20230624

Clinical trials in conduction system pacing

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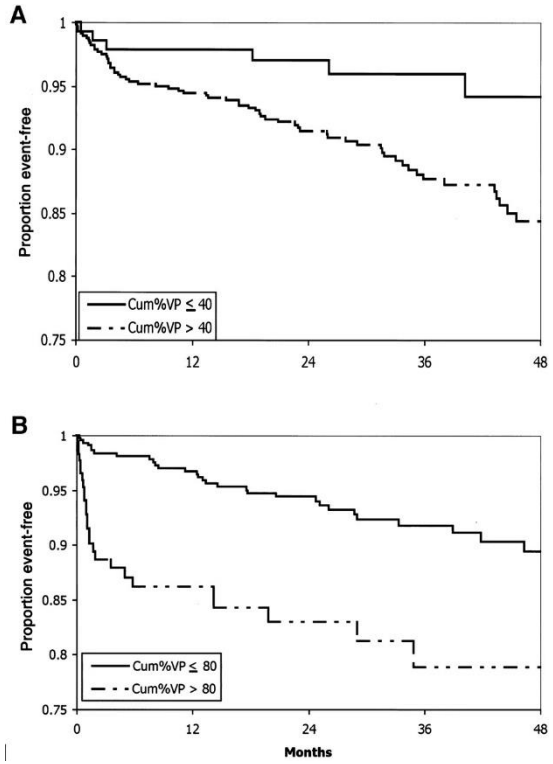
Pacing Indications

Indication	Pacing option
Bradycardia	Right ventricular apical pacing RV septal pacing Outflow tract pacing Biventricular pacing

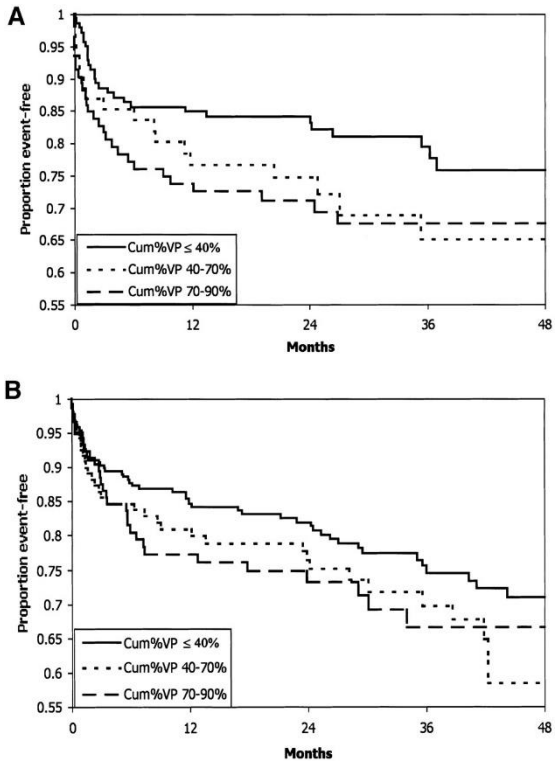
MOST trial

MOde Selection Trial

HF Hospitalization



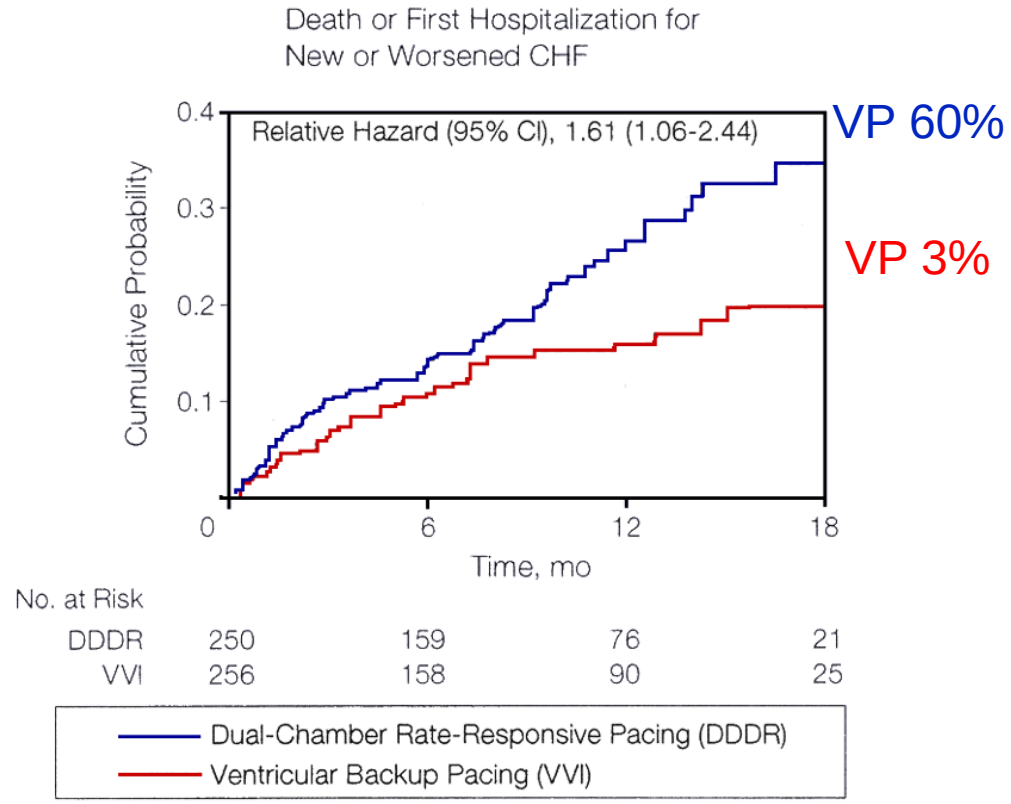
AF



- ✓ DDDR versus VVIR - SN dysfunction
- ✓ VP >40% - HFH, AF ↑

DAVID trial

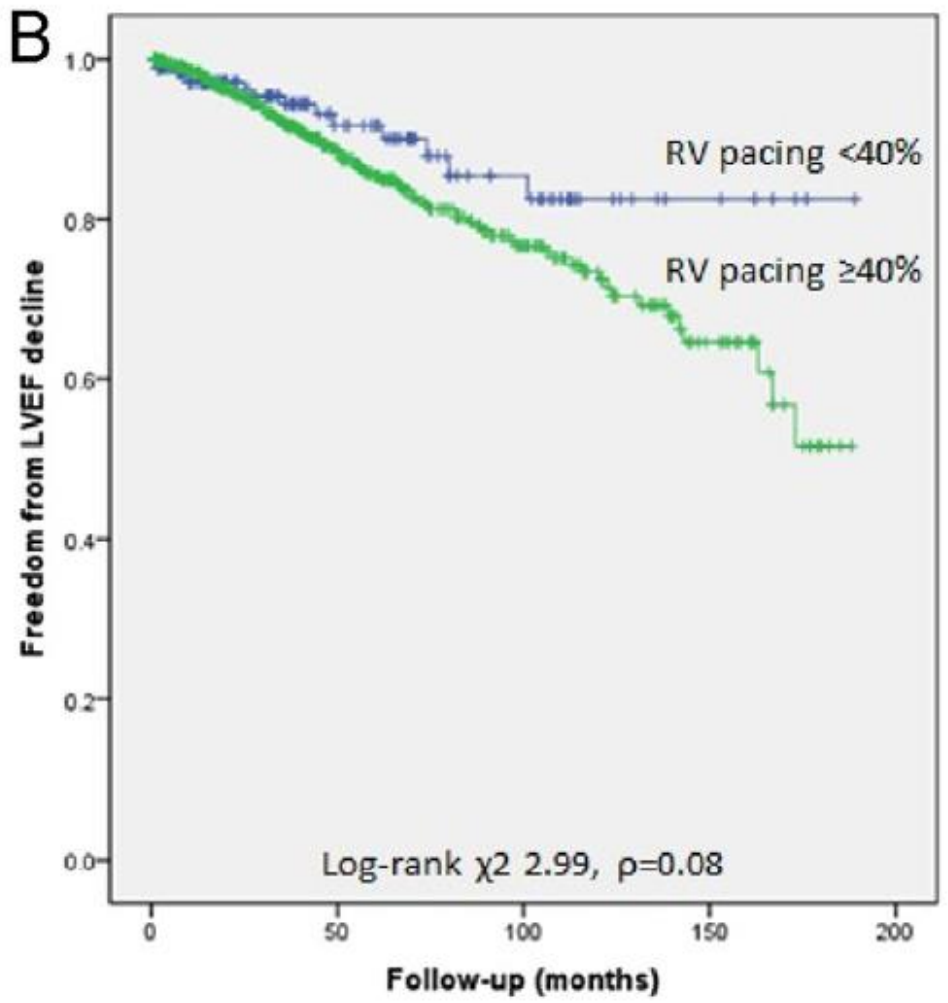
Dual Chamber and VVI Implantable Defibrillator Trial

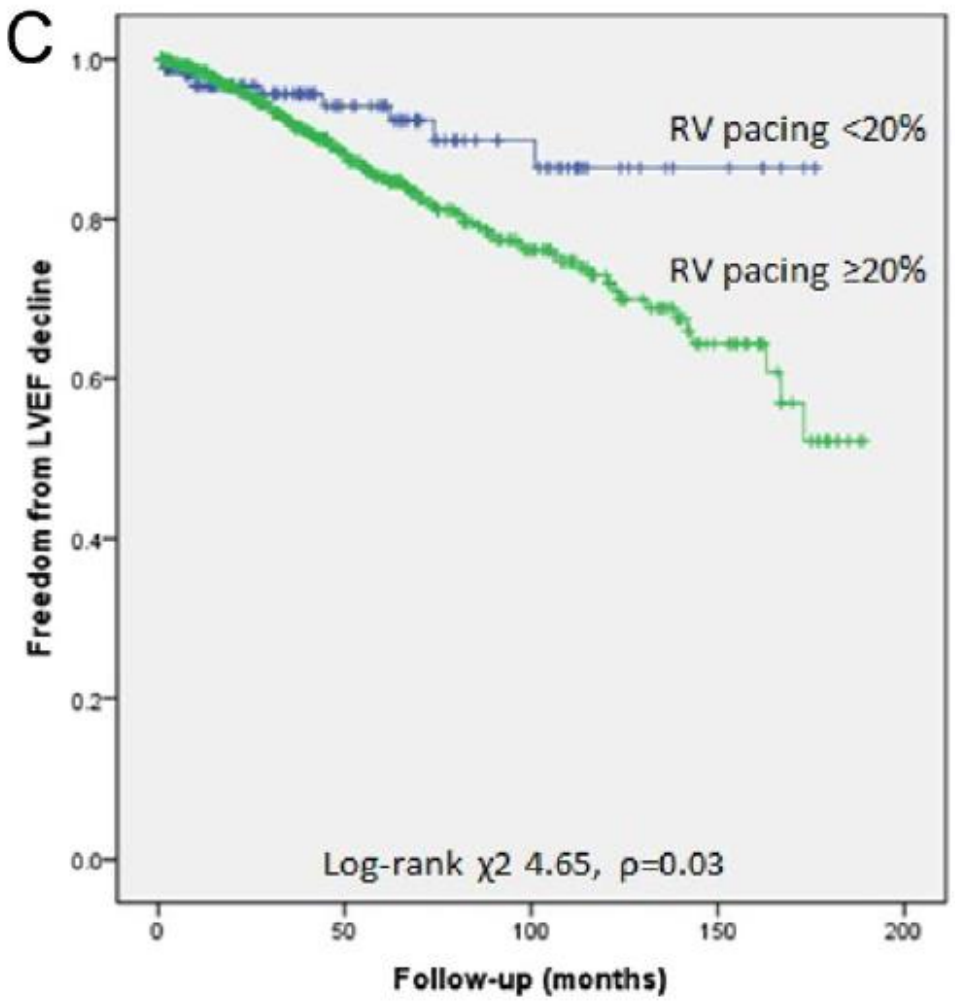


- ✓ ICD indication but No indication for PPM
- ✓ EF < 40%
- ✓ DDDR 70 BPM versus VVI 40 BPM

Sweeney M, Circulation 2003; Willkoff BL, JAMA 2002

Predictor of pacing induced cardiomyopathy





Kiehl EL, Heart Rhythm 2016

PIC is common

Pacing-induced cardiomyopathy (PIC) in Major Trials

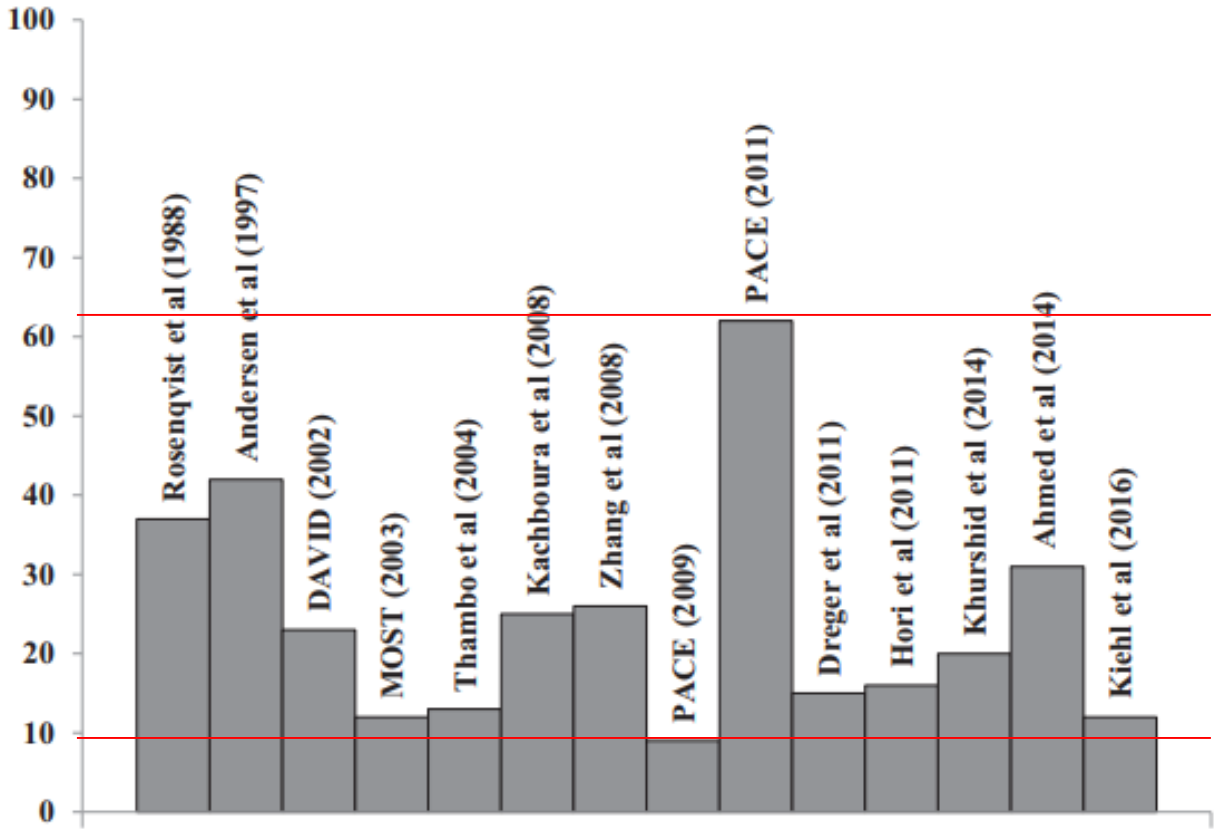


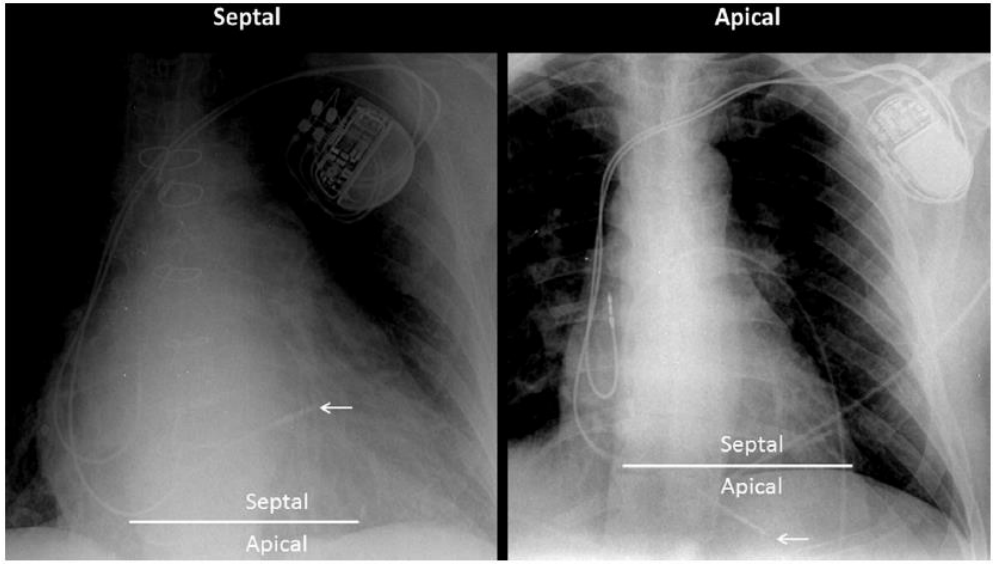
Table 1
Incidence of heart failure and pacing-induced cardiomyopathy in studies of right ventricular pacing

Clinical Trial or Study	Number of Patients	Follow-up (Mean)	Pacing Mode	Permanent Pacemaker Implantation Indication	Clinical Heart Failure/ Pacing-induced Cardiomyopathy
Rosenqvist et al,[48] 1988	168	4 y	AAI vs VVI	SND	15% vs 37%
Andersen et al,[49] 1997	225	8 y	AAI vs VVI	SND	23 vs 42% (NYHA III-IV
DAVID,[26] (2002)	506	8 mo	DDD vs VVI	—	23% vs 13% (HF + death)
MOST,[28] (2003)	2010	2.8 y	DDD vs VVI	SND	12% vs 10%
Thambo et al,[3] 2004	23	9.7 y	DDD	Congenital AVB	13% (NYHA II–III)
Kachboura et al,[50] 2008	43	18 mo	DDD and VVI	AVB	25%
Zhang et al,[34] 2008	304	7.8 y	DDD and VVI	AVB	26%
PACE,[40] (2009); PACE,[51] (2011)	163 163	1 y 2 y	DDD vs CRT DDD vs CRT	SND and AVB SND and AVB	—
Dreger et al,[16] 2011	26	25 y	DDD	AVB	
Hori et al,[52] 2011	367	113 mo	DDD and VVI	SND and AVB	16%
Khurshid et al,[17] 2014	277	3.3 y	RVP	SND and AVB	20%
Ahmed et al,[53] 2014	91	28 mo	DDD and VVI	AVB	31%
Kiehl et al,[7] 2016	823	4.3 y	DDD, VVI, AAI + MVP, DDI	AVB	12%

Abbreviations: AVB, AV node block; PPM, permanent pacemaker implantation; SND, sinus node dysfunction.
Studies of ventricular pacing showing a wide range of incidence of LV dysfunction and clinical HF with RVP.

Cherian TS, Upadhyay GA. Card Electrophysiol Clin. 2018.

We cannot solve this problem in “RV”



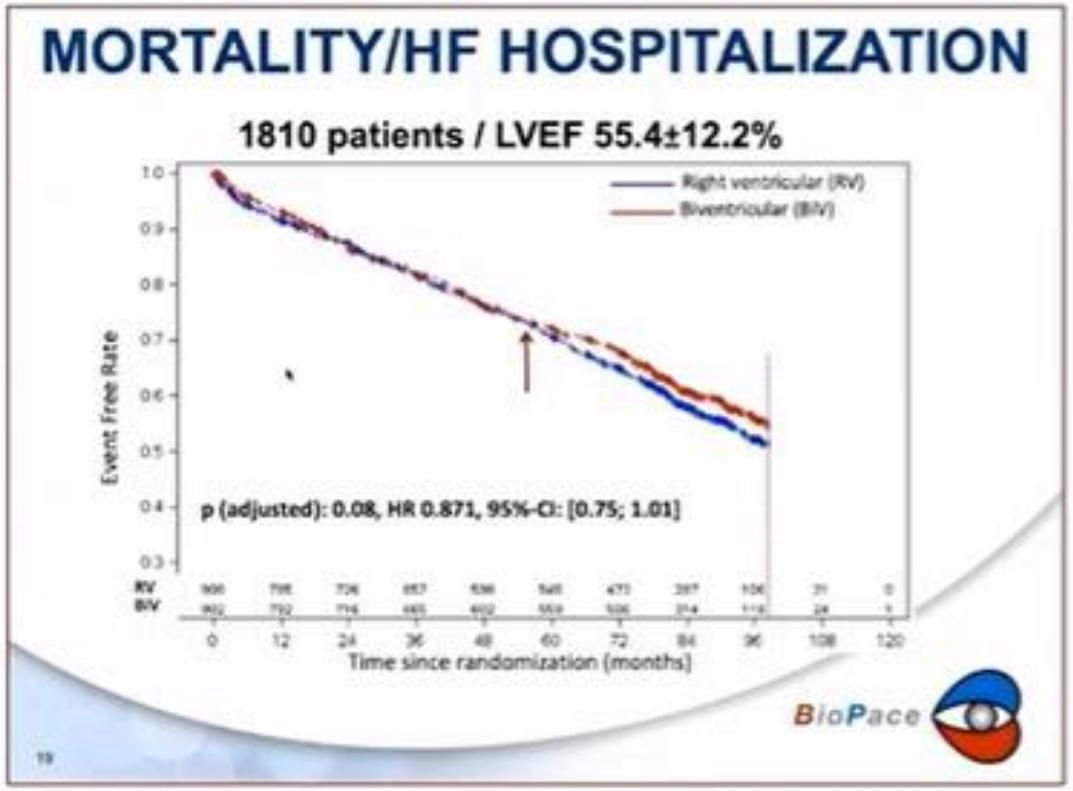
	Univariate			Multivariate		
Factor	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Male gender	2.38	1.28–4.41	.006	2.15	1.14–4.02	.02
Age (per 1 y increase)	1.00	0.98–1.02	.9			
Body mass index (per 1 kg/m^2 increase)	0.99	0.95–1.03	.6			
Coronary artery disease	1.20	0.69–2.12	.5			
Atrial fibrillation or flutter	0.97	0.56–1.69	.9			
Hypertension	1.04	0.57–1.92	.9			
Diabetes	1.28	0.68–2.42	.8			
Heart block after cardiac surgery	0.67	0.36–1.24	.2			
β-Blocker use	0.72	0.41–1.28	.3			
ACE inhibitor or angiotensin receptor blocker use	1.11	0.64–1.94	.7			
Left ventricular end-diastolic diameter (per 1 cm increase)	1.12	0.71–1.74	.6			
Left ventricular end-systolic diameter (per 1 cm increase)	1.42	0.84–2.40	.2			
Left ventricular ejection fraction (per 1% increase)	0.97	0.94–1.00	.05	0.97	0.95–1.00	.09
Heart rate (per 1 beat/min increase)	0.99	0.98–1.01	.3			
Left bundle branch block	1.21	0.44–3.38	.7			
Right bundle branch block	0.70	0.33–1.49	.4			
Native QRS duration (per 1 ms increase)*	1.03	1.02–1.05	<.001	1.03	1.01–1.05	<.001
Single-chamber ventricular pacemaker	1.25	0.58–2.67	.8			
Apical right ventricular lead location	0.62	0.34–1.13	.1			
Paced QRS duration (per 1 ms increase)	1.01	0.99–1.03	.3			
Ventricular pacing percentage (per 1% increase)	1.00	0.99–1.02	.7			

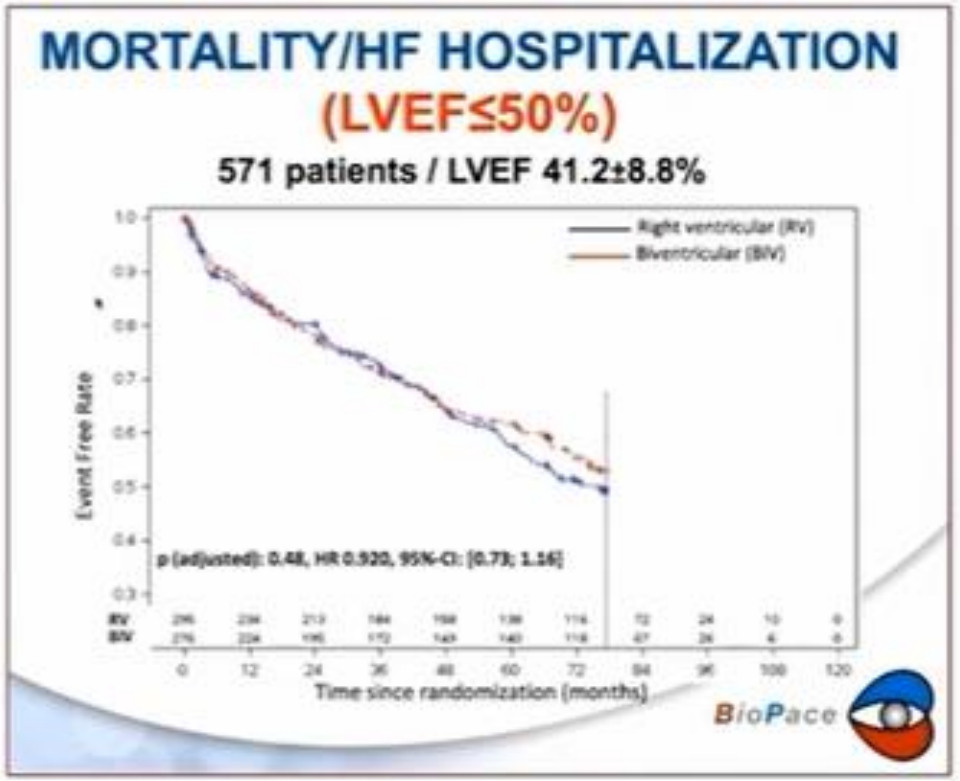
Variable	Hazard ratio	95% CI	*P*
Age at implant	1.01	0.99–1.03	.265
Sex: male	1.40	0.87–2.26	.170
Atrial arrhythmia	1.20	0.75–1.92	.454
Hypertension	1.55	0.90–2.65	.112
Lower preimplant LVEF	1.047	1.002–1.087	.042
Apical lead placement	0.70	0.44–1.12	.139
Paced QRS	1.00	0.99–1.01	.545
≥20% RV paced	6.76	2.08–22.0	.002

Khurshid S, et al. Heart Rhythm 2014
Kiehl EL, et al. Heart Rhythm 2016

BIOPACE
BiV pacing for AV block to prevent cardiac desynchronization

Indications for V pacing, EF >40%





"Biventricular pacing disappoints in BIOPACE trial" 2014/9/1 ESC congress media

BLOCK-HF

EF < 40%, CAVB

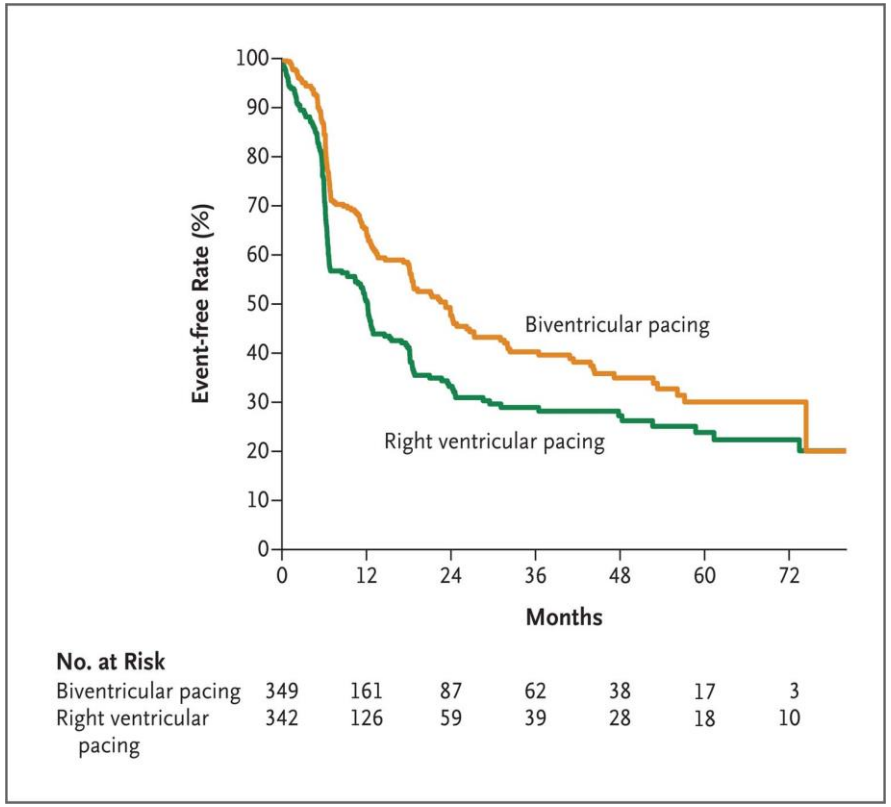
Primary Outcome

45.8%	Composite of death, urgent care visit for HF and LV remodeling HR 0.74 (95% CI 0.60–0.90)	55.6%

Secondary Outcomes

33.5%	Death or urgent care visit 0.73 (95% CI 0.57-0.92)	40.6%
22%	Hospitalization for heart failure 0.70 (95% CI 0.52-0.93)	26.3%

Primary Endpoint (Mortality/HF/LVESVI)



Curtis AB et al. N Engl J Med 2013

Pacing Indications

Indication	Indication
Bradycardia	Right ventricular apical pacing RV septal pacing Outflow tract pacing His bundle pacing Left bundle branch area pacing - Left bundle branch pacing - LV septal pacing

Conduction system pacing

- Most physiological form of ventricular pacing
- Conduction occurs through native His-Purkinje system
- No pacing induced dyssynchrony
- Both AV and VV synchrony can be achieved at the same time.

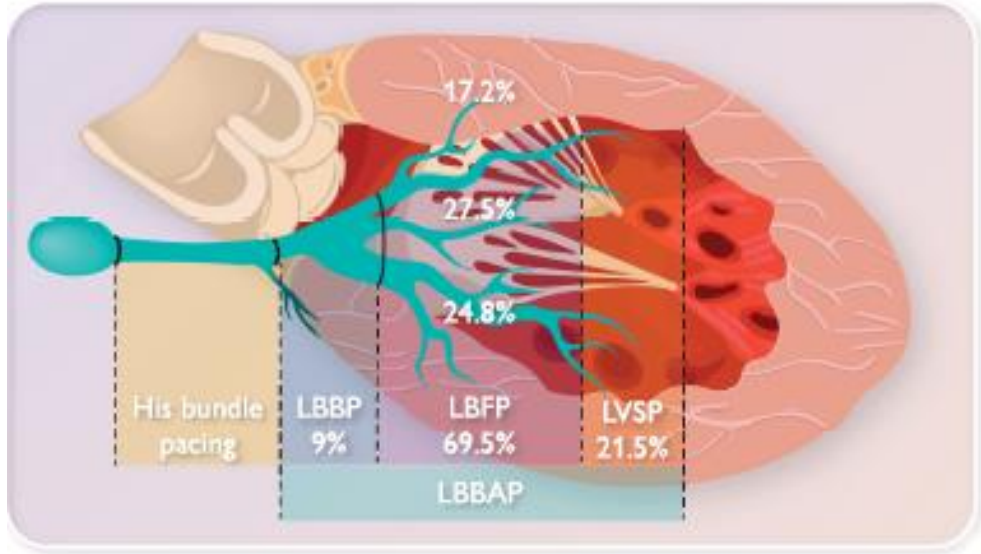


Figure A.

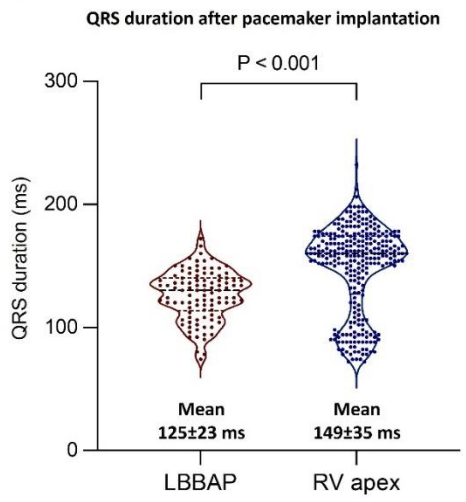
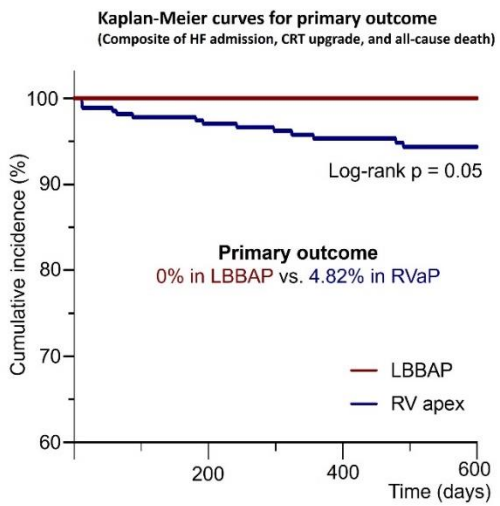


Figure B.



Jastrzebski M, et al. EHJ 2022, Lee SR, Lee KY, et al. preliminary

His Bundle Pacing

Procedural Challenges

Success rates vary from 70-92%
Difficulty in fixation in 10%
Small target-requires precision
Limited tool set
Lower success in infranodal, HV block
1% transient AV block, 2.5% persistent RBBB

Threshold Challenges

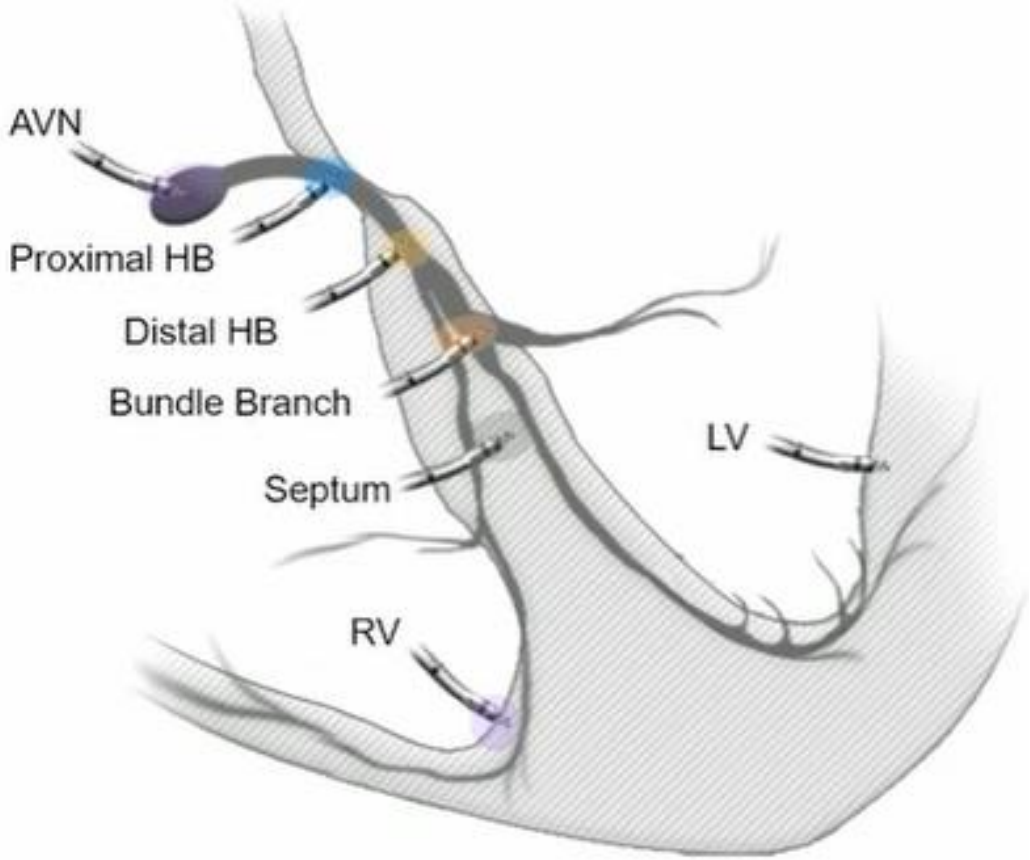
High pacing threshold in 10% at implant
Unpredictable threshold increase in 10% at follow-up
Lead revision ~5%
Higher BBB correction thresholds

Sensing Challenges

Smaller R waves (1-3mV)
Ventricular undersensing
Atrial oversensing

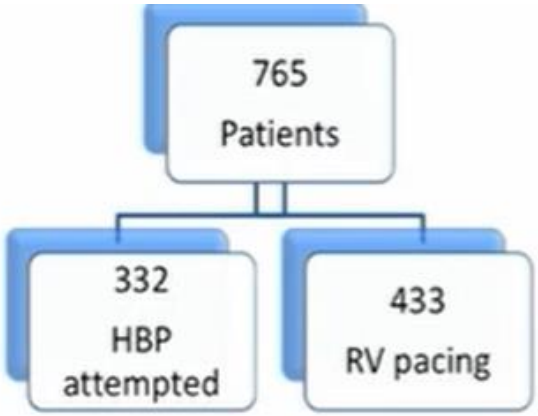
Left bundle branch pacing

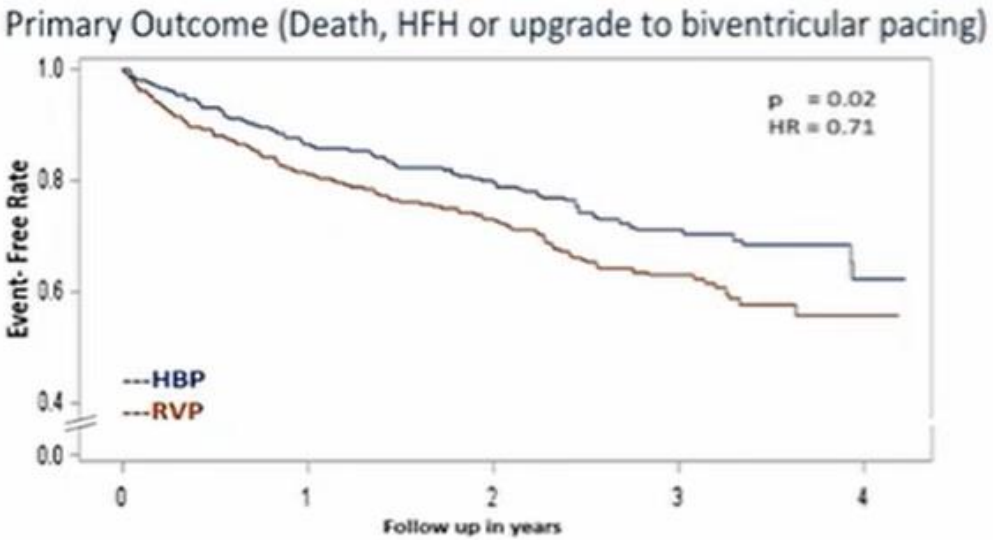
- Stable, low thresholds
- Pacing beyond the site of block
- Large R waves, no oversensing
- Left septal myocardial capture



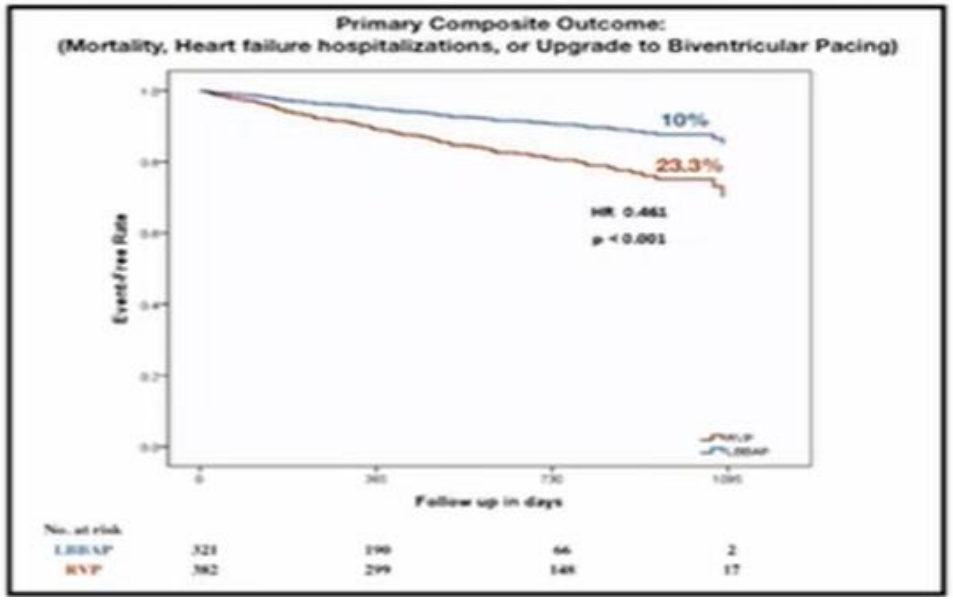
Clinical outcomes [Observational]

HBP vs. RVP





LBBAP vs. RVP

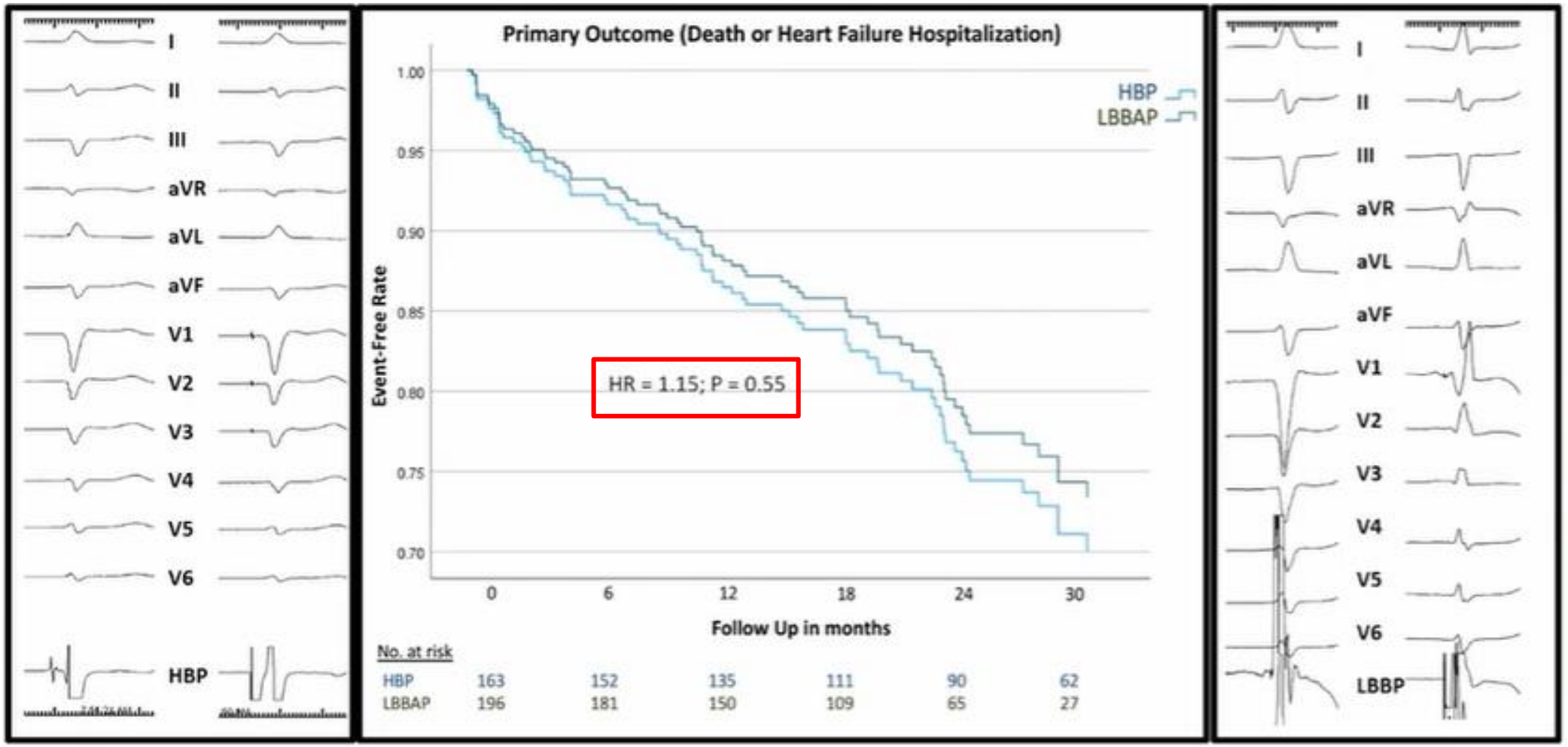


Abdelrahman M, et al. JACC 2018; Sharma PS, et al. Heart Rhythm 2022

HBP vs. LBBAP in pacing indication [Observational]

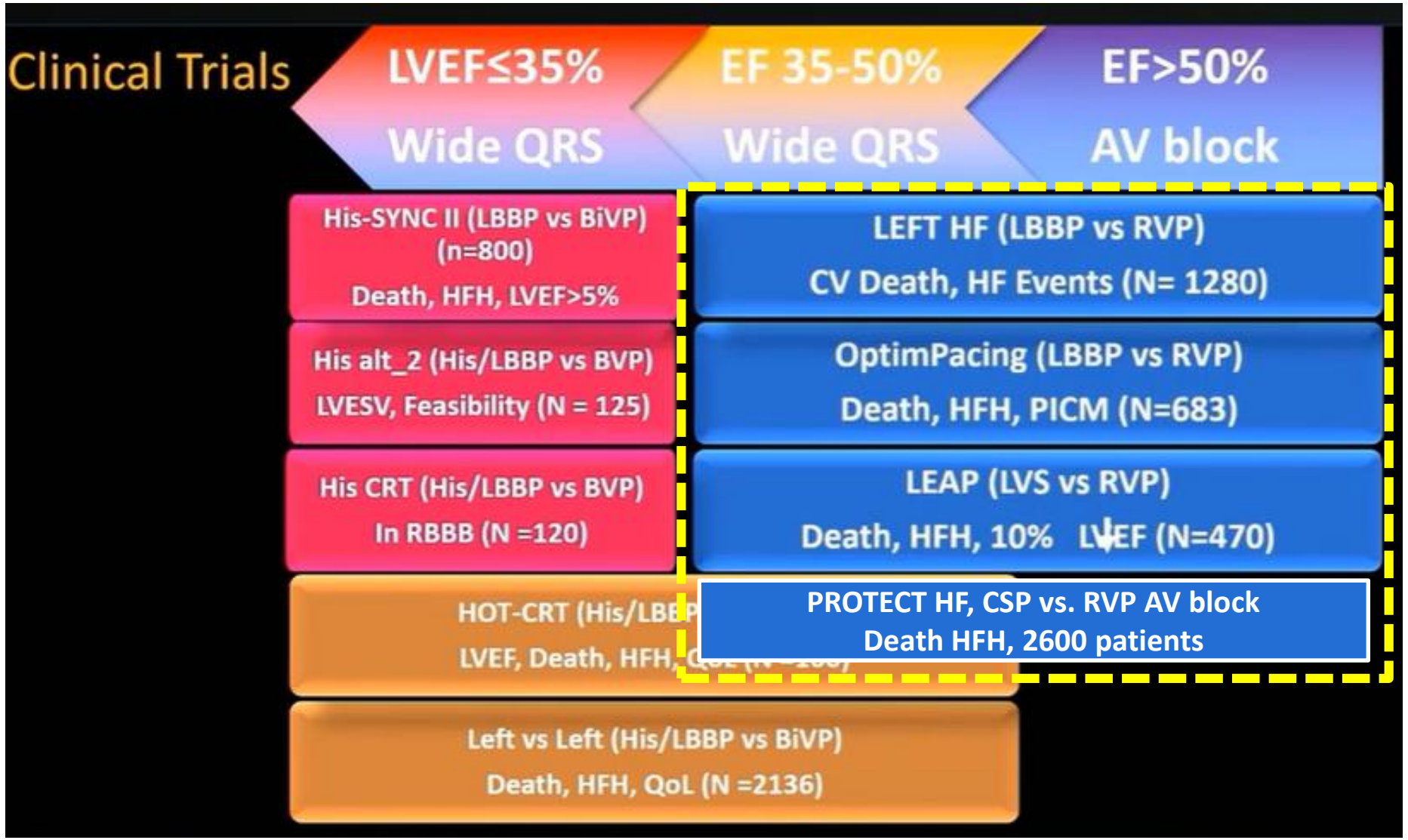
HBP

LBBAP



Vijayaraman et al. JCE 2022

Ongoing clinical trials



Adapted from EHRA 2023 Dr. Vijayaraman

PROTECT-SYNC: LBBAP vs RVP in patients with Vp>40% anticipated
:ClinicalTrials.gov ID: NCT05585411

PReventive Effect Of Left Bundle Branch Area Pacing Versus righT vEntricular paCing on All Cause deaTh, Heart Failure Progression, and Ventricular dysSYNChrony in Patients With Substantial Ventricular Pacing (PROTECT-SYNC): Multicenter Prospective Randomized Controlled Trial

ClinicalTrials.gov ID NCT05585411

Sponsor Yonsei University

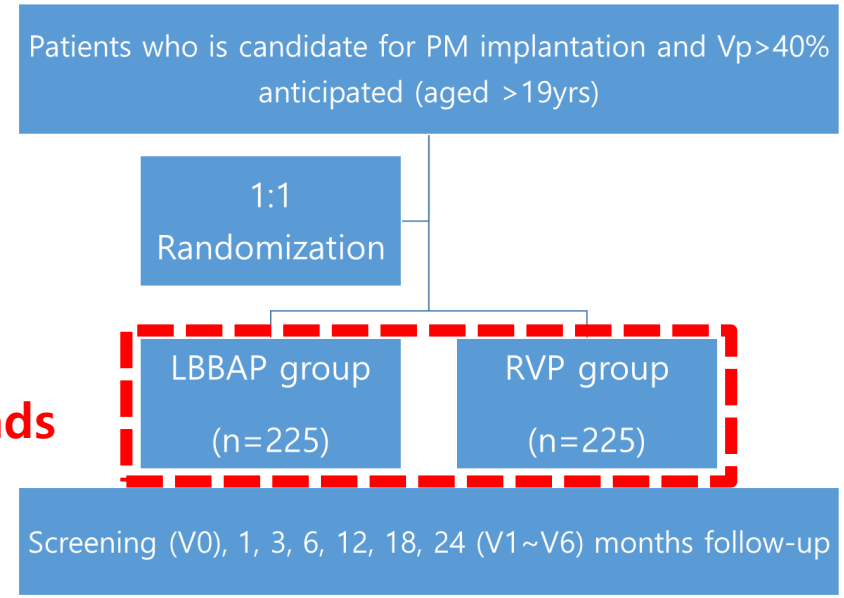
Information provided by Yonsei University (Responsible Party)

Last Update Posted 2022-10-18

8 tertiary center

- Yonsei University Severance Hospital
- Seoul National University Hospital
- Asan Medical Center
- Bucheon Sejong Hospital
- Kyung Hee university Medical Center
- Seoul St. Mary Hospital
- Chungbuk National University Hospital
- Gyeongsang National University Changwon Hospital

450 patients
With stylet driven leads



Primary analysis : Composite of All cause death + heart failure hospitalization + occurrence of pacing induced cardiomyopathy or an upgrading to biventricular CRT)

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Pacing Indications

Indication	Pacing option
Cardiac Resynchronization	Biventricular pacing
	His-bundle pacing
LBBB	Left bundle branch are pacing
RBBB	- Left bundle branch pacing
IVCD	- Left ventricular septal pacing
Mixed disease	LOT CRT
Right ventricular pacing	HOT CRT
AV node ablation in AF	

Limitations of BVP for CRT

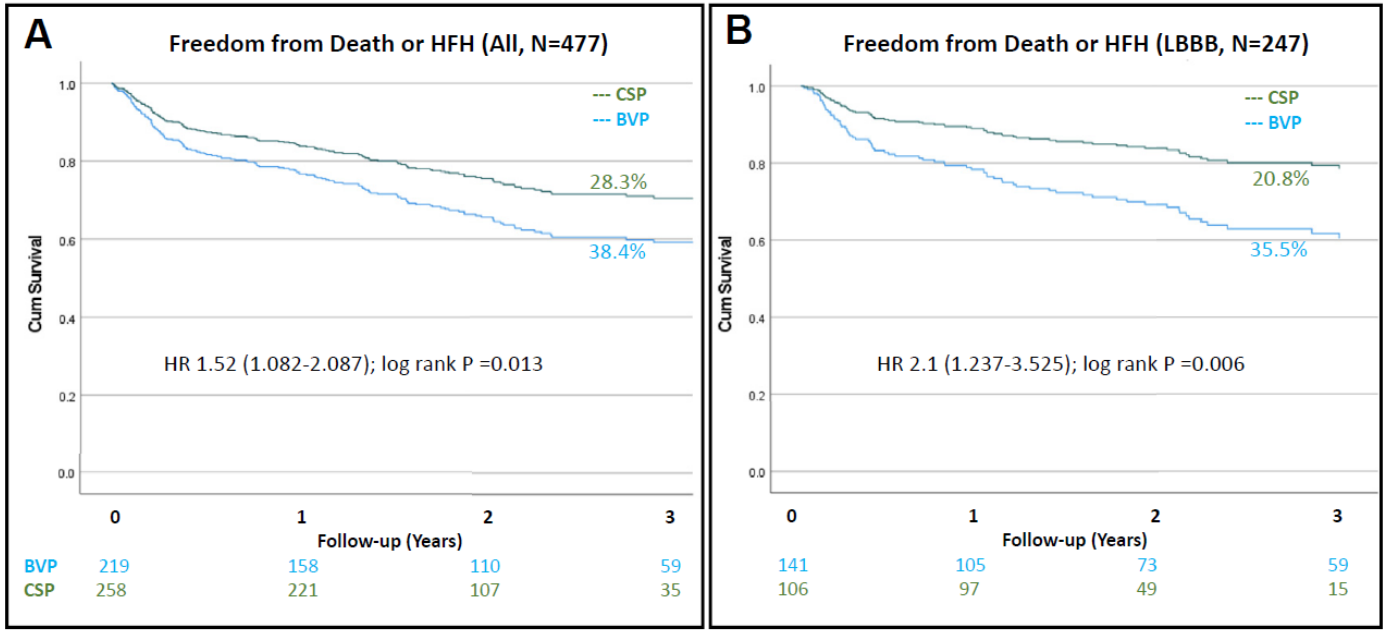
- Non-physiological RV endocardial and LV epicardial pacing
- Dependent on venous anatomy
- Phrenic nerve stimulation
- Scar related latency limiting BVP efficacy
- ~30% non-response or reduced response
- Minimal efficacy in RBBB, IVCD, normal QRS, AV block
- Opportunity to improve further

CSP vs. BiV in pateints requiring CRT [Observational]

Clinical outcomes of CSP (HBP or LBBAP) compared to BiV pacing in pateints requiring CRT

A non-randomized, observational, retrospective, two-center study showed CSP improved clinical outcomes when compared to BiVP in a large cohort of patients with class I or II indications for CRT. CSP was associated with significant reduction in the combined endpoint of time to death or heart failure hospitalization (28.3% vs 38.4%; HR 1.52; CI 1.082-2.087; p=0.013).

Time to Death or Heart Failure Hospitalization

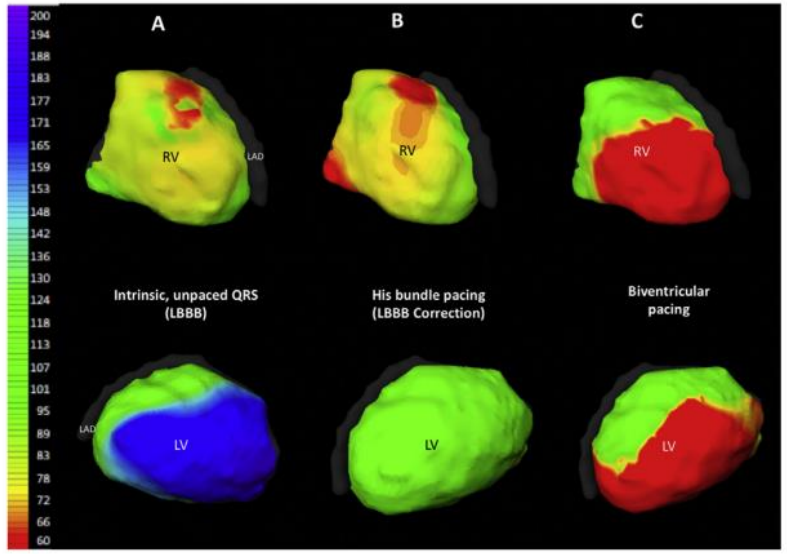


His resynchronization vs. Biventricular pacing

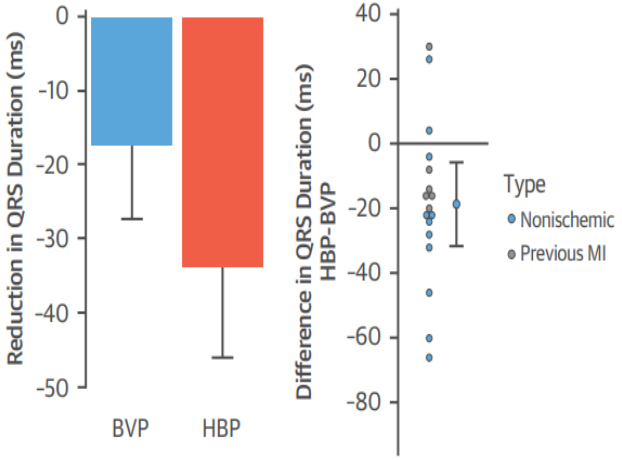
His Resynchronization Versus Biventricular Pacing in Patients With Heart Failure and Left Bundle Branch Block

Ahran D. Arnold, MBBS,[a,*] Matthew J. Shun-Shin, BMBCh,[a,*] Daniel Keene, MBChB,[a] James P. Howard, MB BChir,[a] S.M. Afzal Sohaib, MBBS, PhD,[a,b] Ian J. Wright, BSc,[a] Graham D. Cole, MB BChir, PhD,[a] Norman A. Qureshi, MBBS, PhD,[a] David C. Lefroy, MB BChir,[a] Michael Koa-Wing, MBBS, PhD,[a] Nick W.F. Linton, MBBS, PhD,[a] Phang Boon Lim, MB BChir, PhD,[a] Nicholas S. Peters, MBBS, MD,[a] D. Wyn Davies, MBBS, MD,[a] Amal Muthumala, MB BChir, MD,[b,c] Mark Tanner, MBBS, MD,[a] Kenneth A. Ellenbogen, MD,[d] Prapa Kanagaratnam, MB BChir, PhD,[a] Darrel P. Francis, MB BChir, MD,[a] Zachary I. Whinnett, BM BS, PhD[a]

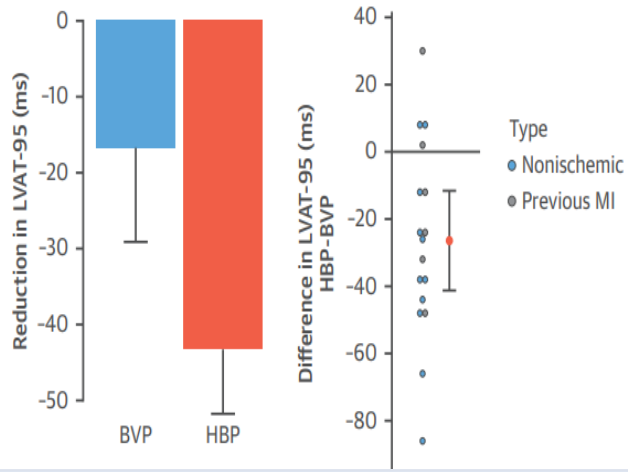
18 pateints with HFrEF and LBBB: HBP + BiV



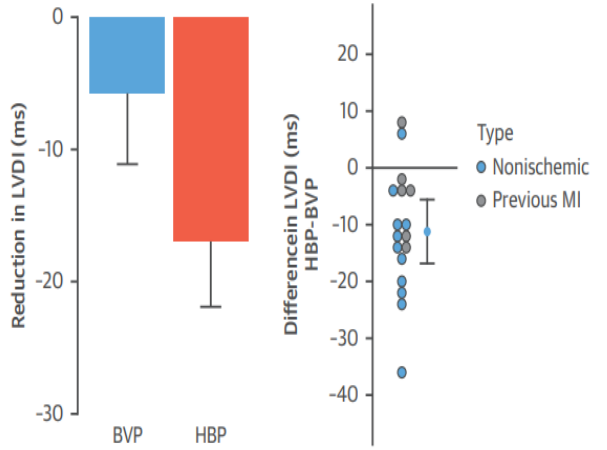
QRSd



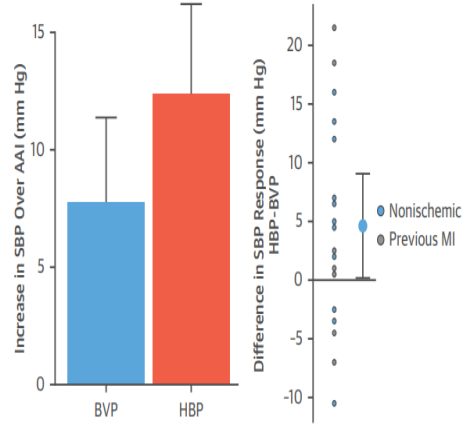
LVAT



LV dyssynchrony index



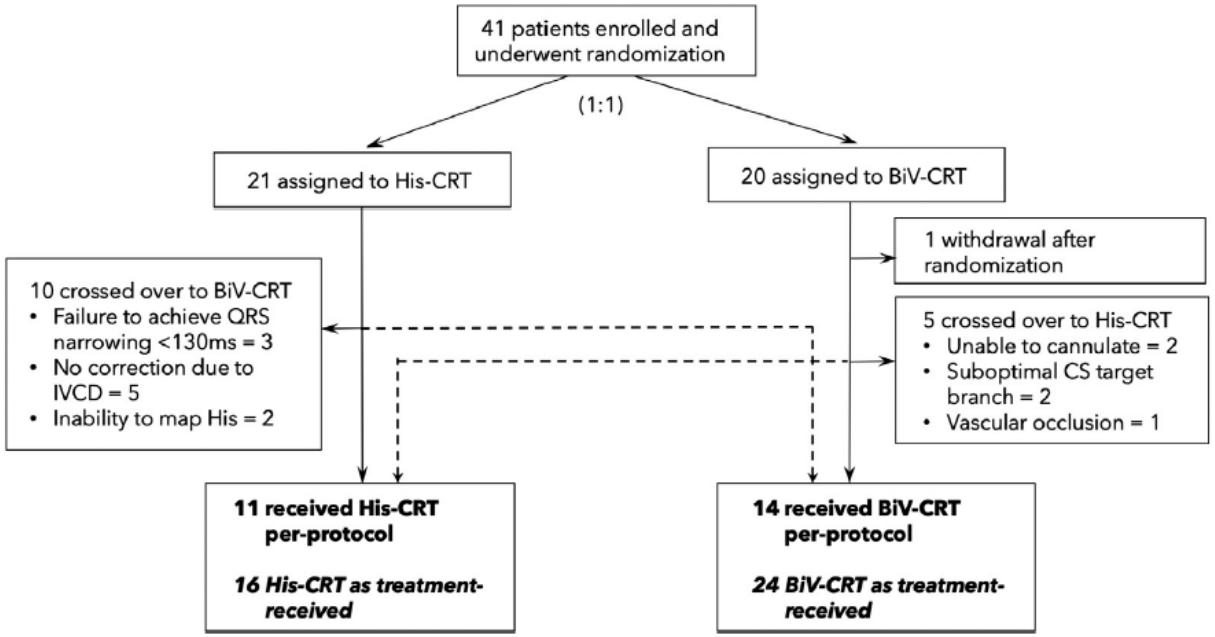
Hemodynamic

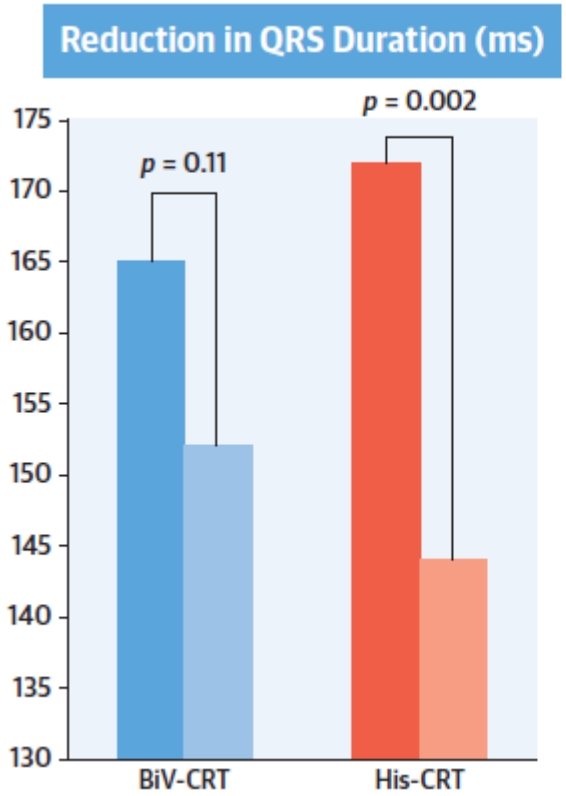


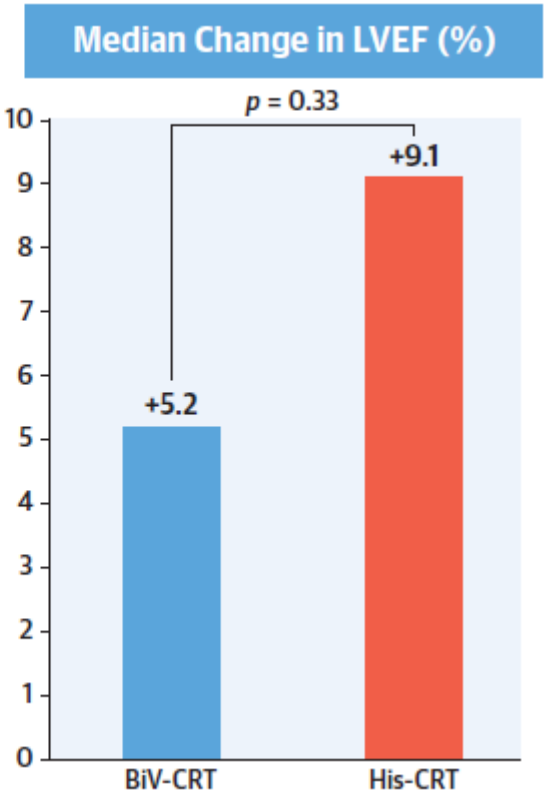
Arnold AD, et al. JACC 2018

His-SYNC pilot trial

EF 28%, NYHA II–IV patients with QRS>120 ms



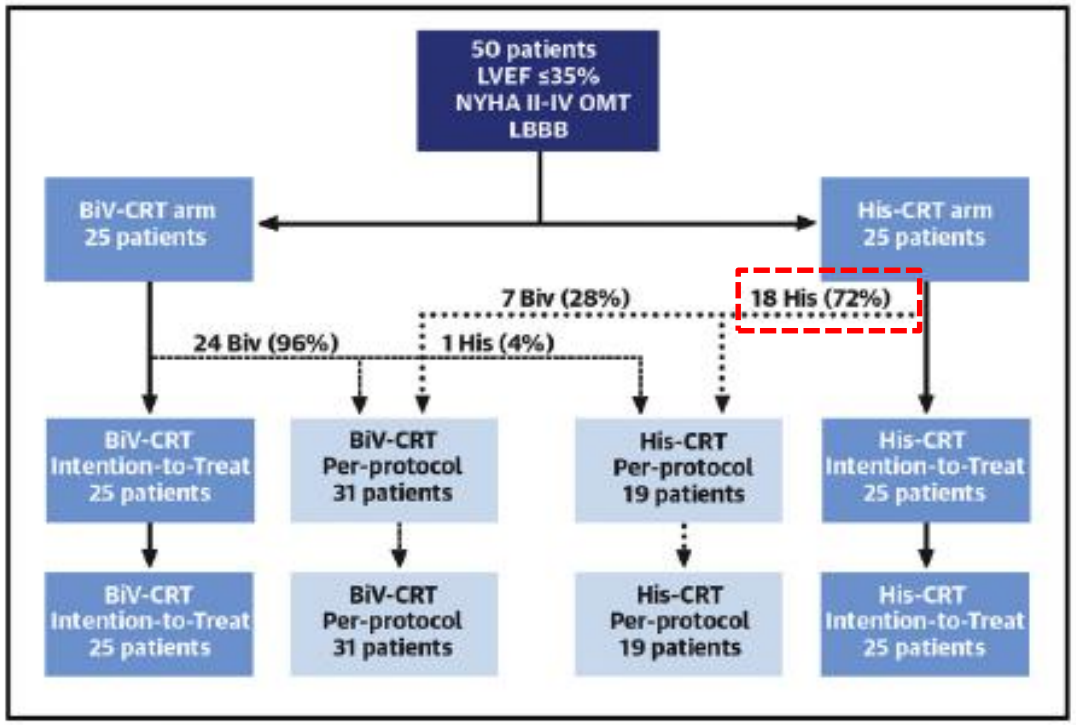




Upadhyay GA, et al. JACC 2019

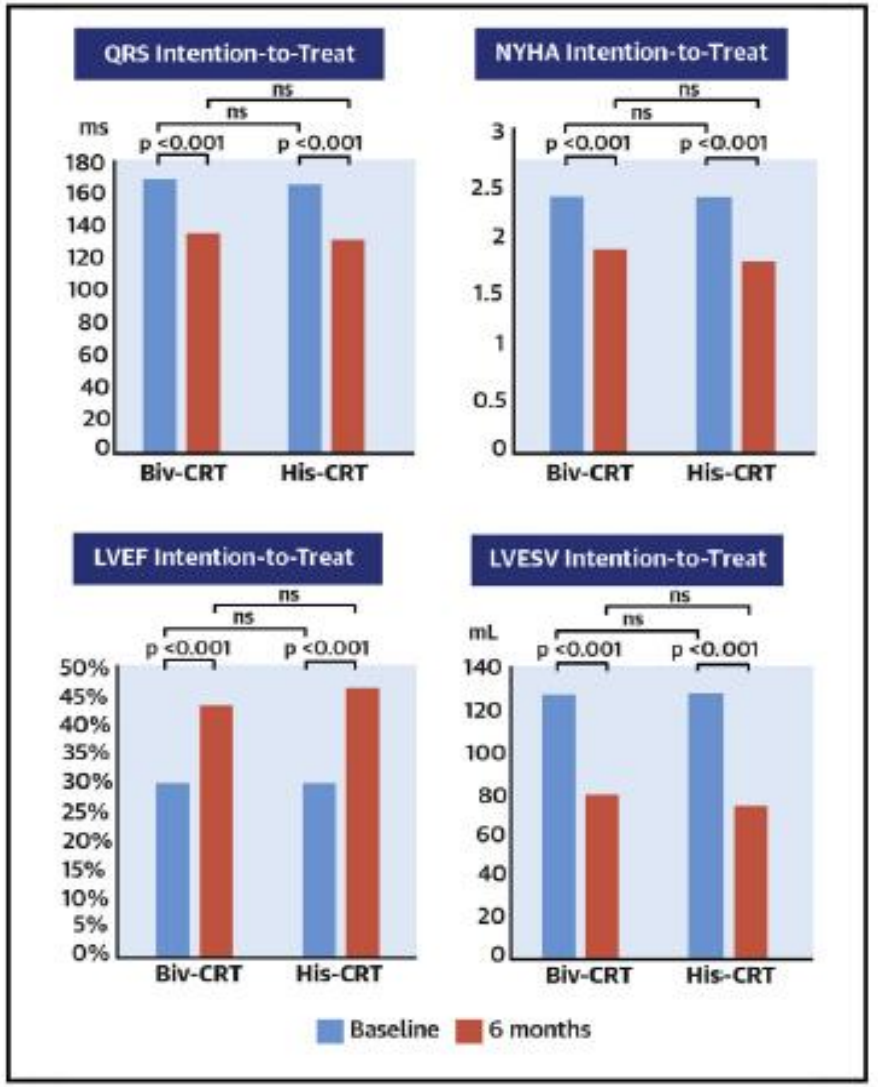
His-Alternative trial

EF <35%,
NYHA II–IV, LBBB,
QRS >130-140ms



Pacing Thresholds	Implantation (V at 1 ms dur)	6-month FU (V at 1 ms dur)
LV-leads (n = 31)	1.1 ± 0.7	1.5 ± 0.6*
His-leads (n = 19)	2.2 ± 1.2	2.4 ± 1.6*

* p <0.05 baseline vs. 6-months FU +p <0.05 His-leads vs. LV-leads



Vinther, M. et al. JACC EP 2021

LBBP-CRT vs. BiV CRT [Observational]

Comparison of LBBAP to Biventricular Pacing in Candidates for Resynchronization Therapy

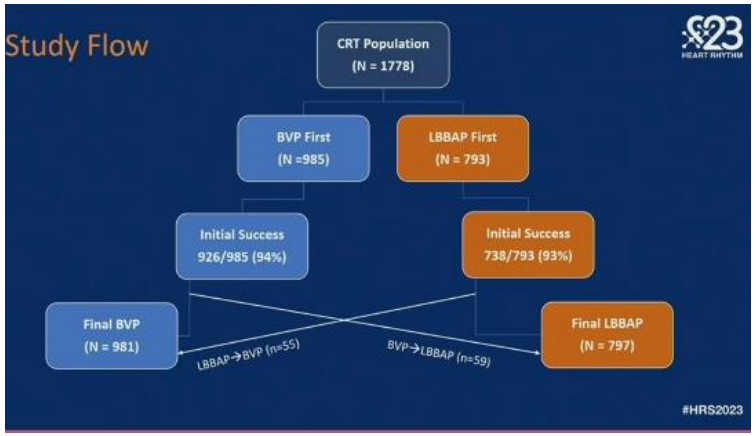
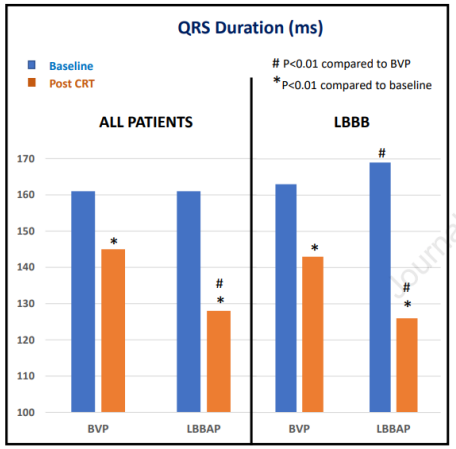
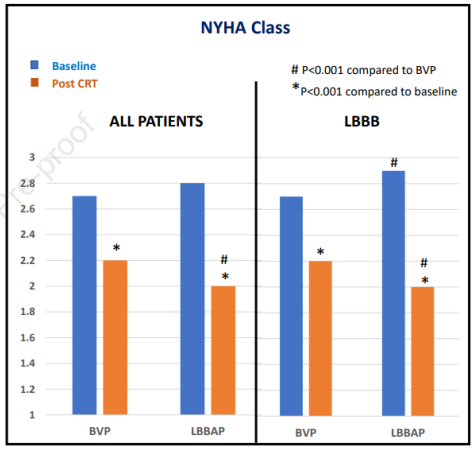
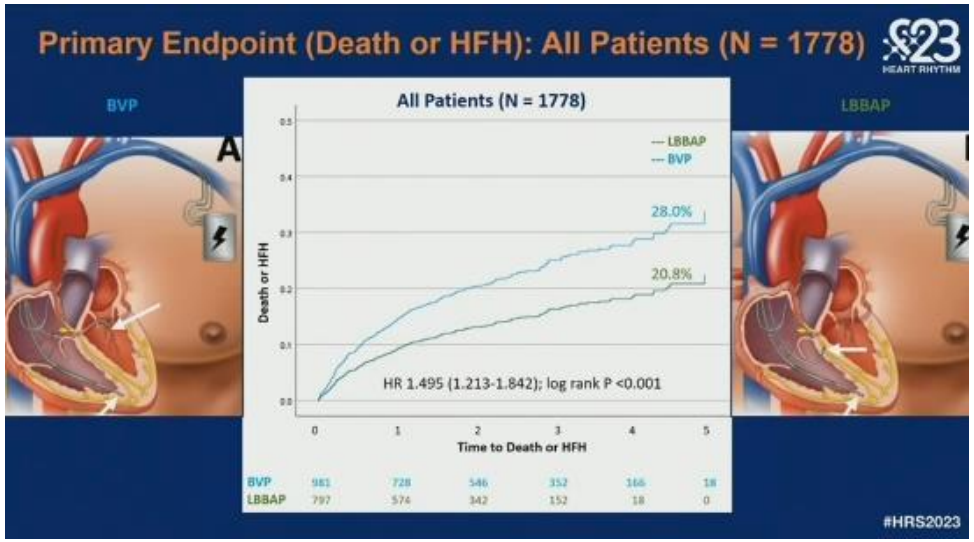
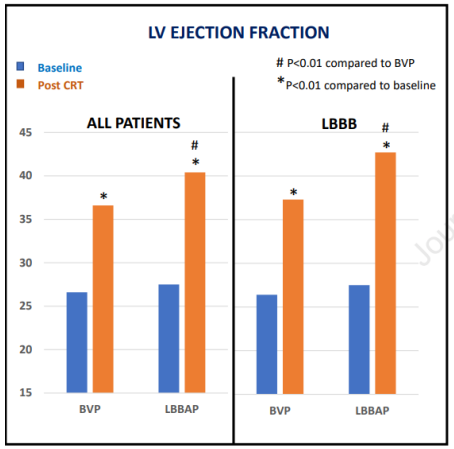


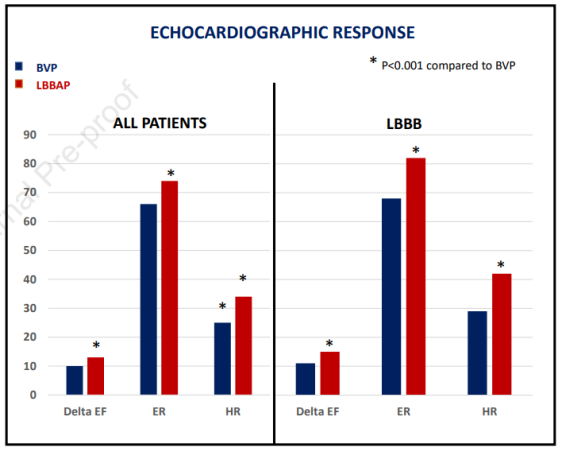
Figure 4: Change in QRS duration and Functional class following CRT









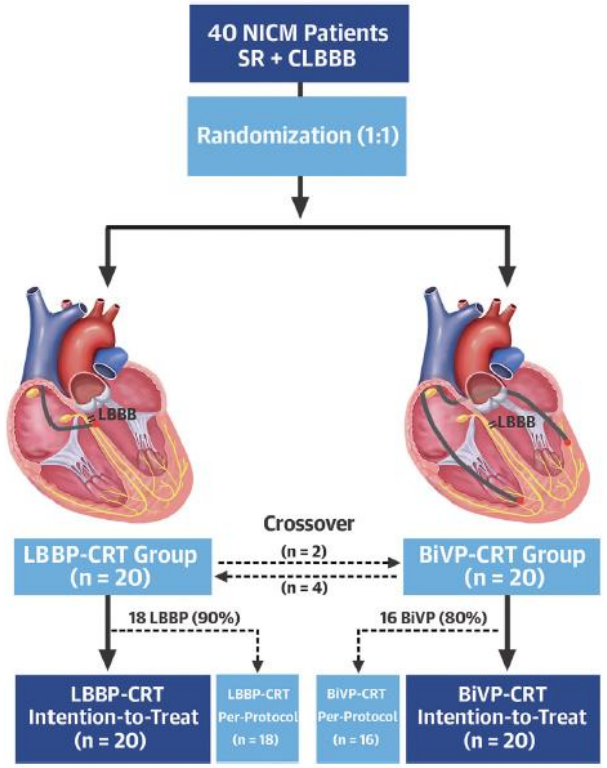


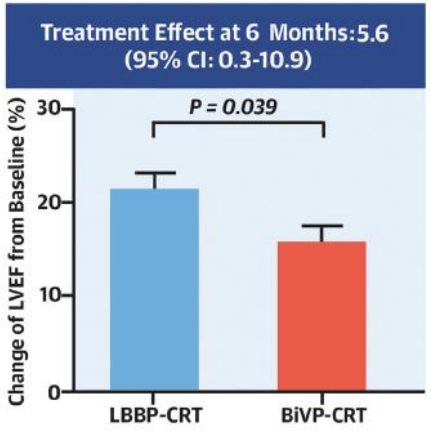
Journal Pre-proof

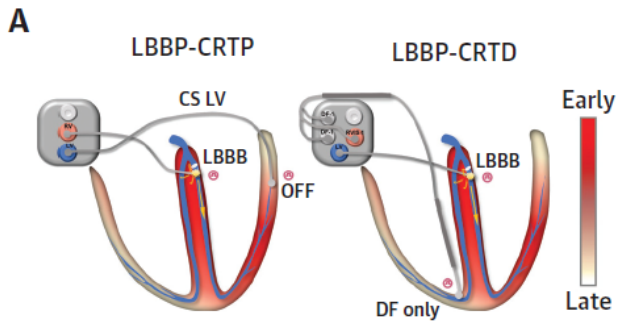
JACC 2023
Adapted from HRS 2023 Dr. Vijayaraman

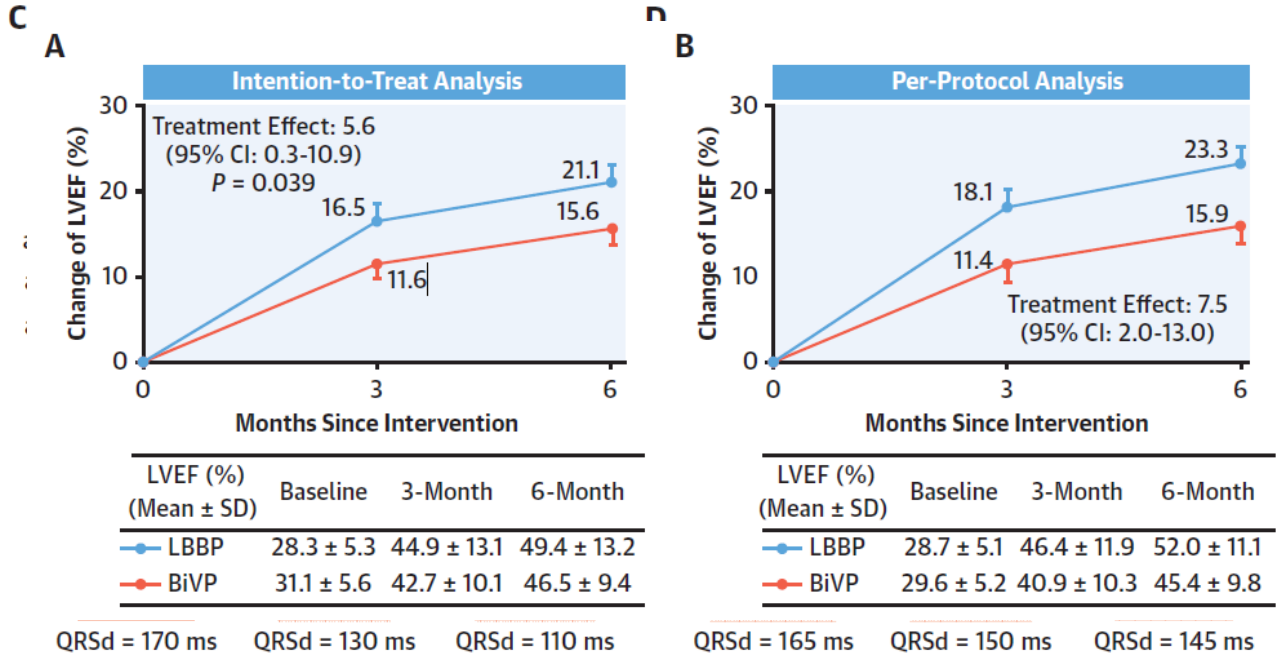
LBBP-RESYNC

EF <35%, NYHA II–IV, LBBB, QRS >130-140ms



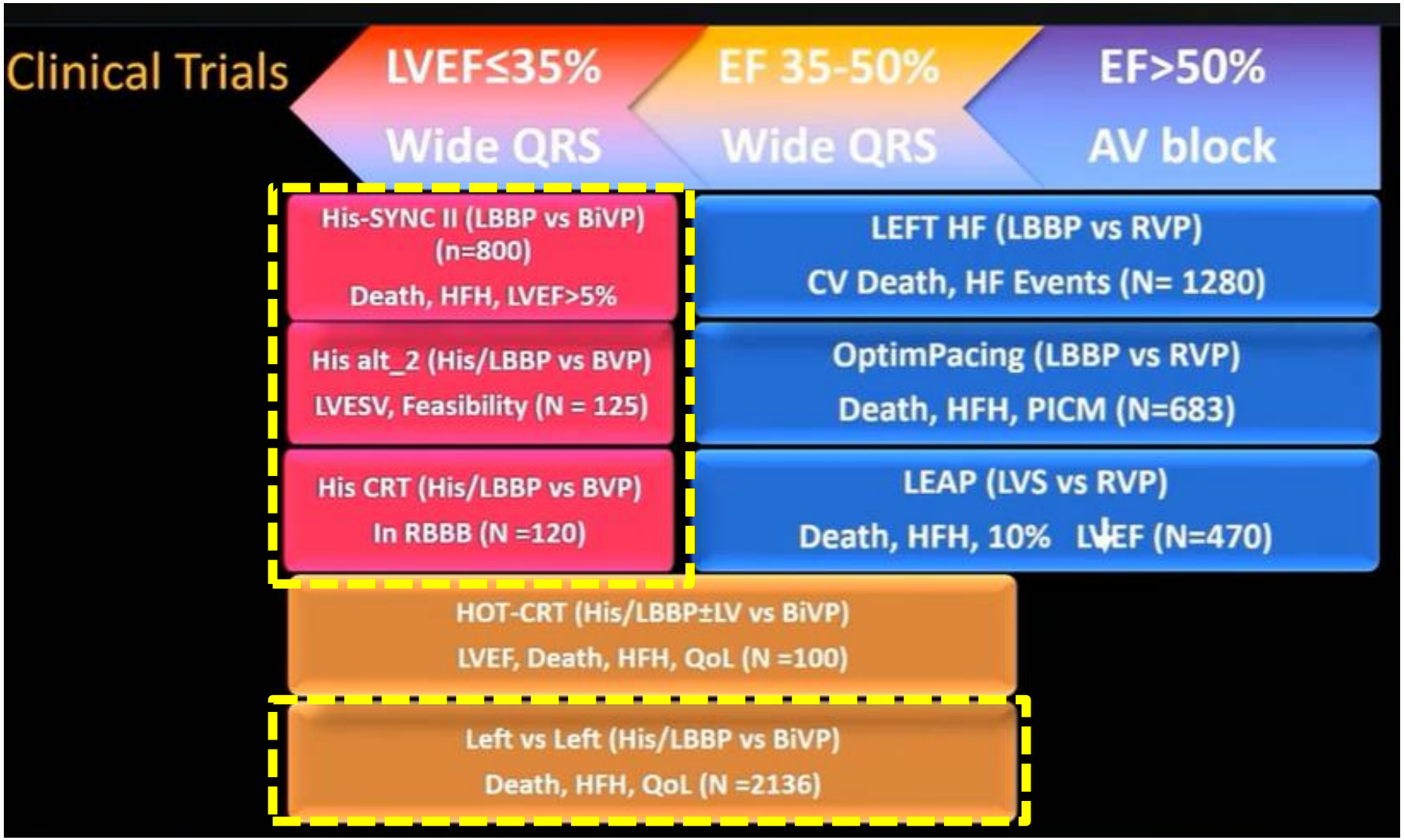






Zou et al. et al. JACC 2022

Ongoing clinical trials

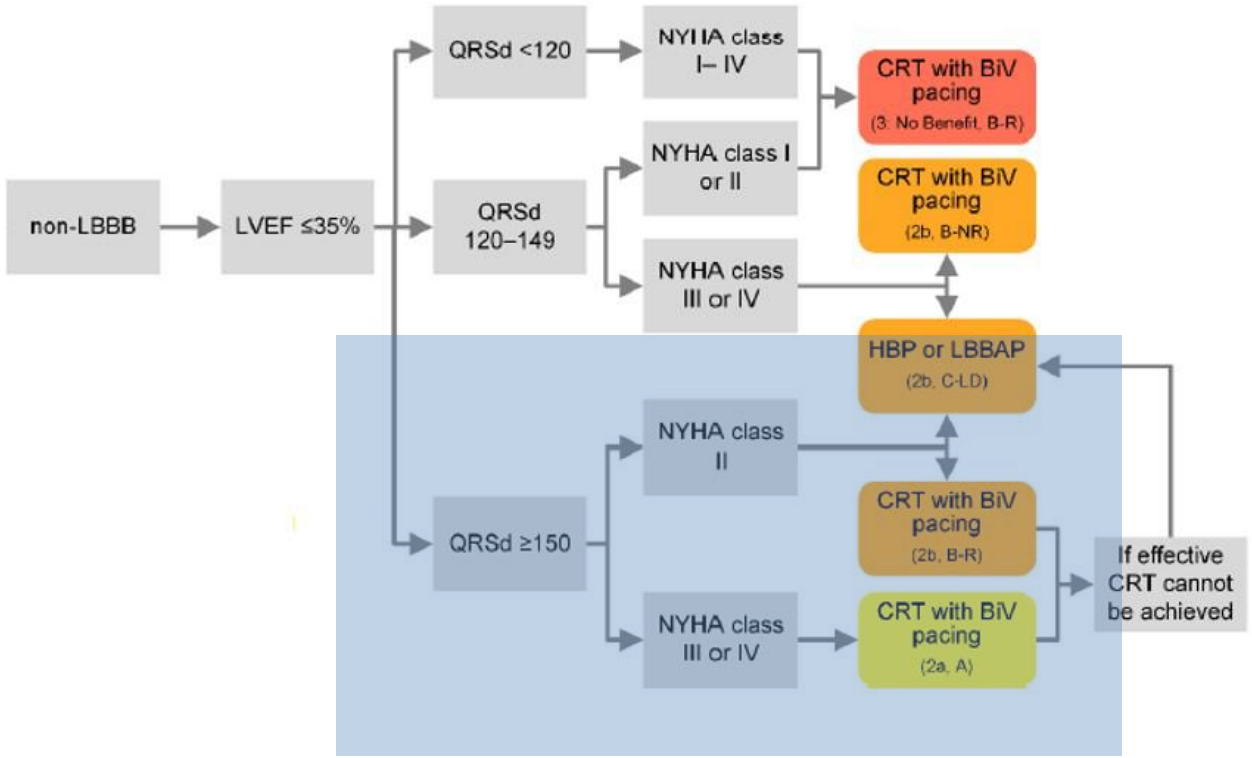


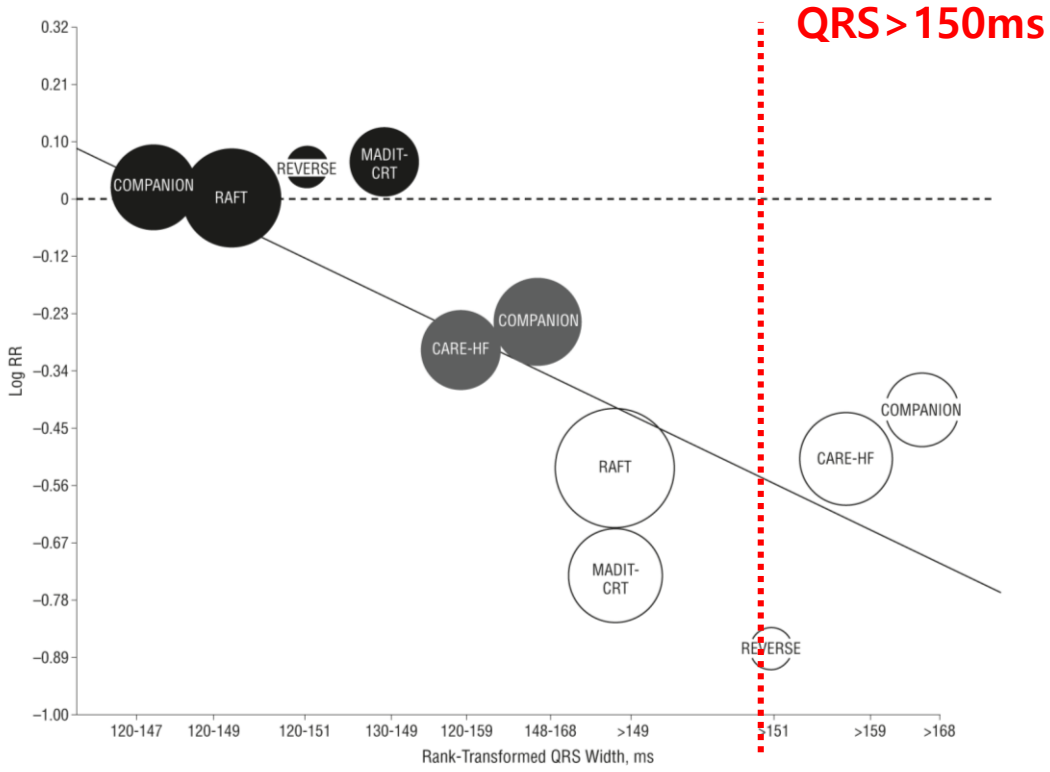
Adapted from EHRA 2023 Dr. Vijayaraman

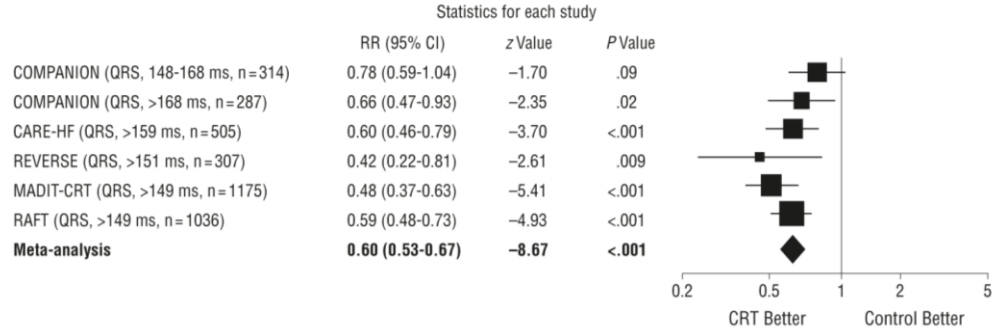
Non LBBB

Non-LBBB – QRS duration > 150ms : CRT Class IIa

Evidence of CSP – only small retrospective

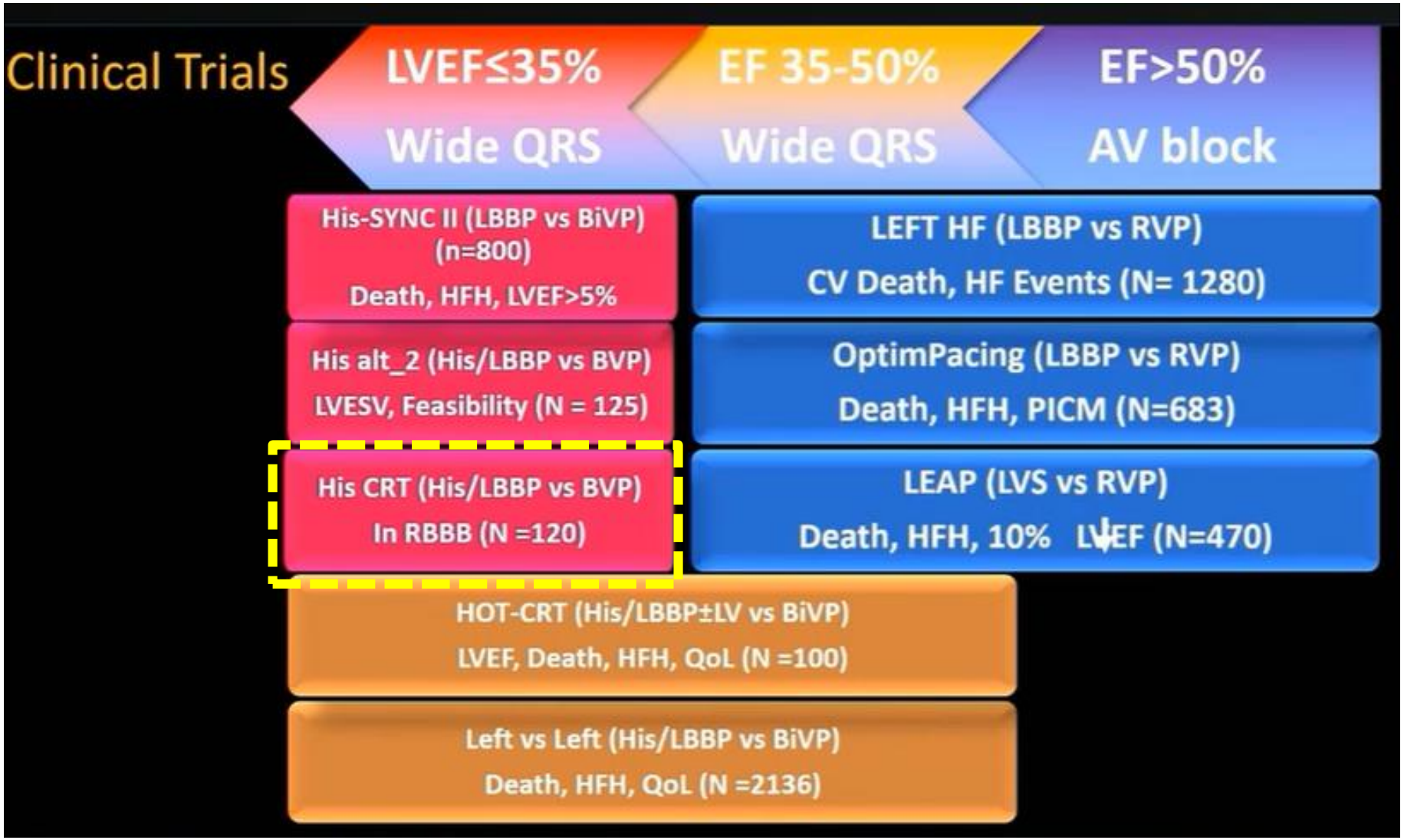






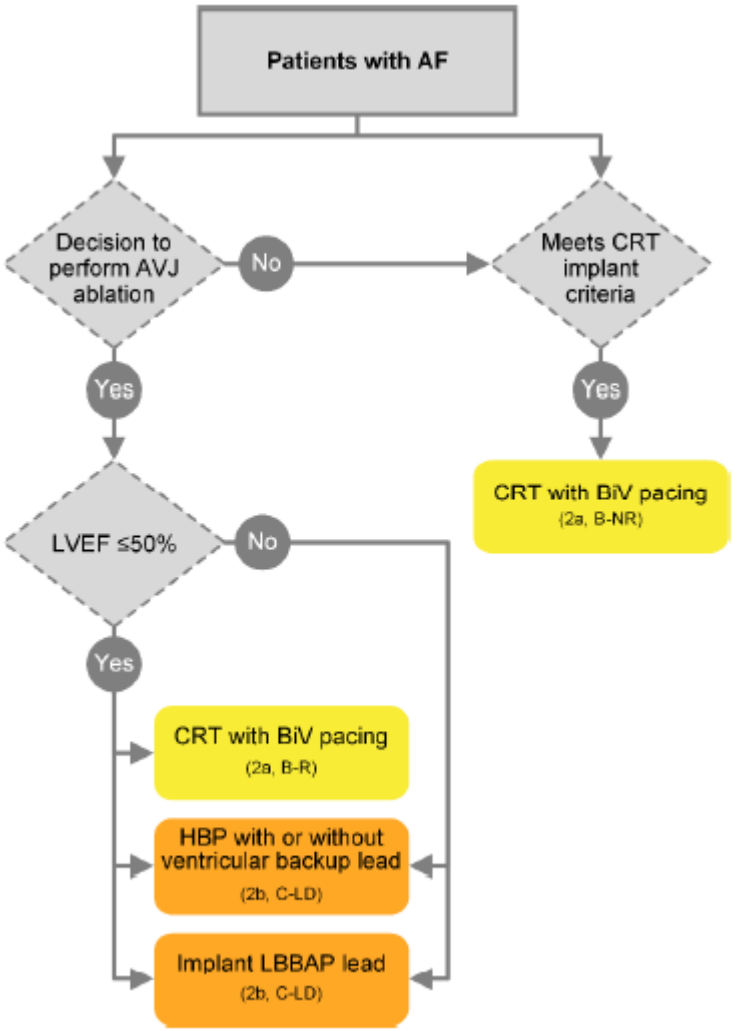
Arch Intern Med 2011

Ongoing clinical trials



Adapted from EHRA 2023 Dr. Vijayaraman

AF AVN ablation with clinical HF

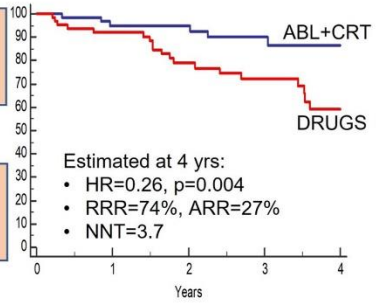


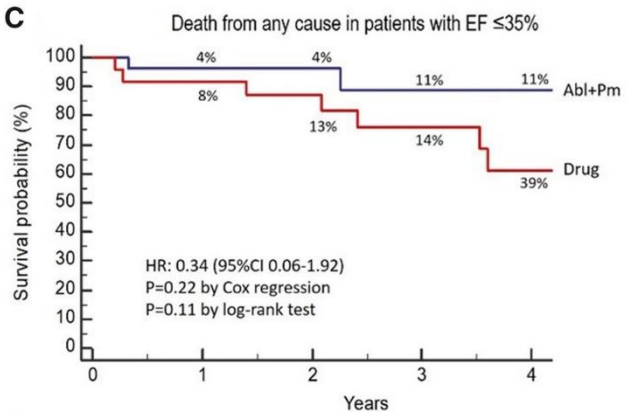
APAF-CRT trials

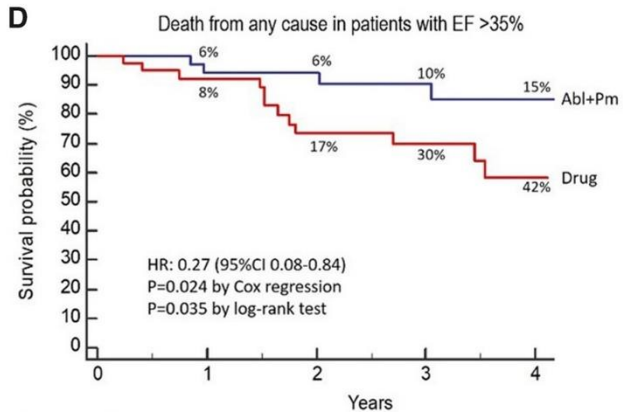
AF > 2 years, mean EF 41% (EF≤35%, 40%), HR 101 bpm

AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: The APAF-CRT Mortality Trial. ***Brignole M et al.***

Trial population	Randomization	Optimization	Death from any cause (ITT analysis)
133 pts with: • Permanent AF • Narrow QRS • ≥1 HF hospitalization • Severe symptoms	**63** Rate control **ABL+CRT**	HR = **70** bpm	**11%** (7 pts)
	70 Rate control **DRUGS**	HR = **82** bpm	**29%** (20 pts)

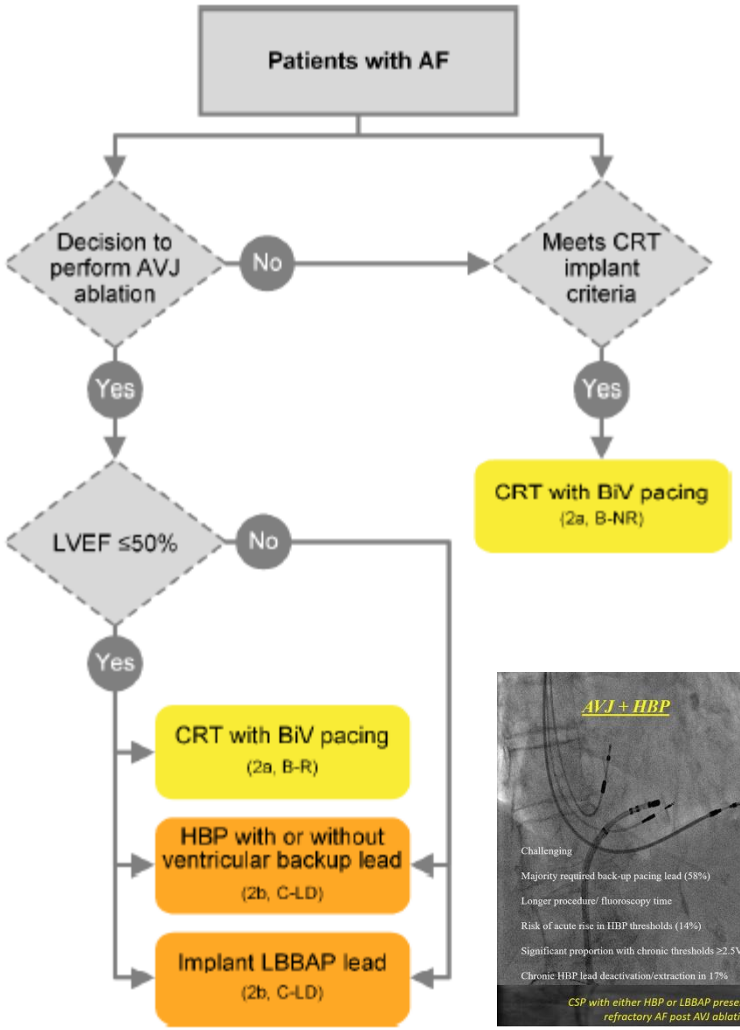


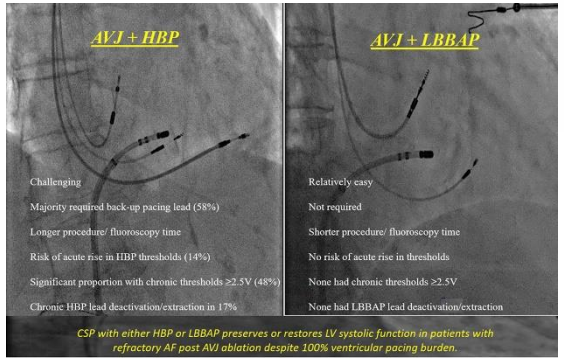




Eur Heart J 2021

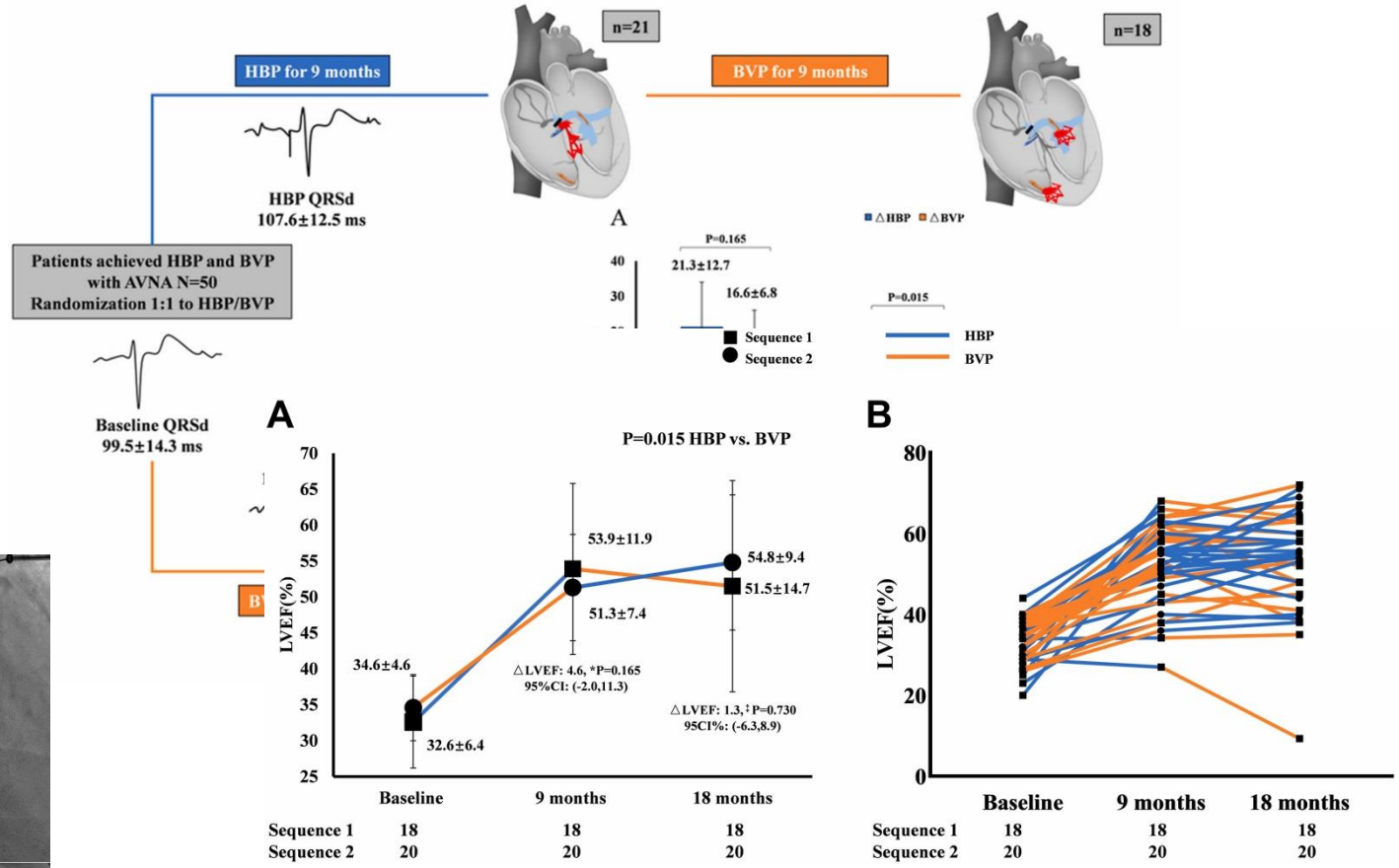
AF, AVN ablation, EF ≤40%





Alternative AF trials

HBP vs BVP AVN ablation, AF, EF≤40%



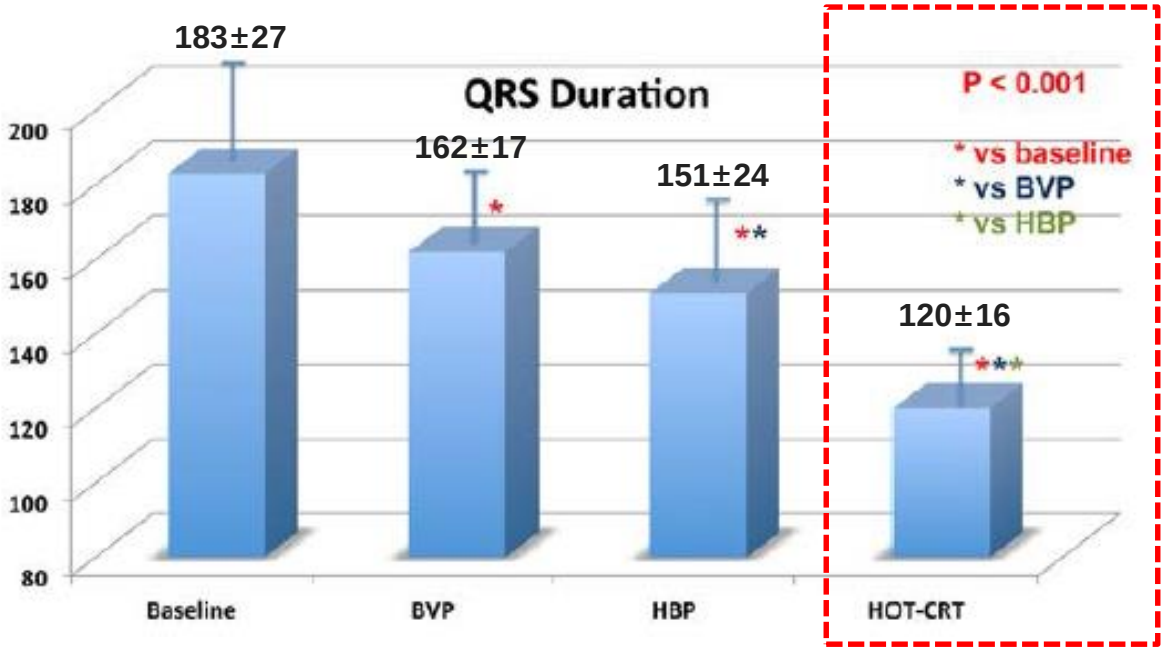
Huang W, et al: A multicenter, randomized, crossover study-The ALTERNATIVE-AF trial. Heart Rhythm 2022,.

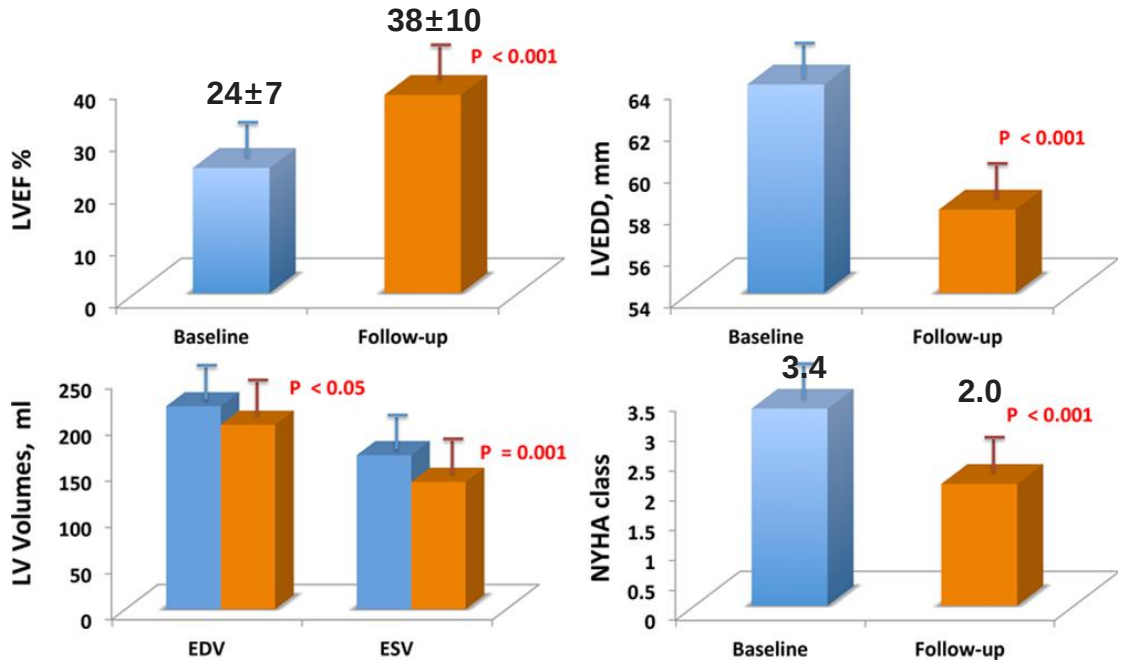
HOT-CRT (Feasibility study)

HOT CRT trials demonstrated the HBP with LV lead implantation resulted in reduction in QRS duration, improvement of EF, LV diameter and symptom relief.

27 Patients LBBB/IVCD, QRSd >140ms
NYHA class III-IV, LVEF <35%

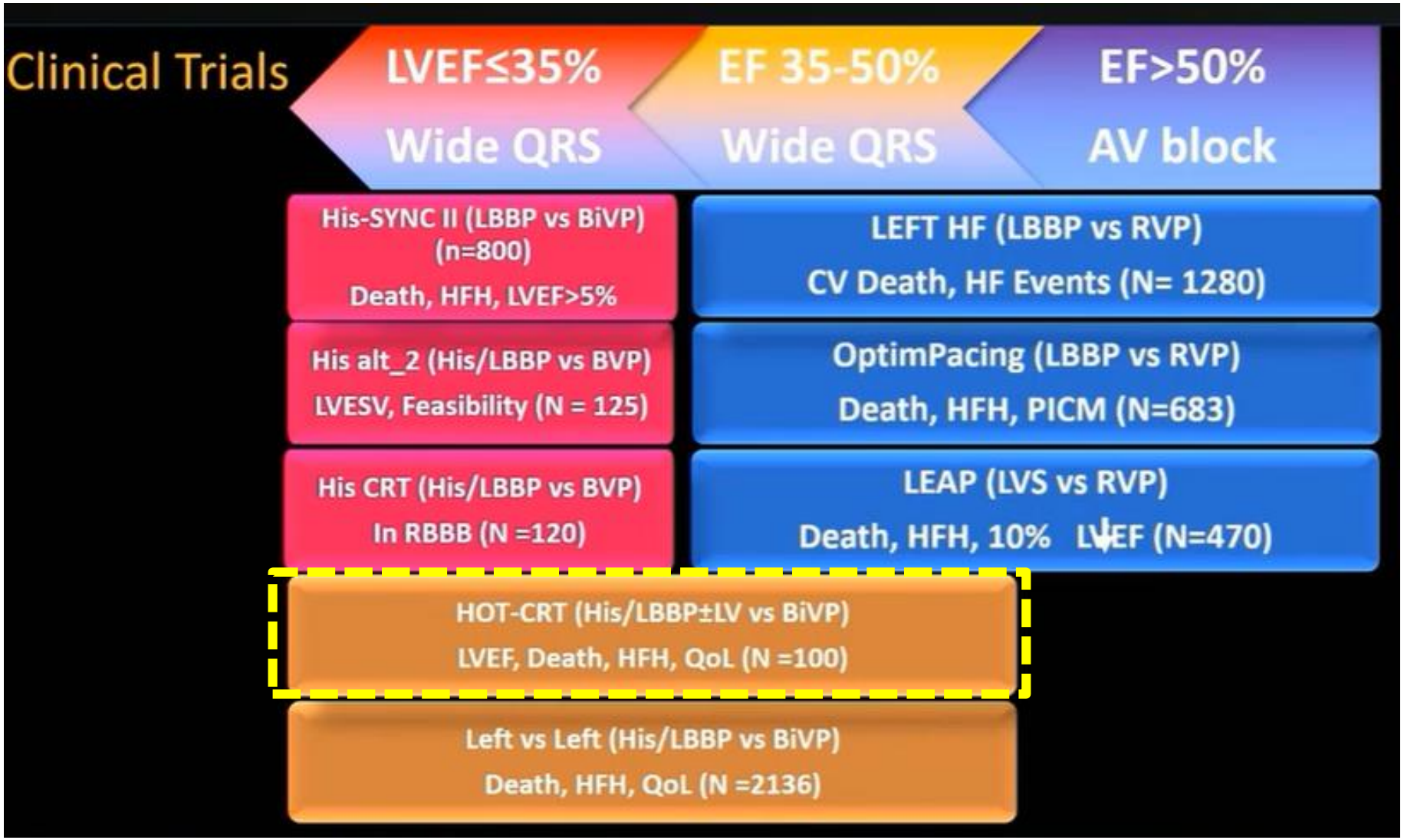
Success rate : 25/27 patients (93%)





Vijayaraman P, Herweg B, Ellenbogen KA, Gajek J. Circ AE 2019

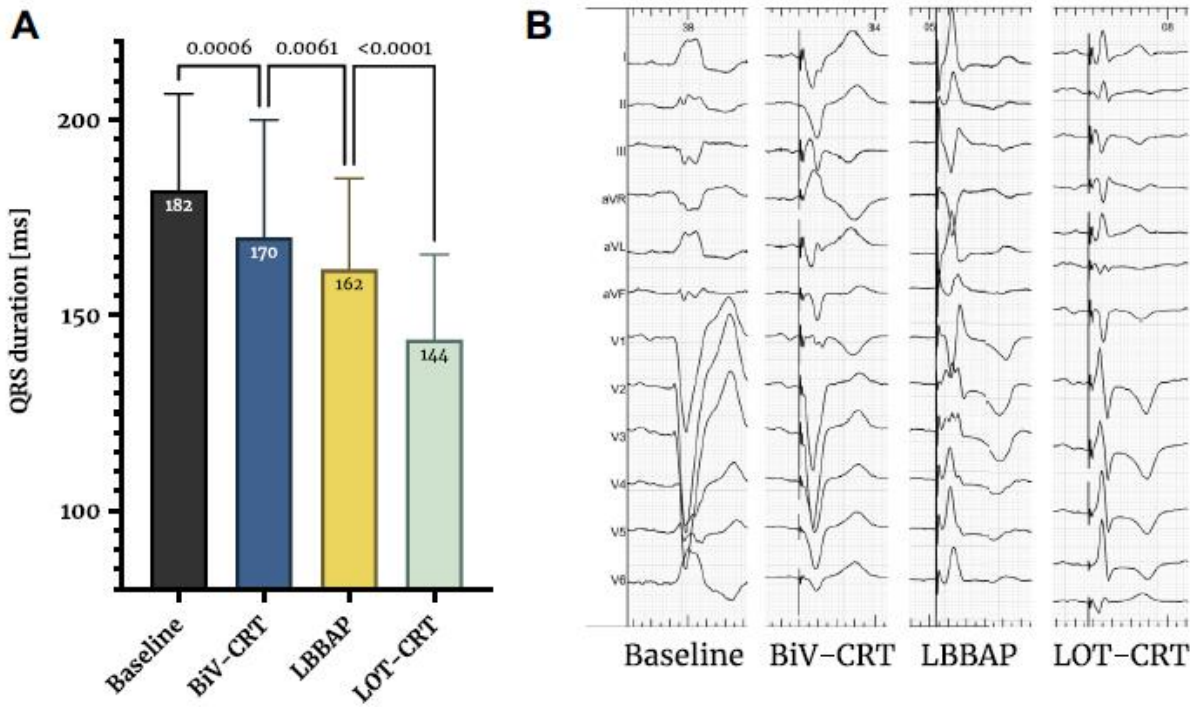
Ongoing clinical trials



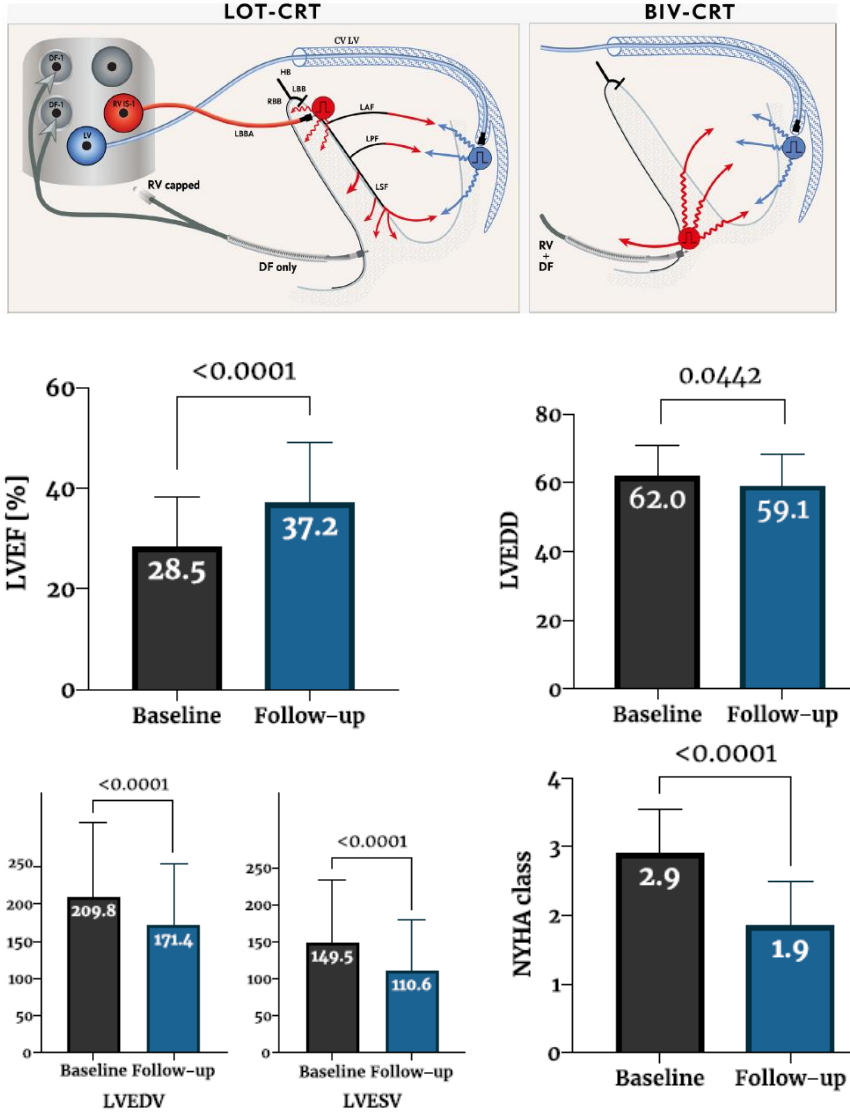
Adapted from EHRA 2023 Dr. Vijayaraman

LOT-CRT [Observational]

112 patients, CRT indications
LBBAP with CS/LV pacing
Successful in 91/112 (81%)



LOT-CRT
Narrower QRSd than BiVP, LBBAP alone
Compared to baseline, improved LVEF, LV volume, NYHA Fc



Jastrzebski M, Vijayaraman P, et al. Heart Rhythm 2021

Summary

- ***Bradycardia***

- HBP, LBBAP > RVP : lower death and HF hospitalization [observational]

- No large-scale randomized controlled trial, especially for LBBAP.

- PROTECT HF, LEFT HF, LEAP, OptimPacing, … PROTECT SYNC

Summary

- ***Bradycardia***

- HBP, LBBAP > RVP : lower death and HF hospitalization [observational]

- No large-scale randomized controlled trial, especially for LBBAP.

- PROTECT HF, LEFT HF, LEAP, OptimPacing, … PROTECT SYNC

- ***Cardiac Resynchronization therapy***

- HBP, LBBAP = or > BiV [observational]

- Small pilot studies prove the findings in observational study using surrogate outcome (QRSd, NYHA Fc Class, BNP, LVEF…)

- No large-scale randomized controlled trial, evaluating clinical outcomes

- LEFT vs LEFT, HIS-SYNC II, …

- Patients with non-LBBB (for CSP, no data), His-CRT trial

- AF AVN ablation (only for HBP, Alternative AF, no RCT data for LBBAP)

- HOT-CRT, LOT-CRT (no RCT data), HOT CRT trial…

Thank you for your attention