF
- **Gradient between PAP and mean PCWP (over 5 mm Hg)** in approximately one-half of all patients with HF
- **Pulmonary artery hypertension** (in 25% to 83% of HF) is a significant factor that affects the reliability of PAP measurement for estimating left-sided filling pressure.
- Critical to know **what the pulmonary resistance** is, or more accurately, the gradient between diastolic PAP and mean PCWP (value less dependent upon blood flow, stroke volume, and change in PCWP itself, but will reflect changes in compliance and distensibility of the pulmonary arteries.

J Am Coll Cardiol. 2017;70(3):389–98
J Am Coll Cardiol 2013;62:D100–8
Circulation 2012;126:975–90

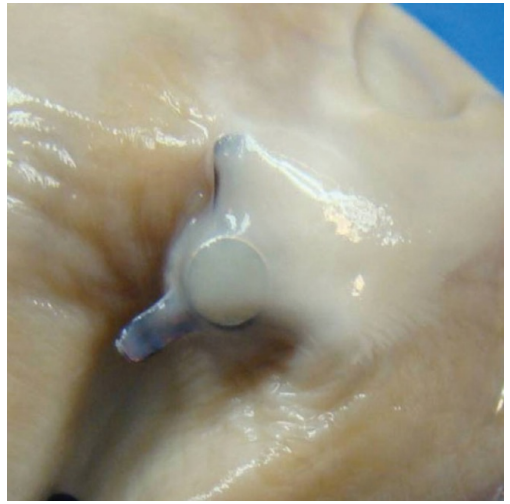
LAPTOP-HF

HeartPOD LAP MONITORING SYSTEM

* Ambulatory NYHA III, with previous HF hospitalization or elevated BNP, regardless of ejection fraction.
* **Enrollment stopped early, due to a perceived excess of implant-related complications**



*The tip of the sensor system lead implanted transvenously into the LA via the atrial septum. The implant powered and interrogated through the skin by wireless transmissions from the patient advisory module

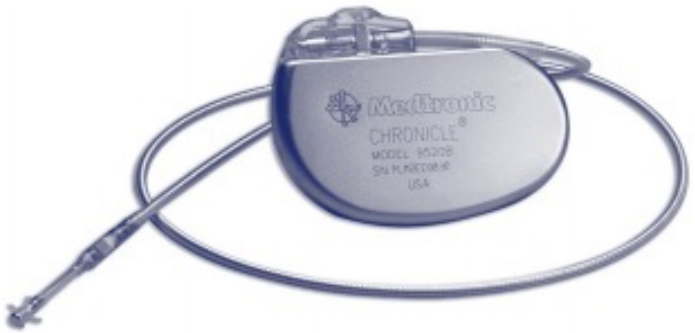


*Autopsy in a patient after 37months of HeartPOD implantation showing endothelialisation of the pressure sensor (reproduced by EJHF with permission by St Jude Medical)

- **The overall trial result negative (no reduction in a combined endpoint of recurrent HF hospitalizations and complications of HF therapy)**
- **When the results were analyzed using the CHAMPION trial endpoint of recurrent heart failure hospitalizations, the results of the LAPTOP-HF trial of were similar to those CHAMPION**
- **(Annualized HFH rates for treatment patients 0.40 vs 0.68 in Control patients, RRR 41%,P=.005)**

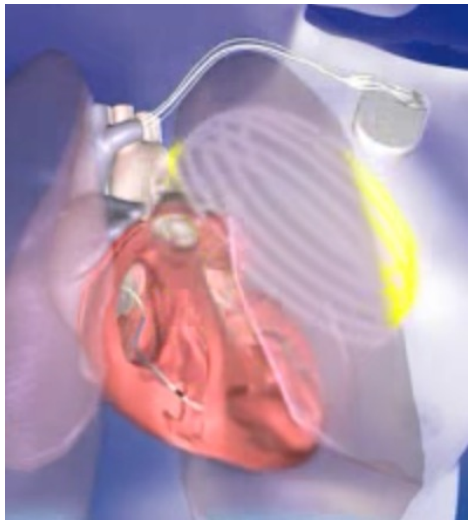
Abraham WT, et al. LAPTOP-HF trial. Card Fail 2016;22:940.

Other pressure monitoring systems



RV MONITOR
ChronicleTM; Medtronic Inc., Minneapolis, MN, USA

REDUCEhf trial prematurely ended after enrolment of 400 patients. No benefit

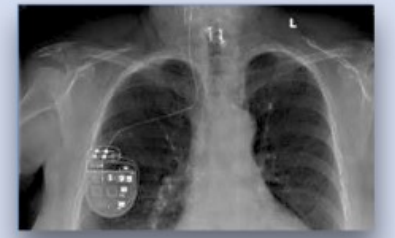


INTRATHORACIC IMPEDANCE MONITORS:
Medtronic Inc. OptiVol Fluid Status Monitor St. Jude Medical (SJM) CorVueTM Congestion Monitor

LUNG FLUID MONITOR
ReDS; Sensible Medical Innovations Ltd, Netanya, Israel.

BAROREFLEX ACTIVATION THERAPY TRIALS

Baroreceptor Activation Therapy



Physiologic target

Parasympathetic activation to quiet persistent sympathetic activation

Target population

Heart failure with reduced ejection fraction on optimal medical therapy

Regulatory status

- Commercially available in Europe (CE Mark)
- PMA approval August 2019
- Pivotal study as part of expedited access pathway including balance of pre and post market data collection and innovative statistical methods

BAROSTIM HOPE4HF (Hope for Heart Failure) 2012 **N=98**	Design: Multicenter, RCT, open-label Inclusion: HF with LVEF #35%,NYHA functional class III Intervention: BAT vs. GDMT Primary endpoint: NYHA functional class, QoL, 6MWT, and 6-month safety	Improvements in all endpoints seen in the BAT group. Major adverse neurological and cardiovascular event-free rate was 97.2%
Gronda et al., 2014 Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac hemodynamics in heart failure: a proof-of-concept study. **N=11**	Design: Open-label Inclusion: NYHA functional class III, LVEF <40% on OMT Intervention: BAT for 6 months Primary endpoint: Measurements of muscle sympathetic nerve activity and measure of QoL and functional capacity	BAT safe and provided chronic improvement in MSNA and clinical variables. May improve these outcomes via modulation of autonomic balance
Zile et al., 2015 Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction: safety and efficacy in patients with and without cardiac resynchronization therapy **N=140** (45 with CRT)	Design: Post hoc analysis Inclusion: Inclusion in BAROSTIM HOPE4HF (Hope for Heart Failure Study), or BAROSTIM NEO System in the Treatment of Heart Failure trial (LVEF <35% and NYHA functional class III) Intervention: Post hoc subgroup analysis of efficacy and safety of BAT in patients with and without CRT Primary endpoint: MANCE, LVEF, QoL scores, and 6MWT	BAT safe and was associated with improved QoL, exercise capacity, NT-proBNP, ejection fraction, and rate of HF hospitalizations in GDMT-treated patients with NYHA functional class III HF. These effects were most pronounced in patients not treated with CRT
Weaver et al., 2016 Surgical experience and long-term results of baroreflex activation therapy for heart failure with reduced ejection fraction. PMID 28043438 (8) **N=146** (76 randomized to BAT)	Design: Multicenter, RCT, open-label Inclusion: Symptomatic HF despite GDMT Intervention: Treatment with BAT and GDMT, or GDMT alone Primary endpoint: 6MWT, NYHA functional class, NT-proBNP level, and QoL	Phase II trial of BAT in HFrEF indicates that the procedure was safe with a pacemaker-like safety profile and a short learning curve.

Modified from Zeitler, E.P. et al. J Am Coll Cardiol HF. 2020;8(4):251–64.

Barostim HOPE4HF

Endpoints

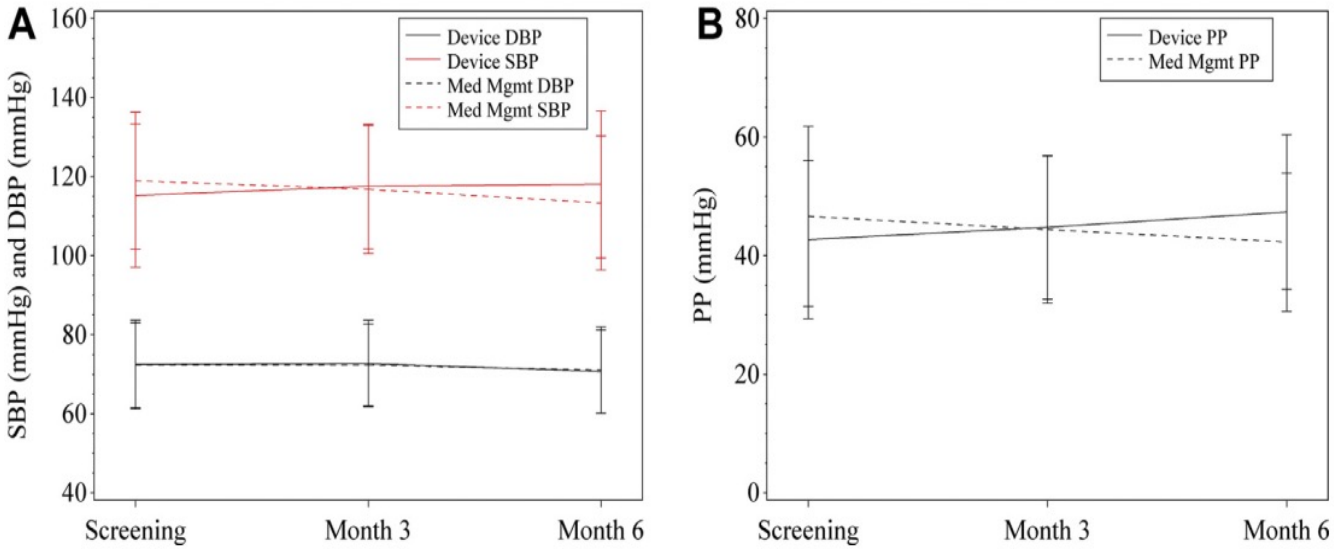
*N=98, GDMT with BAT vs without BAT, LVEF≤35% and NYHA class III

Effect of BAT on Primary Efficacy End Points (Change From Baseline to 6 Months)

	Treatment Group		Control Group		Difference	
	n	Mean ± SE	n	Mean ± SE	Mean ± SE	p Value
NYHA functional class (% improved, same, worse)	64	55%, 42%, 3%	54	24%, 67%, 9%	0.002	
MLWHFQ QoL	64	−17.4* ± 2.8	54	2.1 ± 3.1	−19.5 ± 4.2	<0.001
6MHW distance (m)	56	59.6* ± 14.1	43	1.5 ± 13.2	58.1 ± 19.8	0.004

*p < 0.001 for within-group change.

Effect of BAT on BP



Abraham W et al. JACC HF 2015 Jun;3(6):487-496.

Barostim HOPE4HF

Endpoints

* N=98, GDMT with BAT vs without BAT; LVEF≤35% and NYHA class III

	US and OUS			US			OUS		
	Device (n = 57)	Med Mgmt (n = 50)	Difference (Mean ± SE)	Device (n = 38)	Med Mgmt (n = 32)	Difference (Mean ± SE)	Device (n = 19)	Med Mgmt (n = 18)	Difference (Mean ± SE)
Number of HF hospitalizations per year									
Before enrollment	0.63 ± 1.5	0.36 ± 1.1	0.27 ± 0.3	0.58 ± 1.2	0.13 ± 0.5	0.45* ± 0.2	0.74 ± 1.9	0.78 ± 1.7	−0.04 ± 0.6
Post-randomization	0.14 ± 0.5	0.31 ± 1.0	−0.17 ± 0.1	0.11 ± 0.5	0.24 ± 1.0	−0.13 ± 0.2	0.21 ± 0.6	0.44 ± 0.9	−0.23 ± 0.2
Change from pre to post	−0.49† ± 0.2	−0.05 ± 0.2	−0.44 ± 0.3	−0.47† ± 0.2	0.11 ± 0.2	−0.58† ± 0.3	−0.53 ± 0.5	−0.33 ± 0.5	−0.19 ± 0.7
Negative binomial 6 months post-randomization	0.12	0.25	52% RR‡	0.07	0.16	54% RR‡	0.20	0.42	52% RR‡
HF hospitalizations days per year									
Before enrollment	6.95 ± 20.7	2.40 ± 8.6	4.55 ± 3.1	2.21 ± 4.6	0.44 ± 1.7	1.77† ± 0.9	16.42 ± 33.9	5.89 ± 13.6	10.53 ± 8.6
Post-randomization	0.67 ± 2.5	2.48 ± 7.4	−1.82* ± 1.0	0.58 ± 2.5	0.88 ± 4.0	−0.30 ± 0.8	0.84 ± 2.6	5.33 ± 10.8	−4.49* ± 2.5
Change from pre to post	−6.28† ± 2.7	0.08 ± 1.7	−6.36† ± 3.3	−1.63* ± 0.8	0.44 ± 0.8	−2.07* ± 1.2	−15.58 ± 7.7	−0.56 ± 4.5	−15.02 ± 9.1
Negative binomial 6 months post-randomization	0.38	2.10	82% RR*‡	0.09	0.67	86% RR‡	0.80	4.91	84% RR‡

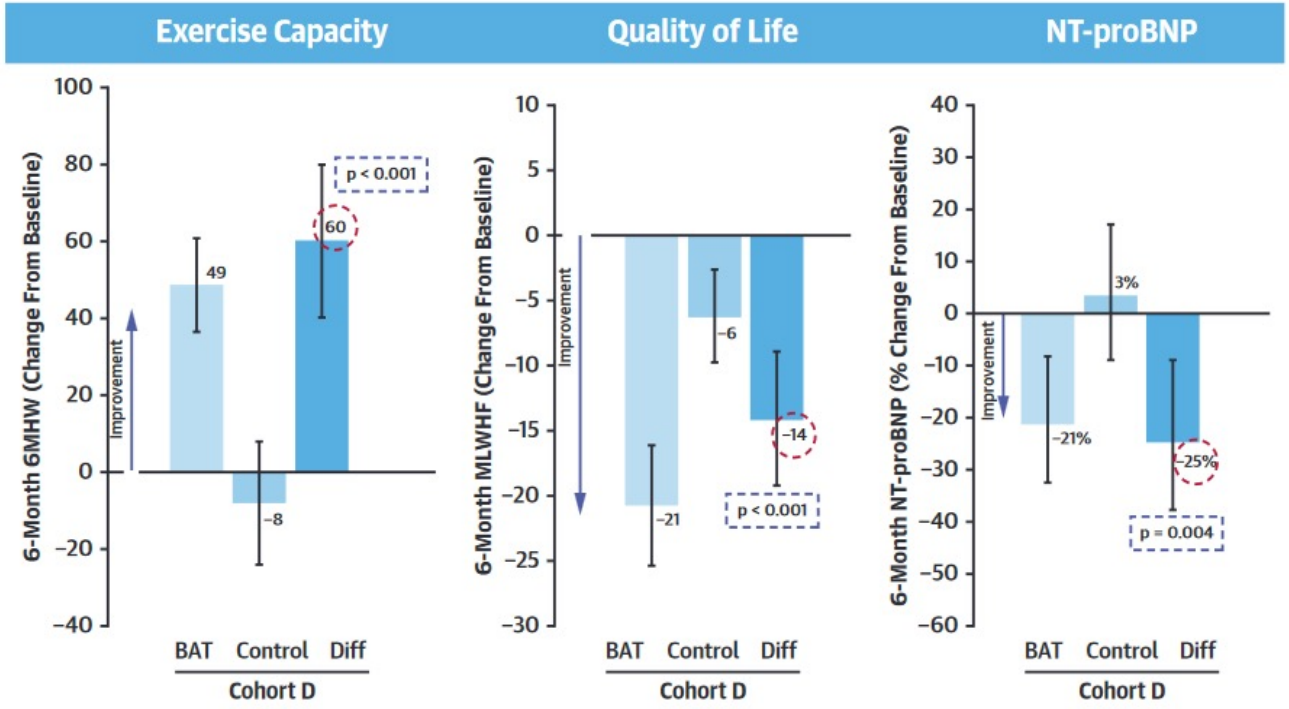
- **BAT safe and improves functional status, QoL, exercise capacity, NTpro–BNP and possibly the burden of heart failure hospitalizations**,
- Patients with subcutaneous ICD or left ventricular assist devices excluded

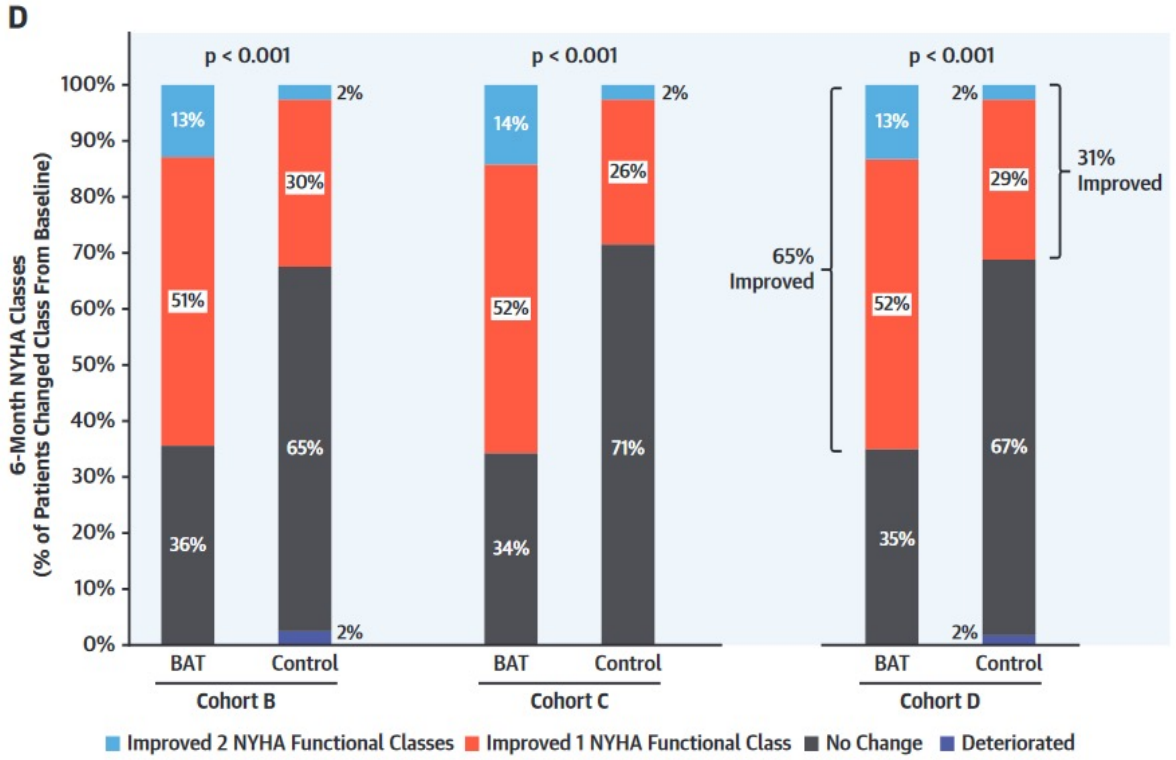
Abraham W et al. JACC HF 2015 Jun;3(6):487-496.

BeAT-HF

Endpoints

*N=140, GDMT with BAT vs without BAT, NYHA class III or class II (recent history of NYHA functional class III); LVEF≤35%; stable GDMT for 4 weeks; and no Class I indications for CRT



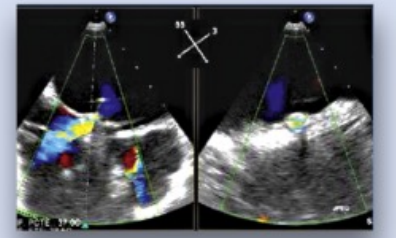


- **BAT safe and significantly improved QOL, exercise capacity, and NT-proBNP**
- Patients with subcutaneous ICD or left ventricular assist devices excluded

Zile M et al. J Am Coll Cardiol 2020;76:1–13

INTERATRIAL SHUNT DEVICE TRIALS

Interatrial Shunt Device



Physiologic target

Shunting of blood volume from left to right heart to relieve left atrial pressure

Target population

Heart failure (with or without LVEF) with elevated left atrial pressures

Regulatory status

- No devices currently approved to establish left to right shunting in heart failure
- Ongoing pivotal evaluation for this indication by multiple manufacturers

Sondergaard et al., 2014 Transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel interatrial implant to lower left atrial pressure. **N=11**	Design: Open-label Inclusion: LVEF ≥45%, at least 1 HF hospitalization in the past year, PCWP at rest ≥15 mm Hg or during exercise ≥25 mm Hg Intervention: Treatment with IASD Primary endpoint: SADEs through 30 days	The IASD was successfully implanted in a cohort of HFpEF patients and resulted in improved hemodynamic values at rest, with encouraging early clinical response
Malek et al., 2015 Clinical outcome of transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel implant. **N=11**	Design: Open-label Inclusion: LVEF ≥45%, at least 1 HF hospitalization in the past year, PCWP at rest ≥15 mm Hg or during exercise ≥25 mm Hg Intervention: Treatment with IASD Primary endpoint: SADEs through 30 days	Placement of the IASD in a cohort of HFpEF patients produced decreased filling pressures and was associated with clinical improvement at 1 yr in most patients
Kaye et al., 2016 1-year outcomes after transcatheter insertion of an interatrial shunt device for the management of heart failure with preserved ejection fraction. **N=64**	Design: Open-label Inclusion: Chronic symptomatic HF (NYHA functional class II or III/ambulatory class IV), LVEF ≥40%, elevated left ventricular filling pressures Intervention: Implantation of interatrial shunt Primary endpoint: MACCE	Evidence of safety and sustained clinical benefit in HFpEF patients 1 yr after interatrial septal shunt device implantation
Del Trigo et al., 2016 Unidirectional left-to-right interatrial shunting for treatment of patients with heart failure with reduced ejection fraction: a safety and proof-of-principle cohort study. **N=10**	Design: Open-label (Canada) Inclusion: NYHA functional class III with chronic HFrEF Intervention: Implant of V-Wave shunt device after trans-septal catheterization Primary endpoints: Clinical and echocardiography evaluations at baseline, month 1, and month 3	Demonstrates initial safety and early beneficial clinical and hemodynamic outcomes in patients with HFrEF
Shah et al., 2018 1-year safety and clinical outcomes of a transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction in the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF I) Trial: a randomized clinical trial. **N=44**	Design: Multicenter, RCT, double-blind, sham-controlled Inclusion: Chronic symptomatic HF, ongoing stable GDMT, LVEF ≥40%, elevated left atrial pressure with gradient Intervention: Implantation of IASD, or intracardiac echocardiogram Primary endpoint: Change in supine exercise PCWP from baseline	Demonstrates the long-term patency of the IASD. Through 1 yr of follow-up, IASD treatment appears safe, with no significant differences in MACCRE in patients receiving IASD compared with those who received sham- controlled treatment
Hasenfuss et al., 2016 A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicenter, open-label, single-arm, phase 1 trial. **N=68**	Design: Open-label Inclusion: Symptoms of HFpEF despite pharmacological therapy, LVEF ≥40%, PCWP at rest >15 mm Hg or exercise >25 mm Hg Intervention: Treatment with IASD Primary endpoints: Safety and performance of IASD at 6 months, measure of clinical efficacy including function capacity and clinical status	Implantation of this IASD is feasible, appears safe, and reduces left atrial pressure during exercise

Modified from Zeitler, E.P. et al. J Am Coll Cardiol HF. 2020;8(4):251–64.

Intratrial shunt device

Endpoints in HFpEF and HFmREF

IASD®, DC Devices Inc., Tewksbury, MA, US

	HFH		NYHA class		6 MWTD (M)		MLWHF	
	Prior year	Year after	Baseline	1 Year	Baseline	1 Year	Baseline	1 Year
Median	1	0	3	2.5	334	364	58	29.5
Range	0 to 6	0 to 5	III–IV	II–III	52–540	240–494	17–70	14–62
Mean	1.5	0.8[1]	3.2	2.5[2]	309.6	351.7[3]	54.9	36.3[4]
STDEV	1.90	1.75	0.42	0.53	158.8	79.4	17.0	16.5

HFH = heart failure hospitalizations, 6MWTD = six minute walk test distance, MLWHF = Minnesota Living With Heart Failure, STDEV = standard deviation.

[1] p = 0.030 vs. baseline.
[2] p = 0.017 vs. baseline.
[3] p = NS vs. baseline.
[4] p = 0.057 vs. baseline.

- **PCWP had significantly decreased by 28% from 19.0 ± 5 to14 ± 3 mmHg (p= 0.005). RAP and SPAP unchanged.**

Malek et al. International Journal of Cardiology 187 (2015) 227–228

Patient	mRAP (mmHg)		mPAP (mmHg)		mPCWP (mmHg)		CI (L/min/m²)		PVRI (Wood/m²)	
	Baseline	30 days	Baseline	30 days	Baseline	30 days	Baseline	30 days	Baseline	30 days
1	5	9	25	23	16	12	2.4	3.5	3.8	3.1
2	15	15	39	20	20	12	2.6	3.3	7.3	2.4
3	11	9	36	39	17	13	2.1	4.7	9.0	5.5
4	7	16	27	27	20	18	2.0	3.5	3.5	2.6
5	12	9	36	25	25	9	2.2	2.9	5.0	5.5
6	12	12	37	32	23	18	2.1	2.3	6.7	6.1
7	N/A	N/A	N/A	N/A	16	N/A	2.7	N/A	N/A	N/A
8	11	9	27	24	18	13	3.3	2.3[a]	2.7	4.1
9[b]	14	14	35	30	20	16	2.0[a]	3.9	7.5	3.6
10[b]	14	11	22	19	18	11	1.9[a]	2.6	2.1	3.1
11[b]	7	N/A	19	26	17	18	1.6[a]	N/A	1.3	N/A
Median (range)	12 (5–14)	9 (9–16)	31 (19–39)	26 (19–39)	19 (6–25)	13 (9–18)	2.3 (1.6–3.3)	–	4.4 (1.3–9.5)	–
Mean ± SD	12 ± 3	11 ± 3	30 ± 7	27 ± 6	19 ± 5	14 ± 3	2.4 ± 0.4	–	4.9 ± 2.7	–
	P = NS		P = NS		P = 0.005					

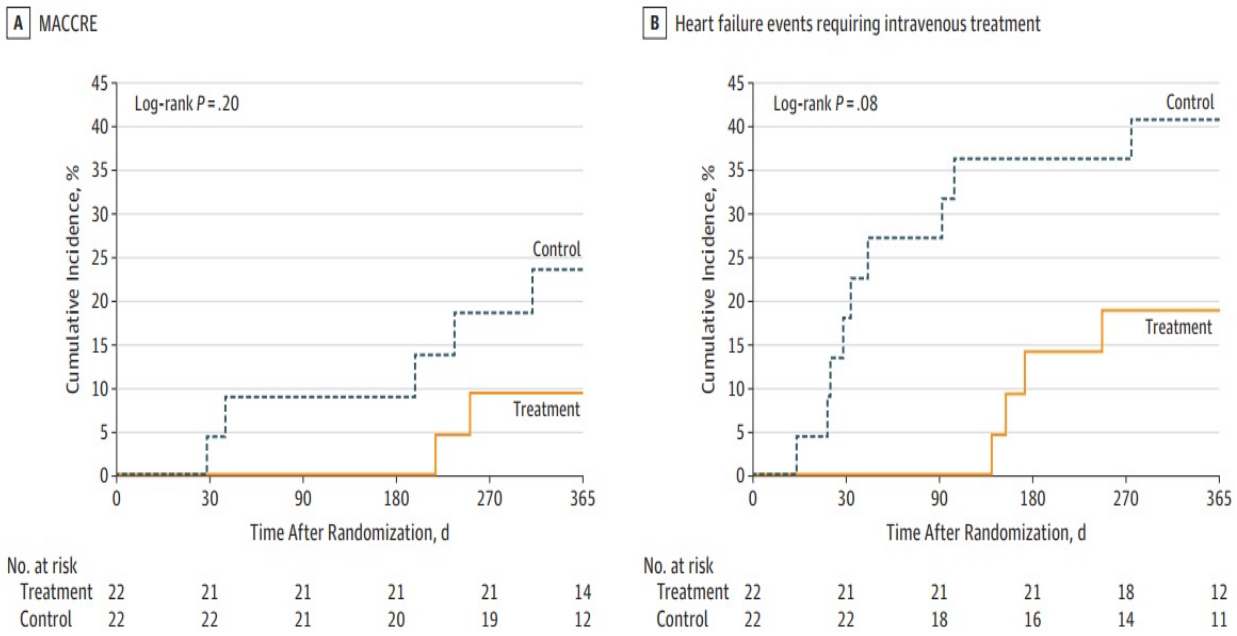
Patient	NT-proBNP		6-MWD (m)		MLWHF score		NYHA class	
	Baseline	30 days	Baseline	30 days	Baseline	30 days	Baseline	30 days
1	461	330	368	410	34	19	III	II
2	416	381	238	ND	70	63	III	IV
3	81	89	330	328	17	24	III	III
4	141	141	128	252	62	30	IV	III
5	54	53	540	522	47	9	III	I
6	N/A	N/A	338	364	46	25	III	II
7	N/A	N/A	52	104	66	68	III	III
8	22	8	360	420	56	16	III	III
9[b]	222	368	180	330	78	45	III	II
10[b]	148	160	450	465	47	32	III	II
11[b]	193	383	480	480	60	30	IV	II
Median (range)	148 (22–461)	160 (8–368)	338 (52–540)	387 (104–522)	56 (17–78)	30 (9–68)		
Mean ± SD	193 ± 153	212 ± 152	322 ± 151	368 ± 123	53 ± 17	18 ± 19		
	P = NS		P = 0.025		P = 0.005			

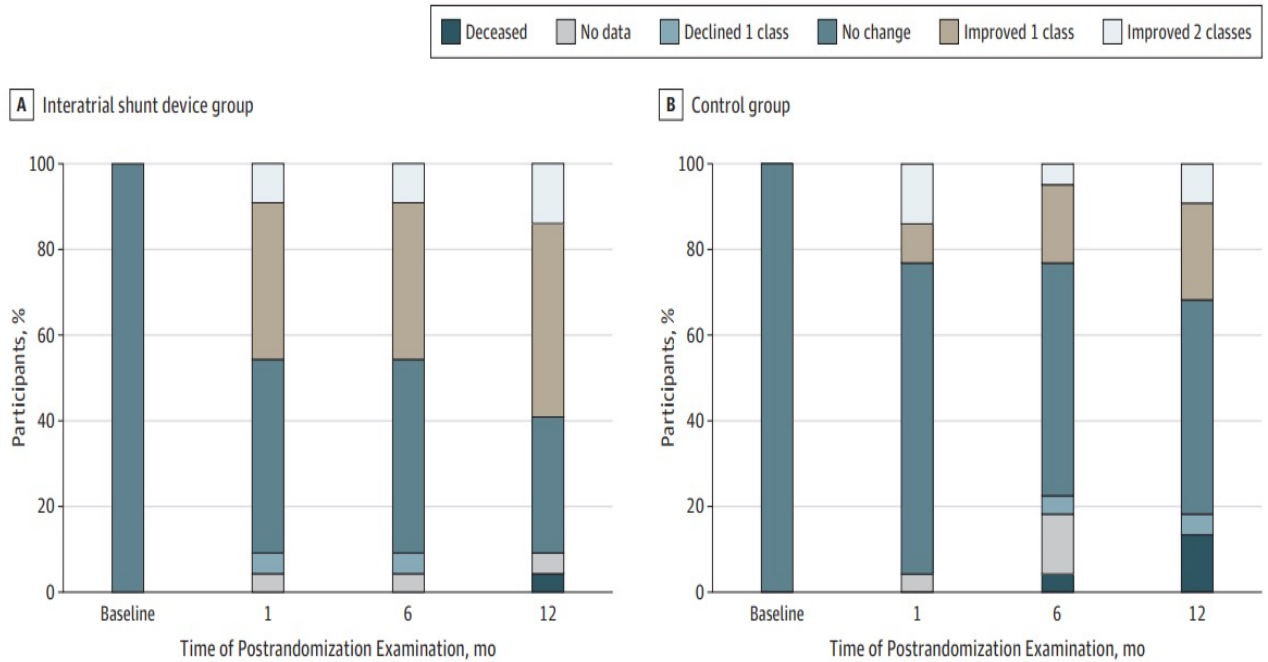
Sondergaard et al. Eur J Heart Fail 2014;16:796–801.

Intratrial shunt device

Primary endpoints in HFpEF and HFmREF

*N=44, IASD implantation vs sham, NYHA III-IV, LVEF≥ 40%, exercise PCWP≥25 mm Hg, PCWP-RAP gradient ≥5 mm Hg.





- 1 year of follow-up, IASD treatment safe, no significant differences in MACCRE (major adverse cardiac, cerebrovascular, or renal events)

Sondergaard et al. Eur J Heart Fail 2014;16:796–801.

Intratrial shunt device

Secondary endpoints in HFpEF and HFmREF

*N=44, IASD implantation vs sham, NYHA III-IV, LVEF≥ 40%, exercise PCWP≥25 mm Hg, PCWP-RAP gradient ≥5 mm Hg.

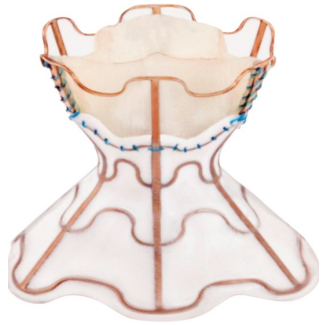
Measure	Median (Interquartile Range) Participants With Interatrial Shunt Device (n = 21)	Control Participants (n = 22)	*P* Value
Cardiovascular death			
Available data, No. (%) [95% CI][a,b]	1 (4.8) [0.1-23.8]	1 (4.5) [0.1-22.8]	>.99
Kaplan-Meier cumulative incidence, % (95% CI)[c]	4.8 (0.0-19.2)	5.0 (0.0-17.6)	.99
Total heart failure-associated admissions/visits, rate per patient-year (95% CI)[d]	0.22 (0.08-0.58)	0.63 (0.33-1.21)	.06
Days alive and without hospitalization	353 (339-363)	340.5 (330-353)	.16
Days alive without heart failure-associated hospitalization	359 (351-365)	351 (331-365)	.17
Hospitalizations for a heart failure-associated event per patient, No. (%)			.09
0	18 (85.7)	14 (63.6)	.13
1	1 (4.8)	4 (18.2)	
2	0 (0.0)	1 (4.5)	
≥3	2 (9.5)	3 (13.6)	

- 1 year of follow-up, IASD treatment safe, no significant differences in MACCRE (major adverse cardiac, cerebrovascular, or renal events)

Sondergaard et al. Eur J Heart Fail 2014;16:796–801.

Intratrial shunt device

Endpoints in HFrEF and HFpEF



V-Wave®, Caesarea, Israel

*N=38, single armopen lable trial, NYHA III or ambulatory class IV

TABLE 2 Procedural and 12-Month Follow-Up Outcomes Measures (N = 38)

Procedural/in-hospital	
Successful device implantation	38 (100)
Shunt patency on procedural TEE	38 (100)
Device embolization/dislocation	0
Need for a second device	0
Procedural time, min	72 ± 24
Hospitalization length (days)	1 (1-2)
Device- or procedure-related MACNE	1 (2.6)
Cardiac tamponade	1 (2.6)
Safety outcomes (12-month follow-up)	
Cumulative device- or procedure-related MACNE	
Death	0
Stroke	0
Cardiac tamponade	1 (2.6)
Device embolization	0
Device infection	0
Reintervention or surgery	0
Overall device- or procedure-related MACNE	1 (2.6)
Cumulative all-cause MACNE	
Death	2 (5.2)
Stroke	0
Systemic embolism	0
Cardiac tamponade	1 (2.6)
Myocardial infarction	0

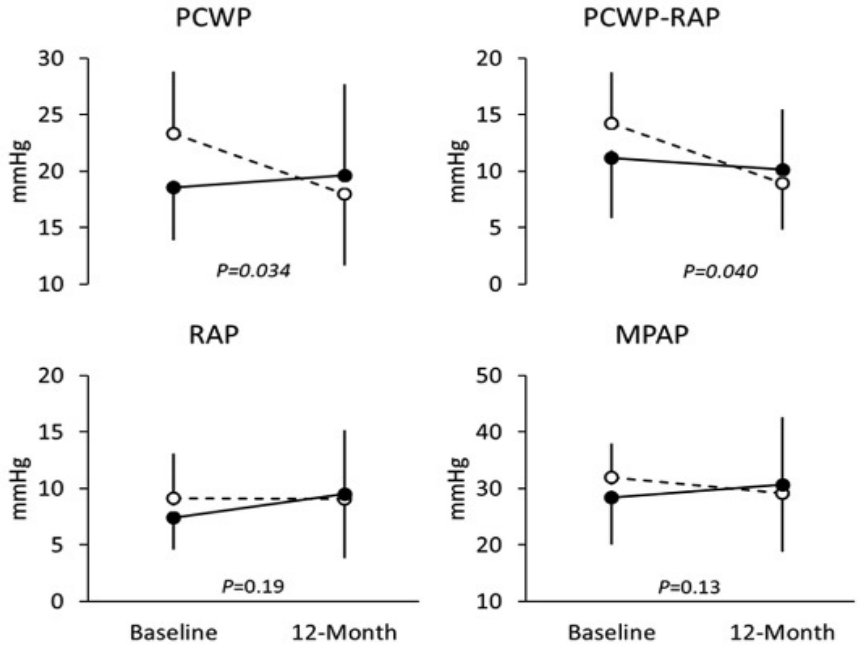
Values are n (%), mean ± SD, or median (interquartile range).
MACNE = major adverse cardiovascular and neurologic event(s); TEE = trans-esophageal echocardiography.

TABLE 3 Functional, Echocardiographic, and Hemodynamic Parameters at Baseline and 3- and 12-Month Follow-Up

	Baseline (n = 38)	3 Months (n = 36)	12 Months (n = 36)	p Value*
Functional status/quality of life				
NYHA functional class III or IV	38 (100)	8 (22)	14 (39)	<0.001
NYHA functional class I or II	0 (0)	28 (78)	22 (61)	
KCCQ/MLHFQ (improvement ≥5 points)	–	27 (74)	26 (73)	<0.001
6-min walk distance (m)	290 ± 112	340 ± 94	324 ± 105	0.012
Laboratory parameters				
ln NT-pro BNP (pg/ml)	7.5 ± 0.9	7.4 ± 1.0	7.5 ± 0.9	0.83
eGFR (ml·min $^{-1}$·1.73 m $^{-2}$)	54 ± 20	55 ± 23	53 ± 22	0.92
Echocardiographic variables				
LVEF, % (HFrEF)	26 ± 7	27 ± 9	28 ± 8	0.54
LVEF, % (HFmrEF, HFpEF)	50 ± 9	52 ± 10	54 ± 9	0.74
MR grade†	3.9 ± 1.5	3.5 ± 1.2	3.5 ± 1.3	0.51
LAVI (ml/m^2)	42 ± 13	42 ± 13	41 ± 15	0.84
TAPSE (mm)	16 ± 4	17 ± 4	16 ± 4	0.94
Cardiac output (l/min)	1.9 ± 1.0	1.9 ± 0.5	1.9 ± 0.4	0.92
Q_p/Q_s	0.99 ± 0.11	1.17 ± 0.12	1.10 ± 0.13	0.005
Hemodynamic status				
PCWP, mm Hg	21 ± 5	20 ± 7	19 ± 7	0.49
RAP, mm Hg	8 ± 4	9 ± 5	9 ± 4	0.51
Mean PAP, mm Hg	30 ± 7	29 ± 8	30 ± 10	0.97

Values are n (%) or mean ± SD. *Kruskal-Wallis test and one-way analysis of variance for ordinal and interval data, respectively. †MR grade: 1 = none to 7 = severe.
KCCQ = Kansas City Cardiomyopathy Questionnaire; LAVI = left atrial volume index; MLHFQ = Minnesota Living With Heart Failure Questionnaire; MR = mitral regurgitation; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Table 1.

FIGURE 4 Changes in Hemodynamic Parameter Values According to Patency Subgroup at Baseline and 12 Months



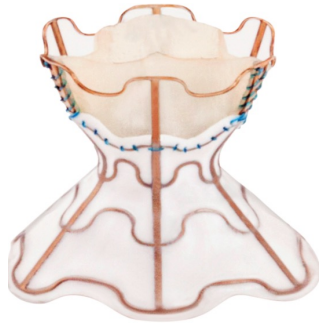
Patent shunt patients **(open circles)** and stenotic or occluded shunt patients **(solid circles)**. P values are for comparisons between subgroups of the differences between baseline and 12 months. MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.

- **Significant improvement in NYHA, QoL, 6MWD**
- **By 12 months, nearly 50% of shunts stenotic**

Del Trigo et al.Lancet 2016; 387: 1290–97
JACC Cardiovascular interventions. 2018 Nov 26;11(22):2300-2310

Intratrial shunt device

Endpoints in HFrEF and HFpEF



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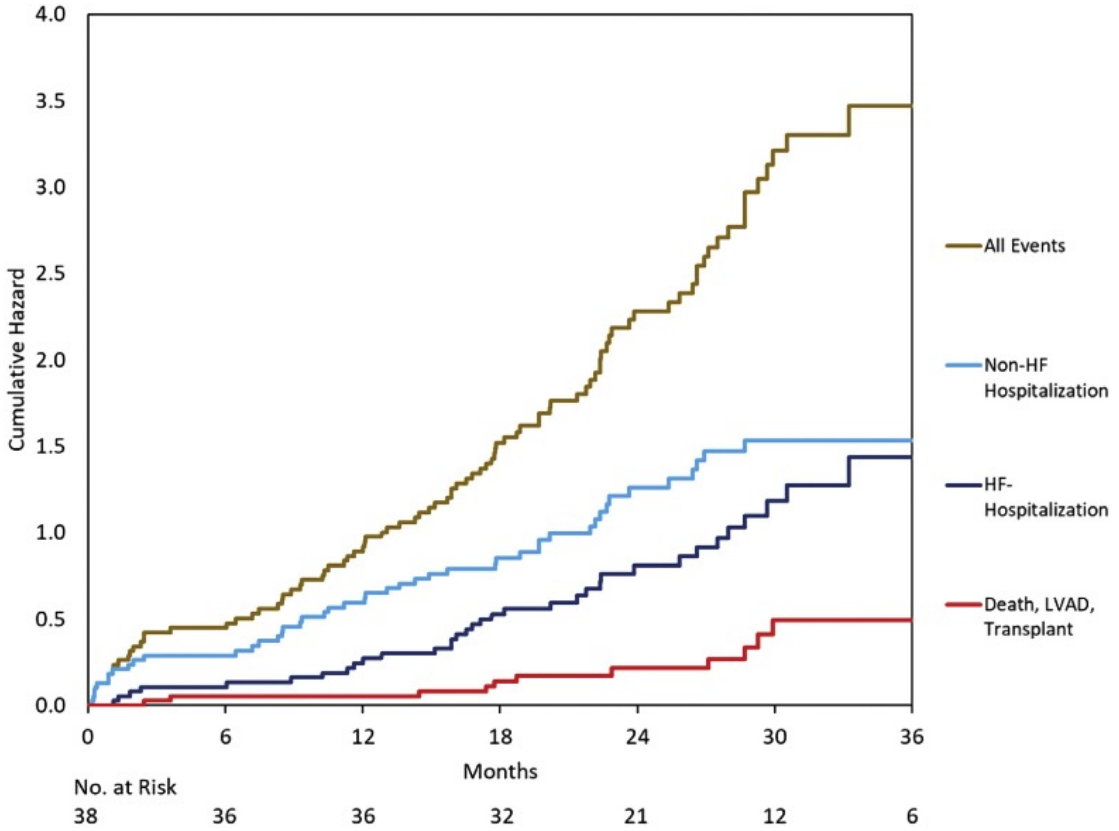
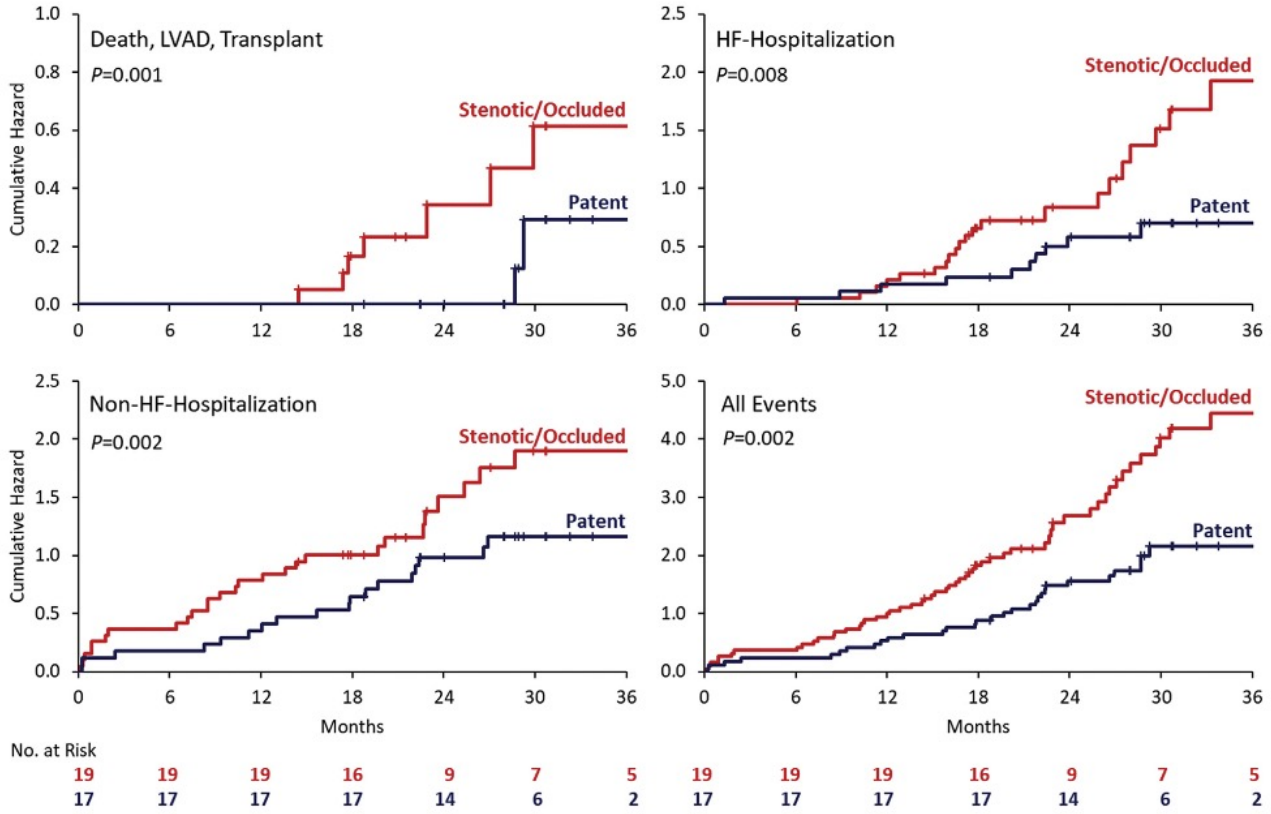
Cumulative Hazard Functions for Clinical Events (All Patients)



Cumulative Hazard Functions for Clinical Events by Patency Subgroup



- **Unknown: Long-term effects of chronic right heart loading, impact of development of atrial arrhythmias (anticoagulation, antiplatelets), mechanical device–device interactions , paradoxical embolism**

JACC Cardiovascular interventions. 2018 Nov 26;11(22):2300-2310

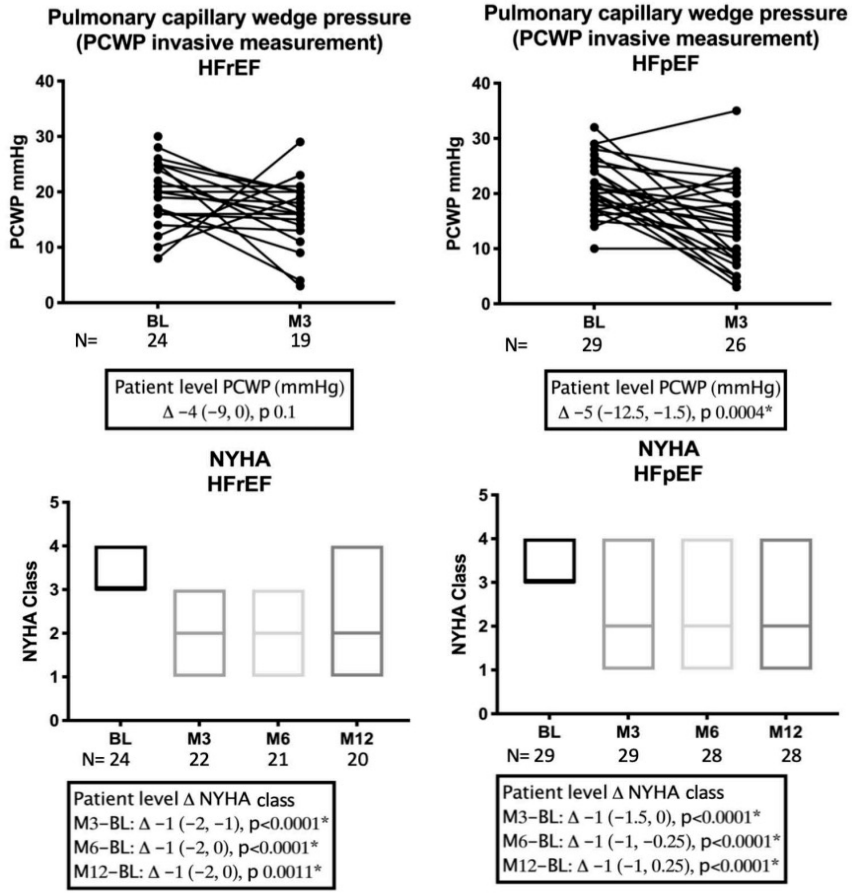
PRELIEVE study

Endpoints in HFrEF and HFpEF

The Atrial Flow Regulator (AFR); Occlutech, Istanbul, Turkey

*N=53 patients (HFrEF n=24 and HFpEF n=29), prospective, non-randomized,first-in-man study in symptomatic HF

	All patients n=53	HFrEF patients n=24	HFpEF patient sn=29
Device removal after implantation,n (%)	0	0	0
Death, n (%)	3 (6)	3 (13)	0
Stroke, n (%)	0	0	0
Myocardial infarction, n (%)	1 (2)	0	1 (3)
Worsening of renal function or newimpairment (without need for dialysis), n (%)	11 (20)	4 (17)	7 (24)
Hospitalisation for heart failure, total events	11	6	5
Hospitalisation for heart failure, n of patients with at least 1 event(%)	6 (11)	3 (13)	3(10)
Atrial fibrillation (new onset or worsening), total events	14	6	8
Atrial fibrillation (new onset or worsening), n of patients with atleast 1 event (%)	11 (20)	5 (21)	6 (21)
SADE, n of patients (%)	1 (2)	0	1 (3)*
SAE rate, total events	64	33	31
Cardiovascular SAE, total events	26	10	16
SAE, n of patients with at least one	25 (47)	13 (54)	12 (41)



Paitazoglou et al. EJHF2021 Feb 8. doi: 10.1002/ejhf.2119

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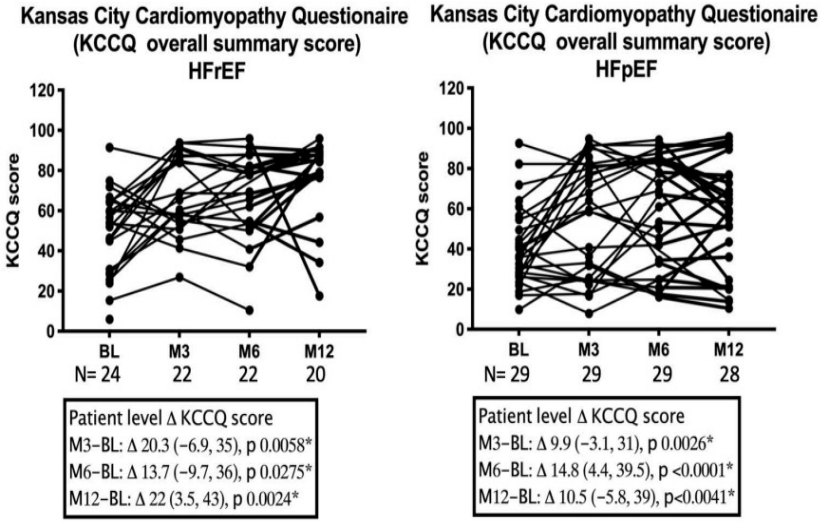
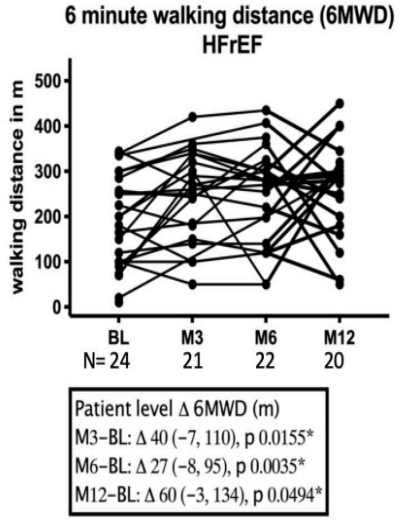
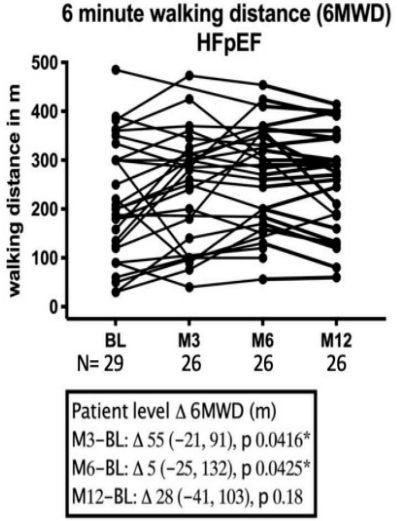
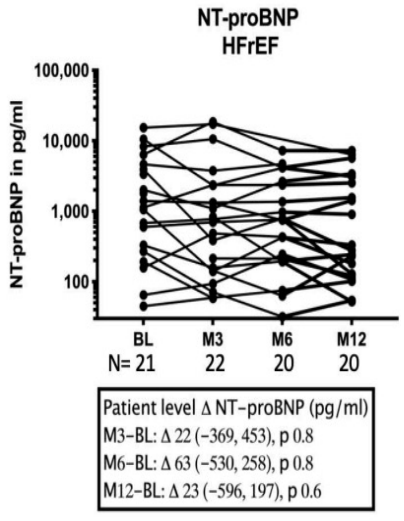
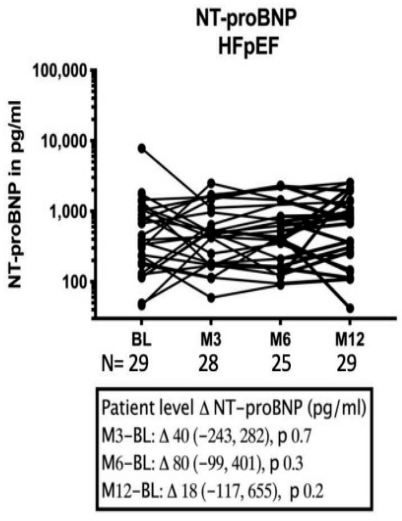








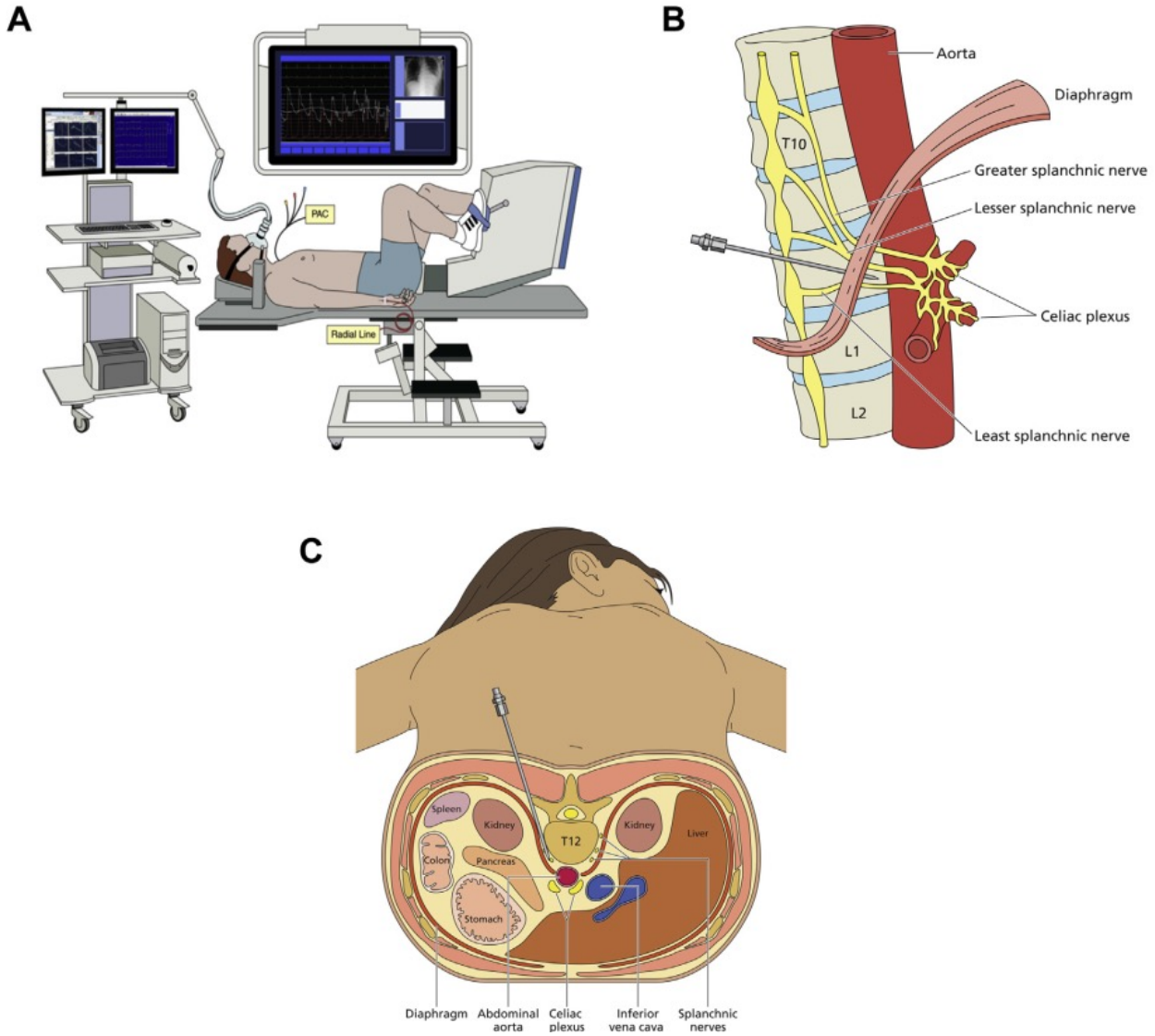


- **Implantation of the AFR device in HF patients was feasible.**
- **No shunt occlusion, stroke or new right HF during 1year follow-up, clinical improvements in certain patients.**

Paitazoglou et al. EJHF2021 Feb 8. doi: 10.1002/ejhf.2119

Splanchnic Nerve Blockade

*N=15, NYHA class II to III, PWCP≥15 mm Hg and/or ≥25 mm Hg at peak exercise, despite GDMT



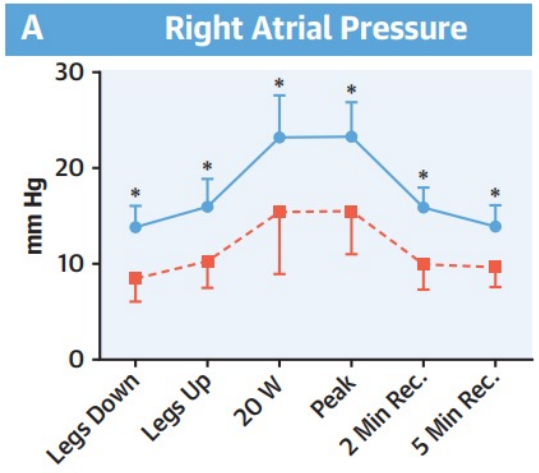
- **Transient effect of Ropivacaine-induced acute SNB**

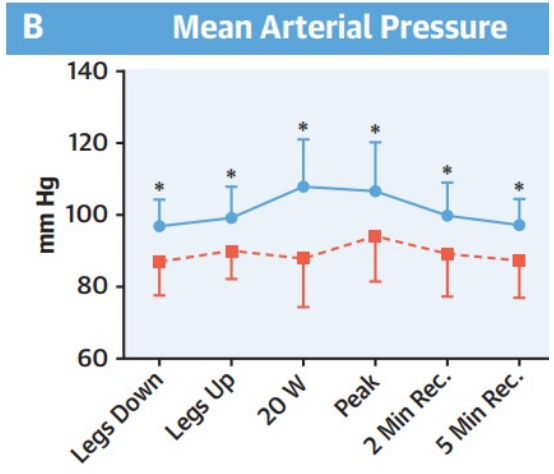
- **Probable mechanisms:**
  - More blood stored in splanchnic vascular reservoir
  - Reduced shifts of blood from the splanchnic to pulmonary vasculature beds
  - Reduced systemic arterial resistance by arterial vasodilation maintained cardiac output despite lower filling pressures.

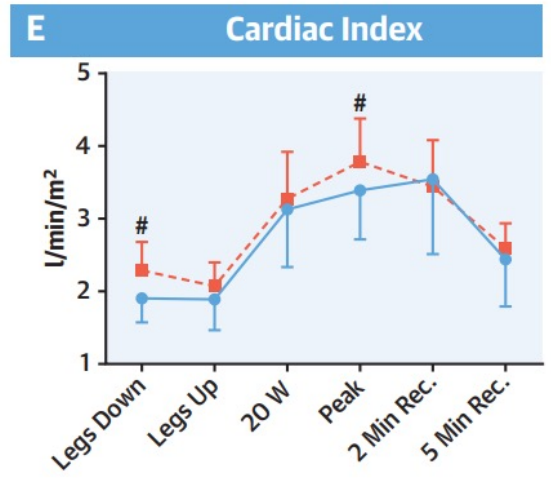
Fudim M et al. J Am Coll Cardiol HF 2020

Splanchnic Nerve Blockade

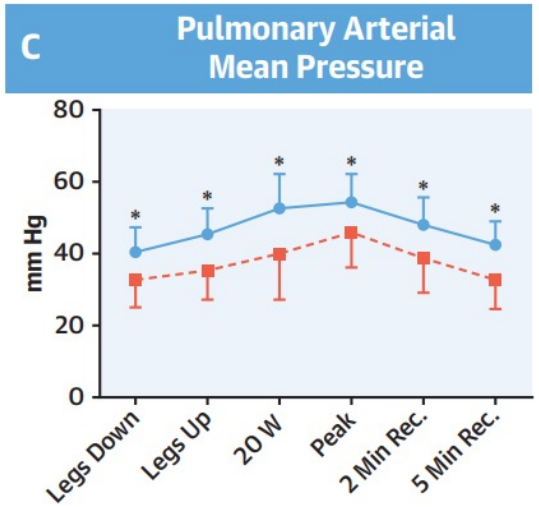
Hemodynamic and Cardiopulmonary Exercise Functional Parameters

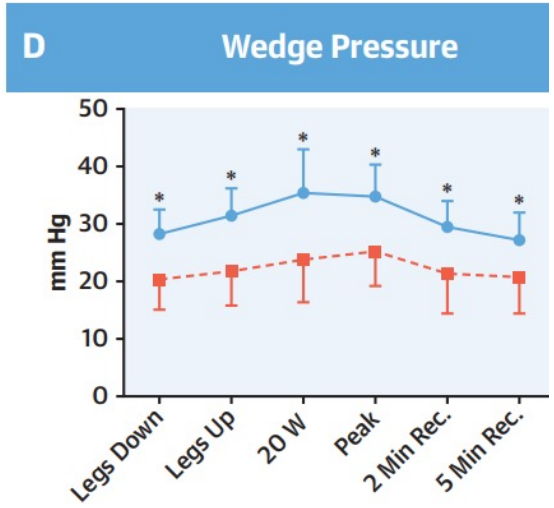


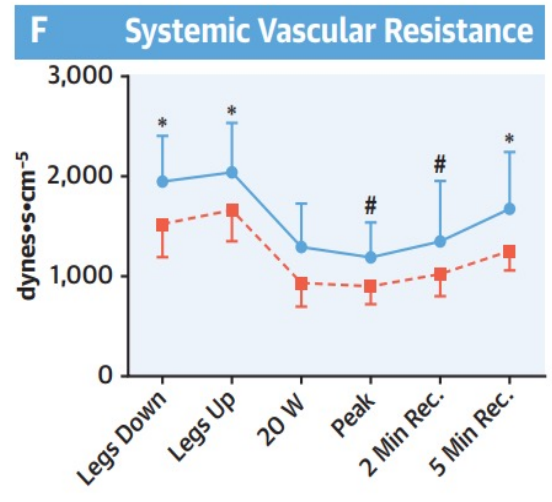


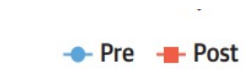


	Pre-SNB	Post-SNB	p Value
Workload, W	33 ± 24	50 ± 30	0.019
Exercise time, min (s)	4:48 ± 96	5:03 ± 91	0.181
Peak VO_2, ml/kg/min	9.1 ± 2.5	9.8 ± 2.7	0.053
VE/VCO_2 slope, %	37.1 ± 7.6	35.1 ± 6.0	0.067
RER	1.14 ± 0.13	1.08 ± 0.11	0.081
Lactate mg/dl	4.5 ± 1.8	4.9 ± 1.7	0.786
Borg perceived exertion*	17.5 ± 1.5	17.9 ± 1.5	0.189
Shortness of breath†	8.6 ± 1.6	6.7 ± 3.3	0.032
Leg fatigue‡	6.1 ± 4.7	7.8 ± 3.4	0.057
6-min walk distance, m	311 ± 68	330 ± 73	0.033
Oscillatory breathing during exercise	6/15	3/15	0.082



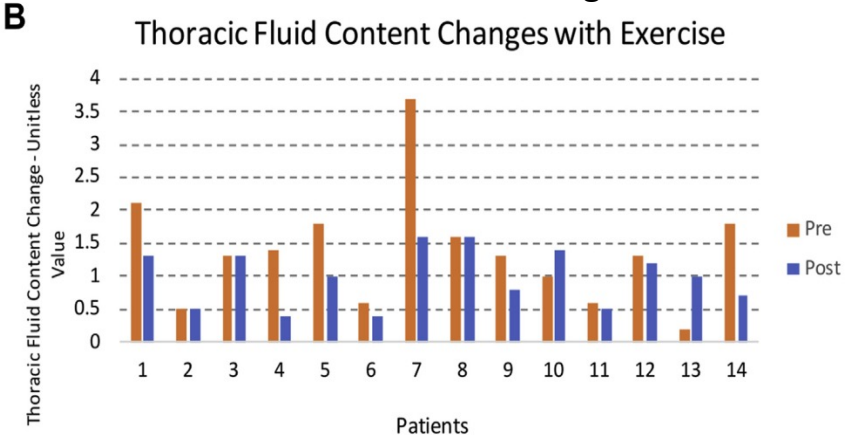






Bioelectrance monitoring

B



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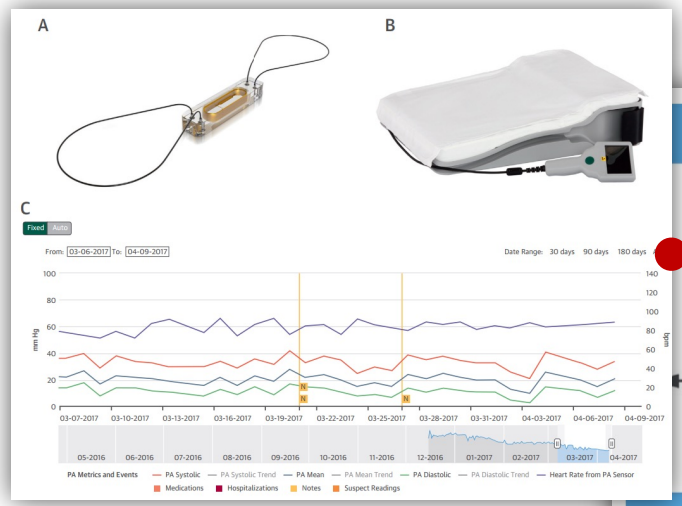
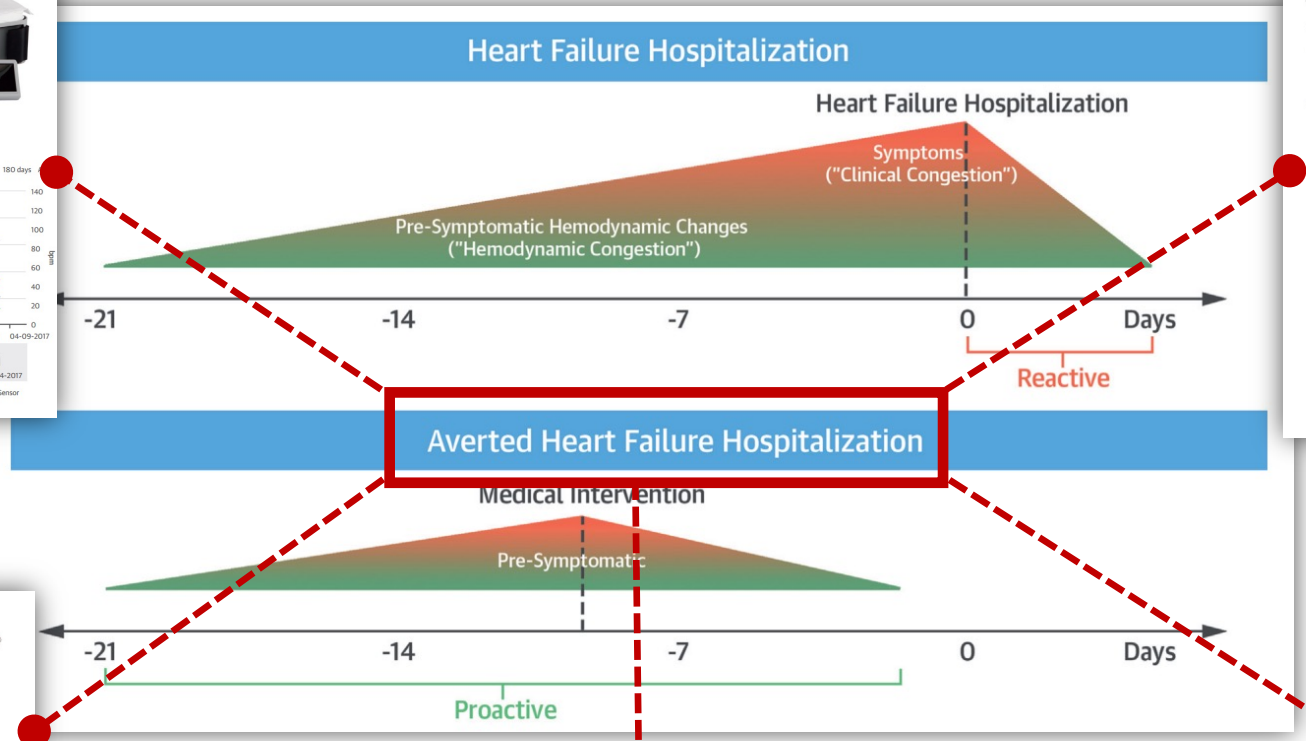
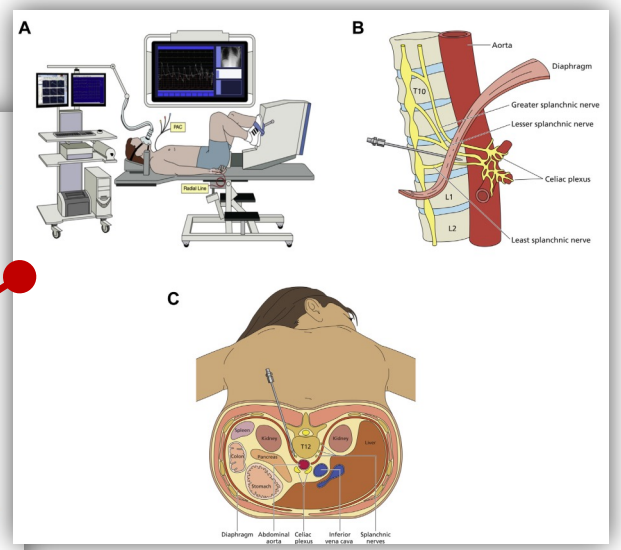
Emerging alternatives for decongesting HF



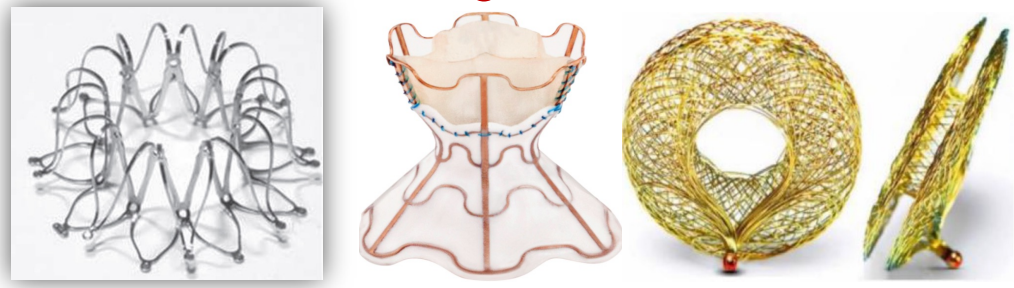
CardioMEMS HF System



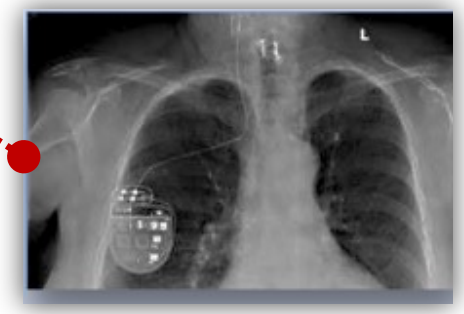


Splanchnic Nerve Blockade

Left atrial pressure monitoring system



Intratrial shunt devices



Baroreceptor activation therapy

The art of being critical is a key to the excellence in medicine

Thomas Eakins, The Agnew Clinic

1889