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# Future Directions in Electrophysiology: A case-based discussion

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85 year old female with history of heart failure and persistent atrial fibrillation with rapid ventricular rates has cardiomyopathy (mildly enlarged LV and LVEF 40-45%), moderate to severe mitral regurgitation, and ongoing fatigue with dyspnea on exertion.

In addition to maximally-tolerated GDMT for cardiomyopathy and HFrEF, what would be your next step?

- A. Optimize rate control and consultation to Valve clinic for MitraClip
- B. Cardioversion and trial of rhythm control with amiodarone
- C. Catheter ablation for persistent atrial fibrillation
- D. Implant of cardiac resynchronization therapy (CRT-P) and AVJ ablation
- E. Implant of left bundle pacing system and AVJ ablation
- F. Micra leadless pacemaker implant and medical therapy for rate control
- G. Ask GPT-4



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## Update on Novel AF Ablation Technology

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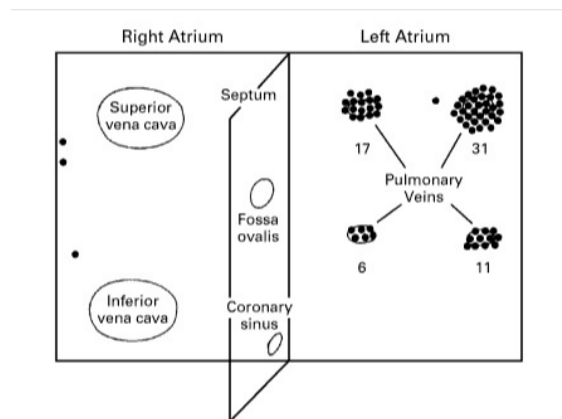
## AF Subtype Different pathophysiology

- Paroxysmal AF:
  - Less than 7 days AF – spontaneous termination is common
  - Focal triggers initiate fibrillatory activity
  - Absence of atrial fibrillation driver sites for maintaining continuous AF.
- Persistent AF:
  - More than 7 days of continuous AF – spontaneous termination is rare
  - Triggering sites play a role, but additional sites maintain atrial fibrillation; without drivers, AF experimentally terminates within minutes.

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## AF Pathophysiology Background – Triggers

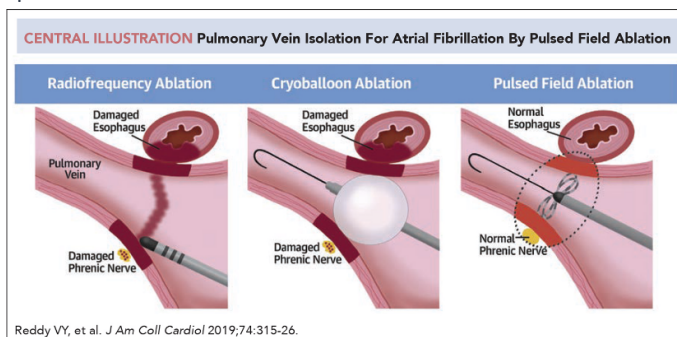
- 1998 – Dr. Haissaguerre et al\* described focal discharges initiating AF
  - 94% of AF triggers were from within the pulmonary veins



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## Pulse Field Ablation (PFA) For Paroxysmal AF

- PFA is an innovative, non-thermal energy source technology
- PFA works by delivering controlled, high-voltage, ultra-short electrical pulses that cause irreversible electroporation



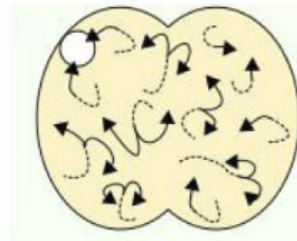
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## AF Pathophysiology PVI / AF Trigger Ablation - Outcomes

- Paroxysmal AF
  - PV isolation alone with optimal contact-force radiofrequency or second-generation cryoballoon ablation has been reported to achieve an approximately 80% 1-year freedom from AF
- Persistent AF
  - PV isolation alone 55% 1-year freedom from AF
  - Perhaps due to the presence of non-PV drivers.
- Ablation of localized AF drivers is theorized to enhance freedom from AF recurrence in persistent AF patients and paroxysmal AF cases driven by non-PV sources.

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## AF Pathophysiology Background



- Dr. Moe's 1959 multiple wavelet hypothesis: atrial fibrillation (AF) is self-sustaining and maintained by multiple independent reentrant wavelets that constantly change.
- Factors for multiple wavelets development: atrial size for sufficient surface area, heterogeneous conduction velocity, and tissue refractory periods.
- Hypothesis' significance: experimentally confirmed in 1985 and contributed to the development of the MAZE surgical procedure.



\*Am Heart J. 1959;58(1):59-70

\*\*Cardiac electrophysiology and arrhythmias, 265-275.



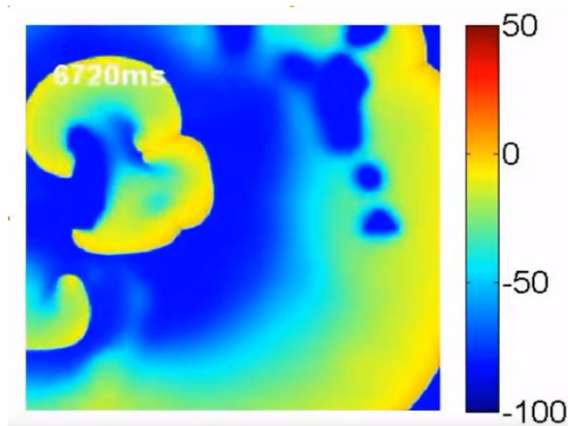
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## AF Pathophysiology Persistent AF driver types

AF drivers are atrial regions that maintain AF

Several types are thought to exist including:

1. Rotors:
  - Spiral wave reentry circuits that maintain atrial fibrillation through self-sustaining rotational activation.
2. Focal impulses:
  - Rapid, localized electrical discharges that initiate and propagate atrial fibrillation.
3. High-frequency or complex rotors:
  - Rotational circuits with irregular or faster electrical activity that can maintain atrial fibrillation.



Hwang M, et al PONE 2016.

<https://doi.org/10.1371/journal.pone.0140695>



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## Ablation of Persistent AF

Many methods have attempted to improve outcomes

1. Focal impulse and rotor modulation (FIRM) mapping: Identifies rotors and focal impulses as drivers of atrial fibrillation.
2. Electrogram-based mapping: Uses complex fractionated atrial electrograms (CFAEs) to identify areas of slow conduction and potential AF drivers.
3. Phase mapping: Analyzes the phase of electrical activation in atrial tissue to identify and localize rotational drivers.
4. Body surface potential mapping (BSPM): A non-invasive technique that records electrical potentials on the body surface to localize AF drivers and guide ablation therapy.
5. High-density voltage mapping: A technique that uses high-resolution electrode catheters to acquire detailed voltage information in the atrium, identifying low-voltage areas associated with atrial fibrillation drivers.
6. Spatiotemporal dispersion mapping: Studies the dispersion of electrical signals over time and space to pinpoint regions of AF drivers



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## AF Driver Mapping with Ripple General Concepts –Ripple Map Display

- Graphical marker displays a combination of:
  - Depolarization frequency
  - Electrogram fractionation
  - Voltage
- The Ripple display corresponds directly to the recorded electrogram, with no interpolation between points or other processing.
- An acquired point is not assigned just a single activation time value
- Ability to visualize all electrical events per acquired point
  - Double potentials
  - Fragmented potentials

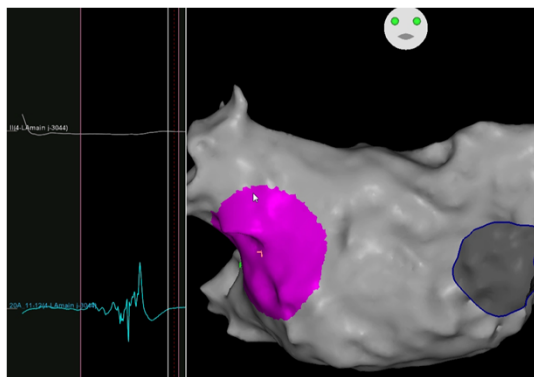


Figure: Fractionated electrogram as displayed by Ripple map

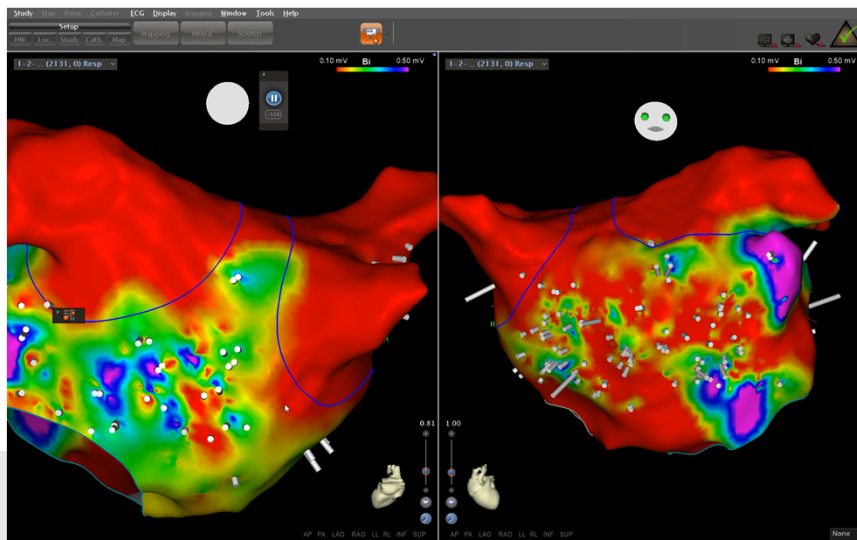


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## AF Driver Mapping with Ripple AF example: Redo AF Procedure - Ripple Map

- Definition: High Frequency Ripple Activation (HFRA)
- Atrial sites with near continuous and high frequency atrial depolarization as displayed by Ripple map

Figure: Bipolar map with Ripple. HFRA observed - left atrial septum

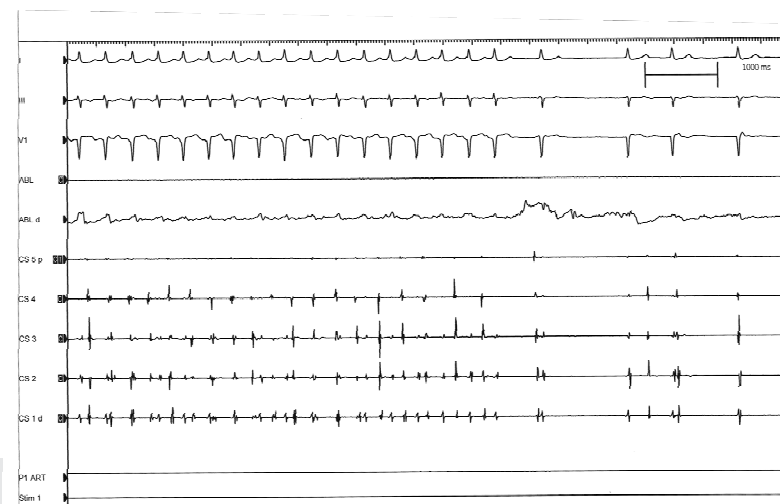


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## AF Driver Mapping with Ripple AF example: LA Septal ablation terminates AF

- Ablation of the HFRA site on LA septum terminated AF to NSR

Figure: Surface and intracardiac electrograms at time of AF termination

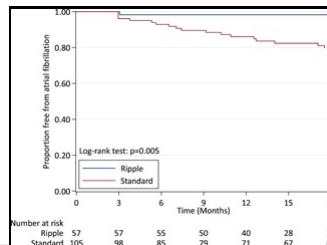


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## AF Driver Mapping with Ripple Ripple Map EGM substudy

- In our prior study involving 162 persistent AF patients, we compared the ablation of high-frequency rotor areas (HFRA) to a standard approach.
- Ripple map guided ablation resulted in higher acute AF termination (91.2% vs 52.4%) and 18-month AF freedom (98.2% vs 81.4%) compared to the standard stepwise approach



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## AF Driver Mapping with Ripple Ripple Frequency Mapping

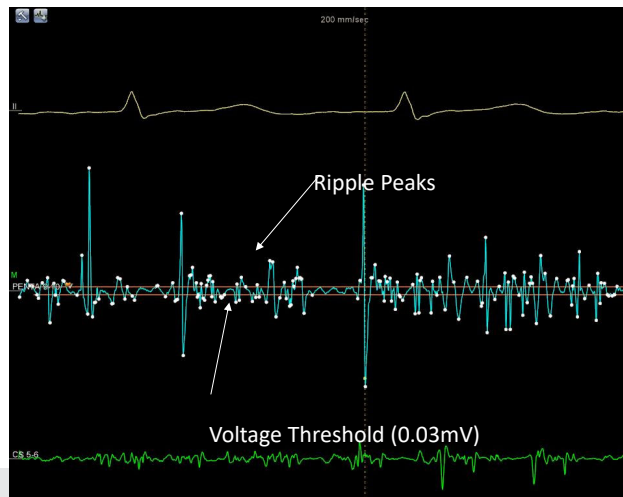


Figure: Example of Ripple Frequency algorithm markers on an electrogram obtained during AF. The white markers represent a Ripple peak that was counted by the algorithm. The Orange lines delineate the pre-set voltage thresholds of  $\pm 0.03\text{mV}$  from baseline  $0\text{mV}$ .



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## AF Driver Mapping with Ripple Frequency Map Example

- 510K FDA approval 2022
- World's 1<sup>st</sup> Case at MHI  
September 2022
- Runs on existing Carto  
mapping system which is  
available in 80% of the  
worlds EP labs

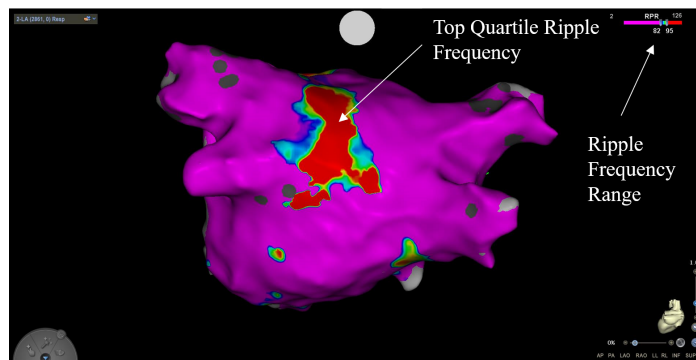


Figure: Example of Ripple Frequency map obtained during sustained AF. Color shading represents the Ripple Frequency. The Ripple Frequency range in this example was 2 to 125 /s. The red color represents Ripple Frequency more than 75% above the maximum (in this case, 95/s). The purple color represents Ripple Frequency less than 65% of the maximum (in this case 82/s). A total of 2861 points were acquired for this map with even distribution across the atrium. Analysis of this map demonstrated a large region of high Ripple Frequency at the confluence of the left posterior PV antrum and posterior wall. Ablation of this location resulted in AF termination to NSR.

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## AF Driver Mapping with Ripple Frequency Study

- During the initial ablation procedure
  - Acute AF termination was observed in **88.1%**
- The fastest quartile of Ripple Frequency was present in non-PV sites necessary for AF termination
  - **90.2%** sensitivity and **86.5%** specificity
- Relatively small regions of the atrium
  - Encompassing only **5.6 ± 5.1%** of the total atrial surface area

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## AF Driver Mapping with Ripple Frequency Study

- Following a mean duration of 13.8 months, and using symptoms, electrocardiogram, Holter monitor, or device interrogation for documentation
  - **92.9%** were free from AF
  - 79.8% were free from any arrhythmia
  - \*average of 1.2 ablation procedures performed per patient.

	Ripple Map
Follow-up duration (days)	406 ± 141
Freedom from Documented Arrhythmia – no. (%)	
AF	78 (92.9)
AT/AFL	70 (83.3)
Any atrial arrhythmia	67 (79.8)
Additional ablation performed for AF or AT/AFL	15 (22.0)
Number of ablations performed per patient	1.2 ± 0.4
Cardioversion for AF or AT/AFL within 90 days of index ablation	15 (17.9)
AAD at last follow-up	18 (26.4)
Holter Performed or Implanted Device Present	26 (31.0)



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## Conclusion

- Pulmonary vein isolation (PVI) alone may not yield sufficiently high success rates in persistent AF patients.
- Previous research supports the hypothesis that high-frequency or complex rotors may be important in many persistent AF cases.
- Automated Ripple Frequency analysis has shown promise as for identifying regions of interest in persistent AF and improving outcomes.



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## **CRT in Patients Post AVN Ablation for Fast Atrial Fibrillation**

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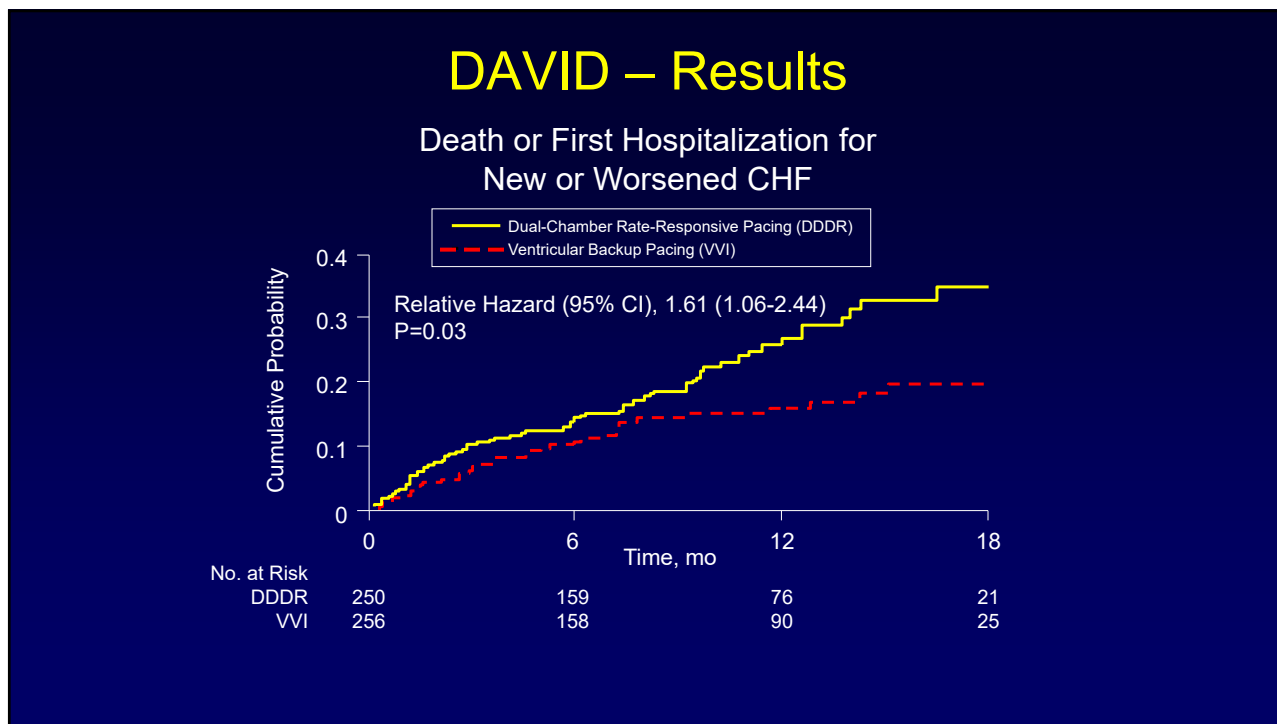
Allina Health

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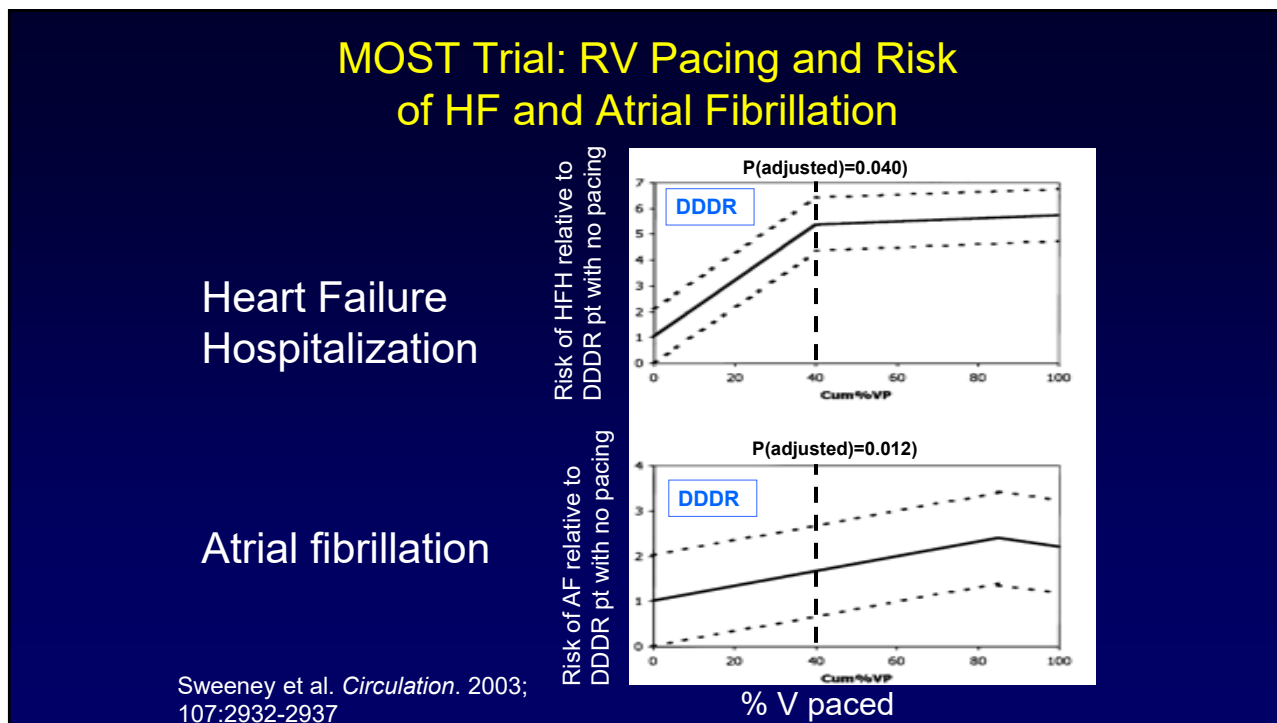
## **General Comments**

1. If you can manage patient with adequate rate and/or rhythm control then that is preferred to AVN ablation and placement of a PPM or CRT device
2. If you need to do AVN ablation for rate control of AF, then have a very low threshold for providing LBBAP and/or CRT rather than standard RV pacing
3. After placement of a CRT device, optimization of programming is essential (but infrequently or inadequately done)

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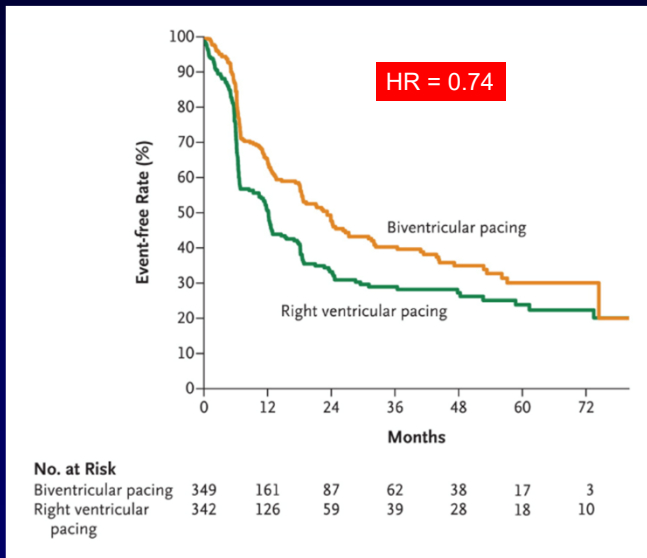


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Block-HF: Freedom from primary outcome event  
 (death, urgent HF visit, > 15% increase LVESV)

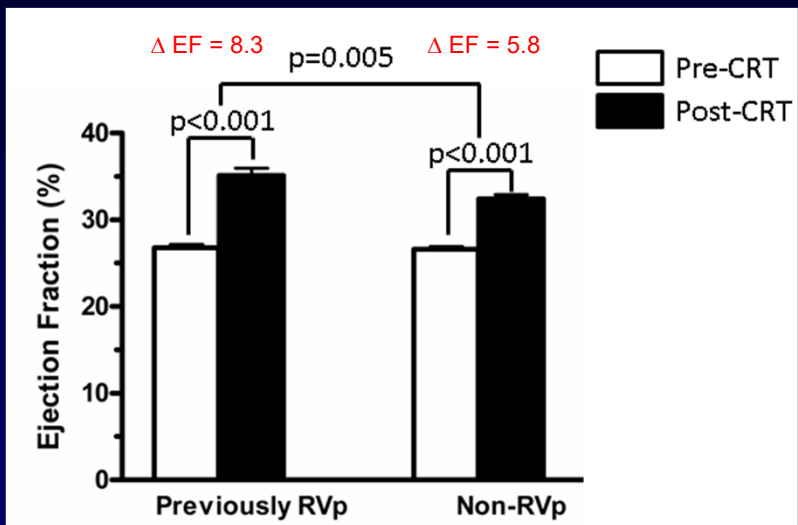
Patient Population

- Pacing for AVB
- HF
- EF  $\leq$  50%



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ECHO Response to CRT in RVp and Non-RVp HF Patients



Gage RM, Burns KV, Bank AJ. Echo and Clinical Response to CRT in HF Patients with and without Previous RV Pacing. *EJHF* 2014.

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## Management of Patients post-CRT

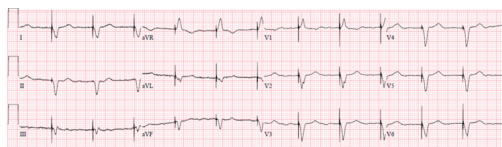
1. All patients post-CRT need to be evaluated and followed closely by a Cardiologist
2. Routine tests needed post-CRT
  - A. Echo
    1. Has EF improved?
    2. Is there mechanical dyssynchrony?
  - B. ECG
    1. Is the patient receiving CRT?
    2. Is there electrical dyssynchrony?
  - C. Device check
    1. What is % CRT delivery?
    2. How is patient programmed?
3. Medical management
  - A. Addition and uptitration of HF meds
  - B. Decrease in diuretic dosages in some patients

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### Electrical/Mechanical Dyssynchrony: Practical Clinical Tips to Identify Patients Needing Optimization



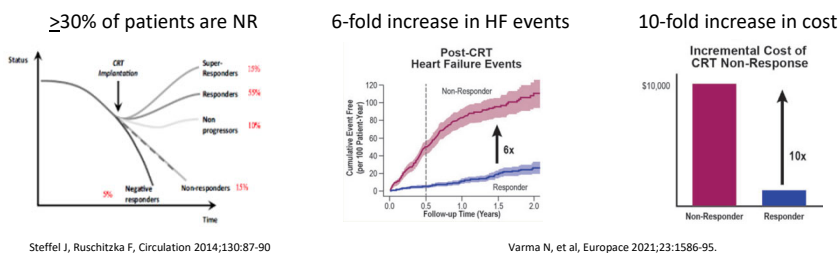
1. Order/review 12-lead ECGs on all patients post-CRT
2. Is QRS really wide? Is QRS amplitude high?
3. Are there deep Q waves in multiple chest leads?
4. Is net AUC V1-6 markedly negative or positive?
5. Is EF low?
6. Is there evidence of mechanical dyssynchrony on echo?
  - Dyssynchronous septum/anteroseptum/ inferior wall
  - "Shudder" of septum/anteroseptum
  - Apical rocking
  - "Hula hoop" motion of LV



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### CRT Nonresponders

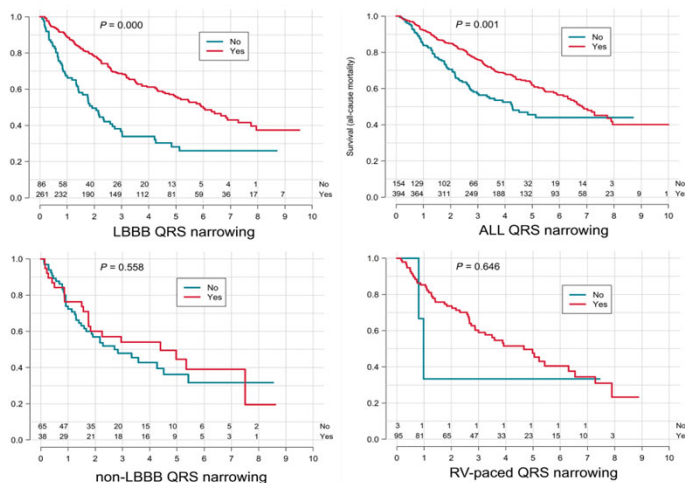
- ~ 160K CRT devices placed in US annually
- > 1M patients with CRT devices in US



There is no well-accepted, proven approach to treating nonresponders (44% of NR receive no treatment)

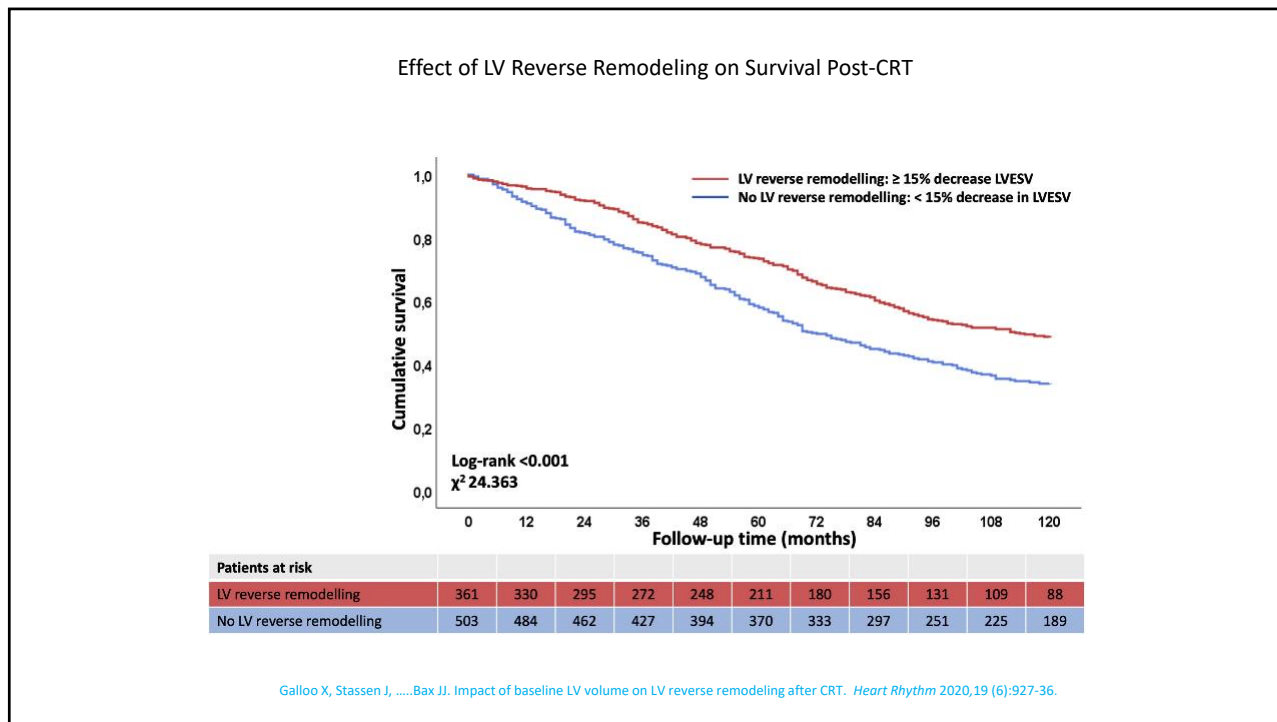
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### All-cause Mortality and Hospital Admission for HF: Patients with and without QRS Narrowing

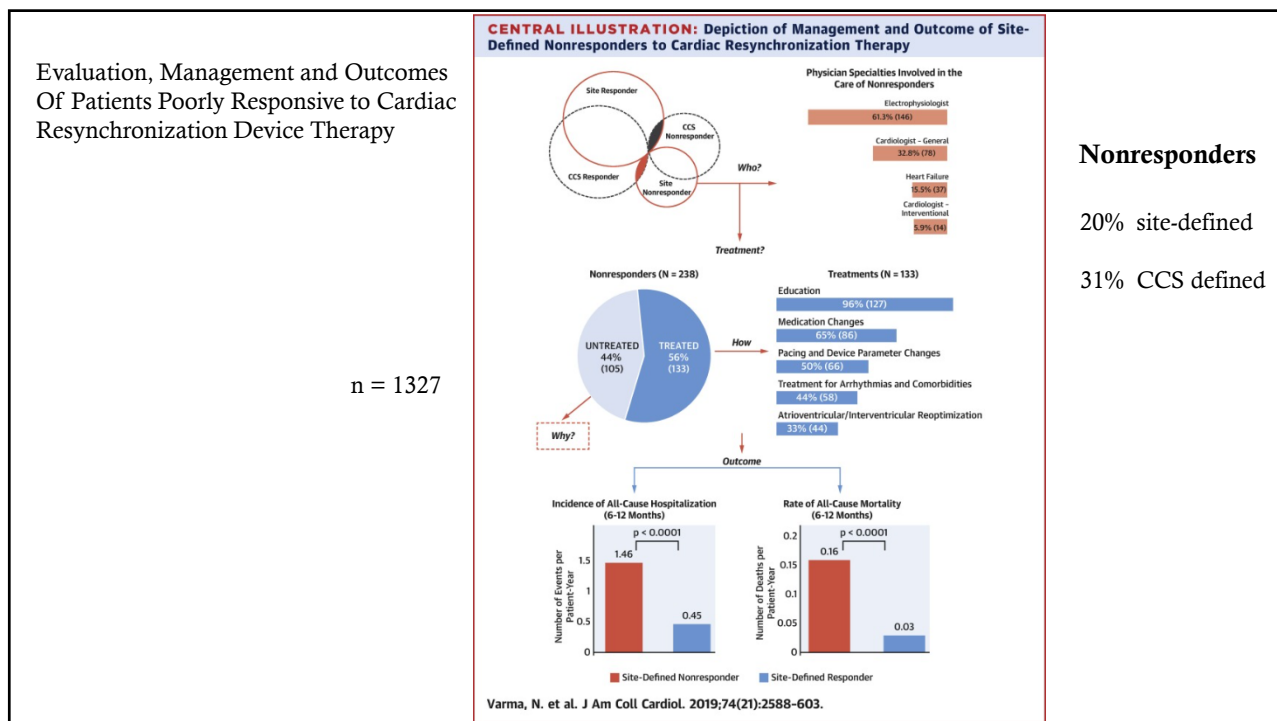


Jastrzebski M, Europace, Volume 21, Issue 2, February 2019, Pages 281–289, <https://doi.org/10.1093/europace/euy254>

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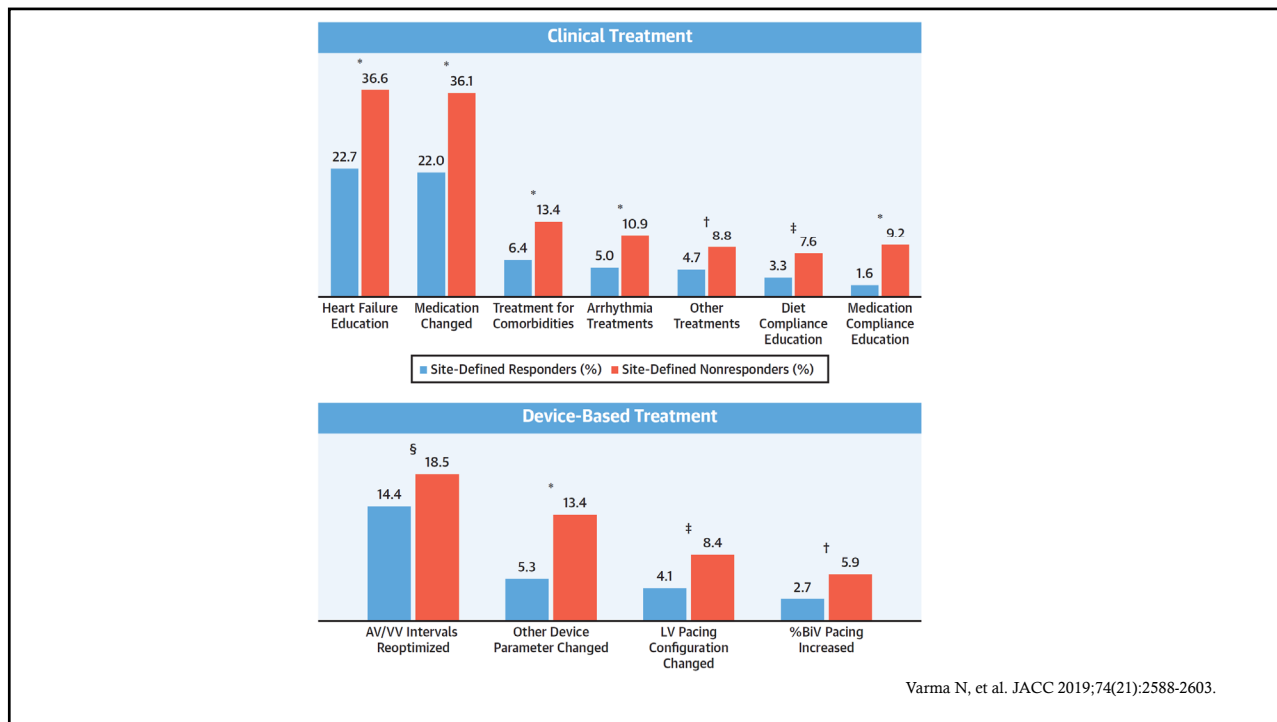


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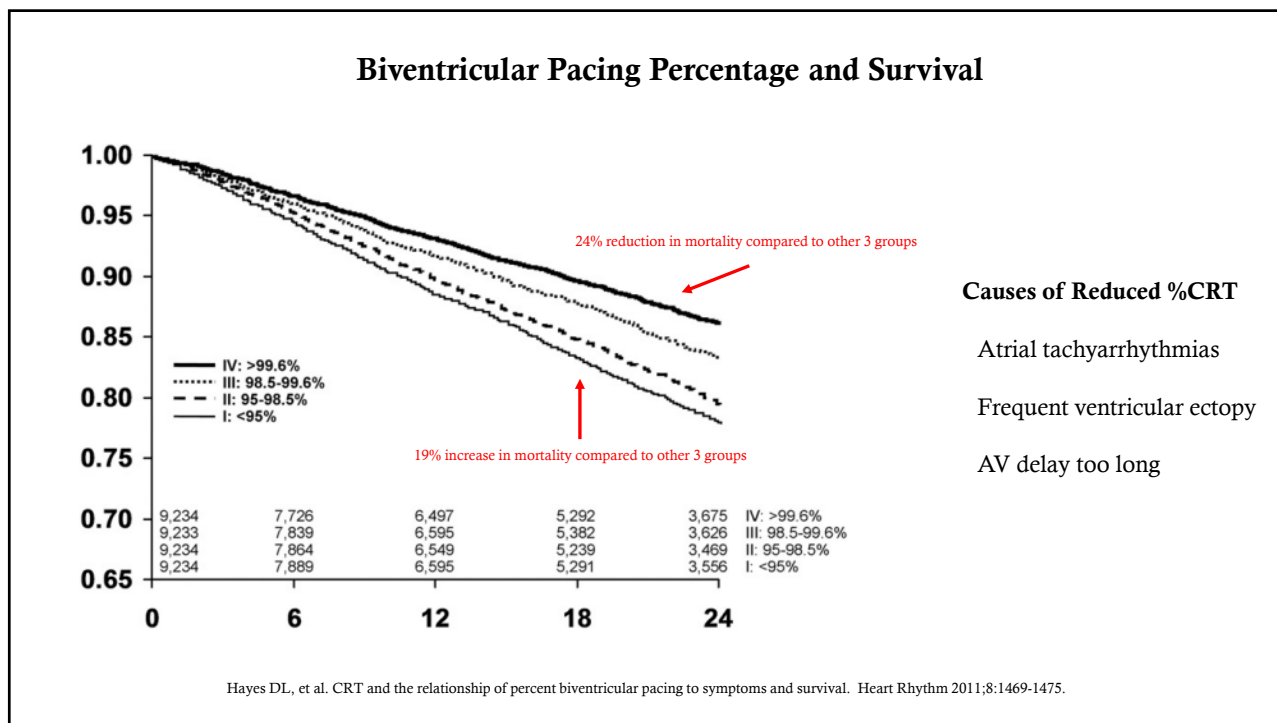


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### CRT Programming (1000's of options)

- Atrial-Ventricular Delay (AVD)
- Ventricular-Ventricular Delay (VVD)
- Atrial sensing vs Atrial pacing
- Biventricular vs. LV-only
- Quadripolar Electrode

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### Effects of 12-lead ECG Optimization of CRT on Patients with and without Delayed Enhancement on Cardiac MRI

- Retrospective study of 130 patients with CRT
- 2007-13: not optimized (standard CRT programming)
- 2014-17: 12-lead ECG optimized (often LV-only or LV preactivation)

A

No DE  
n = 44

B

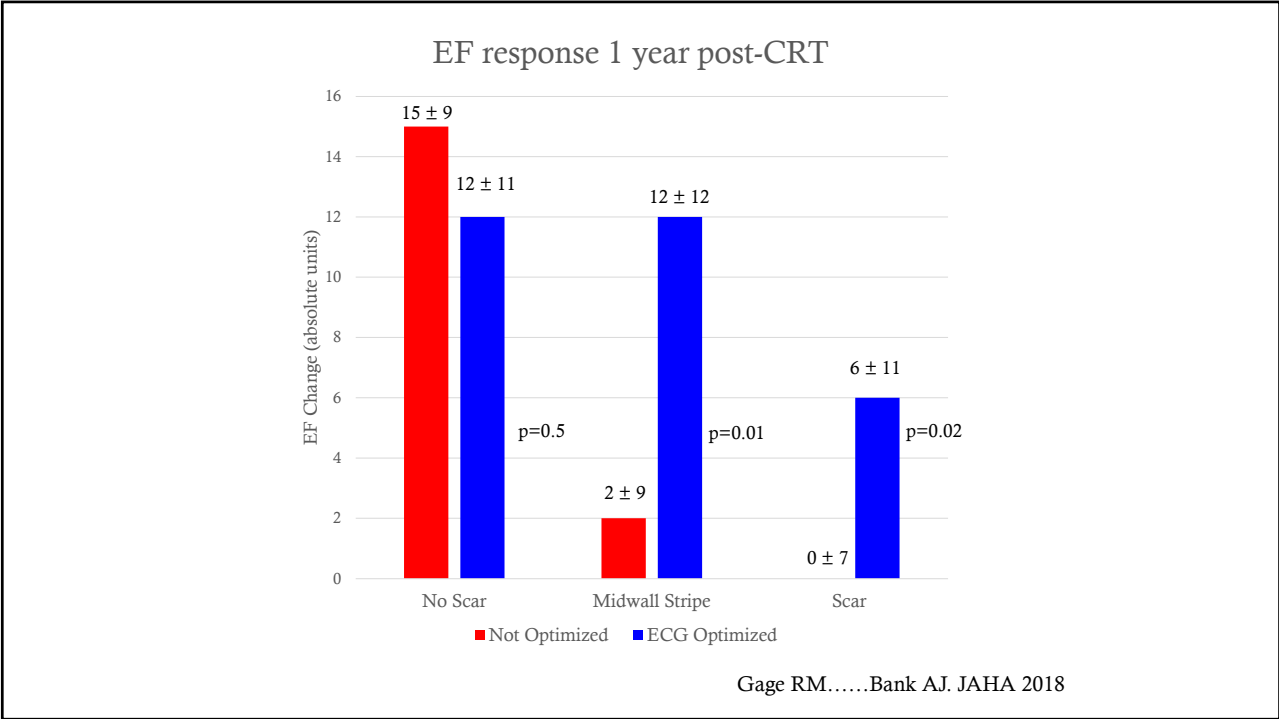
Scar  
n = 56

C

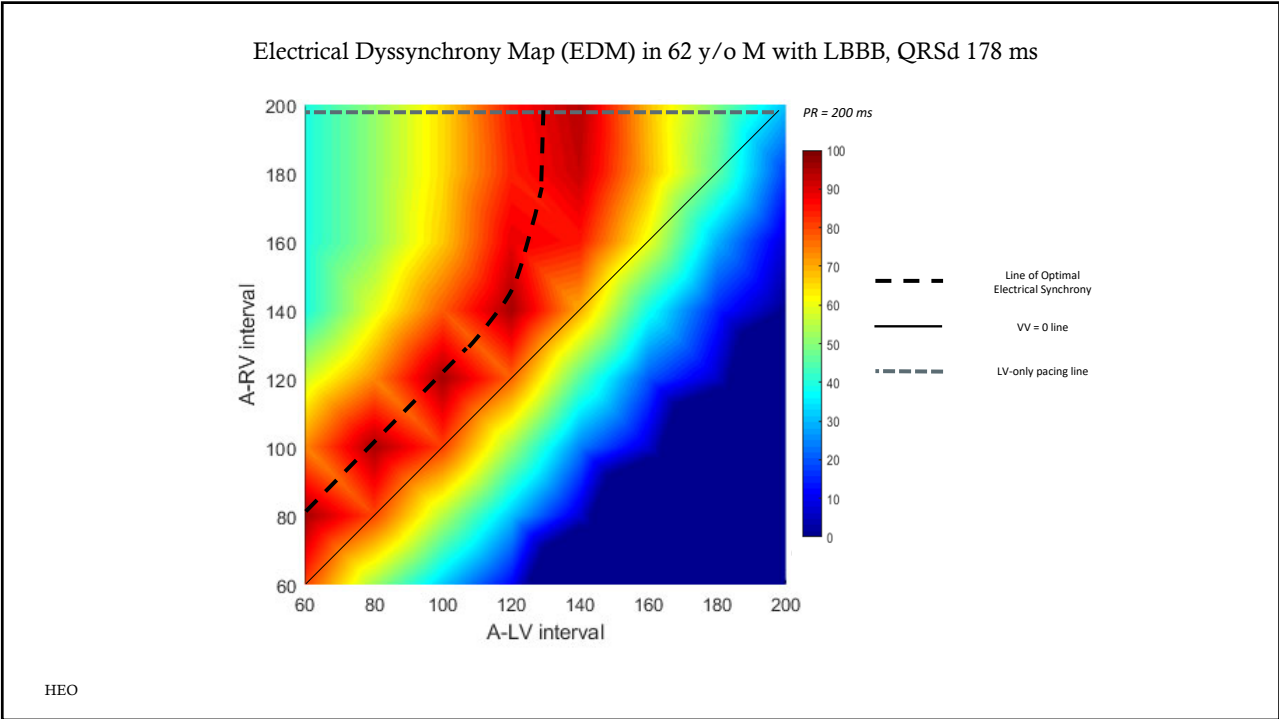
Midwall fibrosis  
n = 30

Gage RM ....Bank AJ. JAHA Open Access 2018

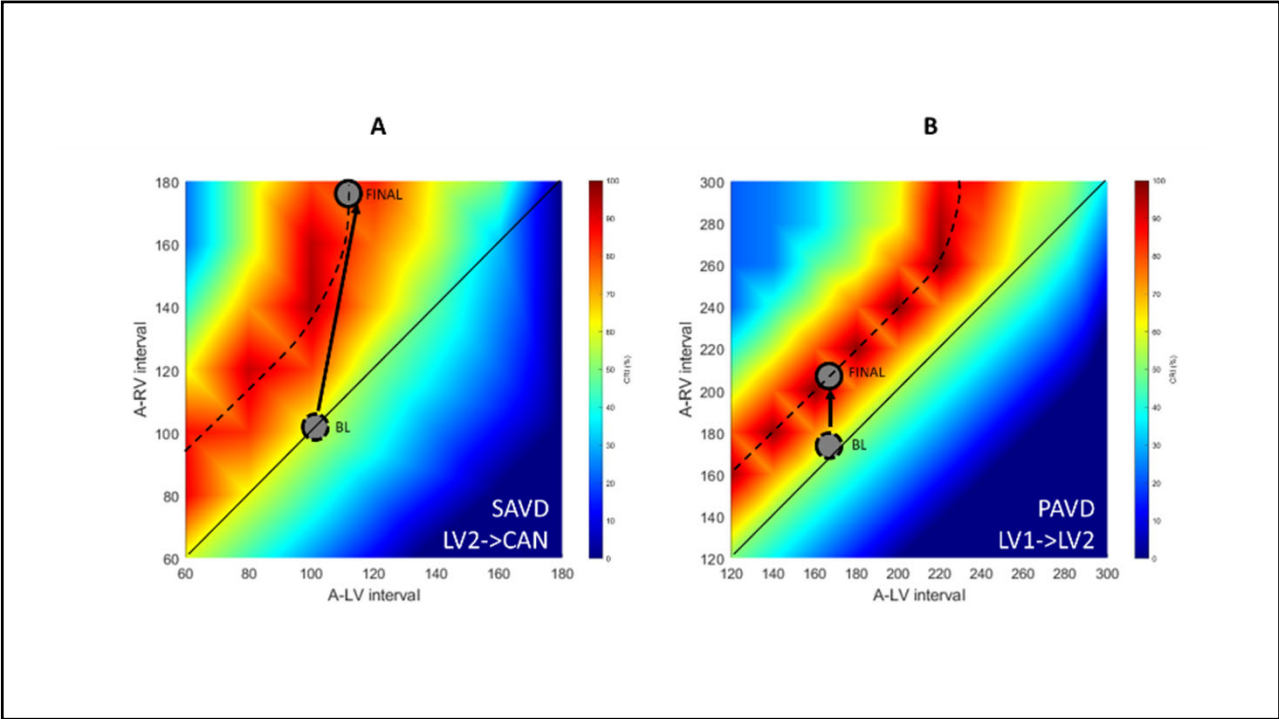
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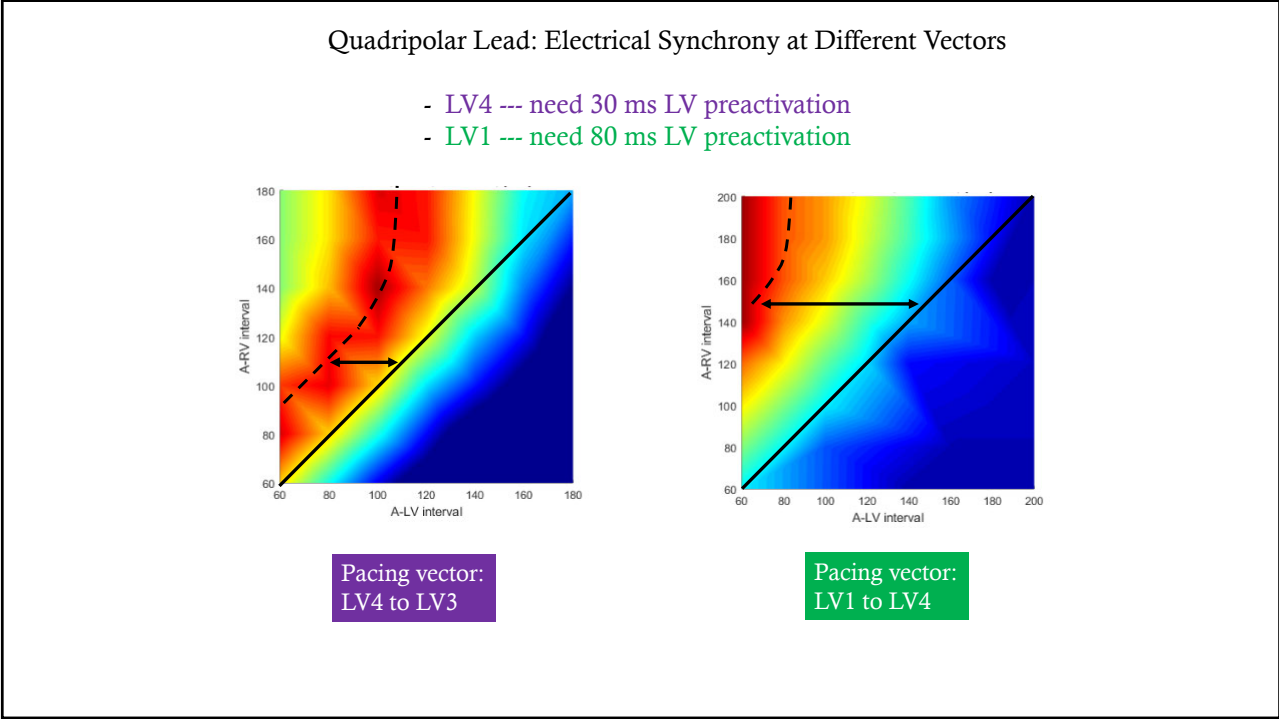
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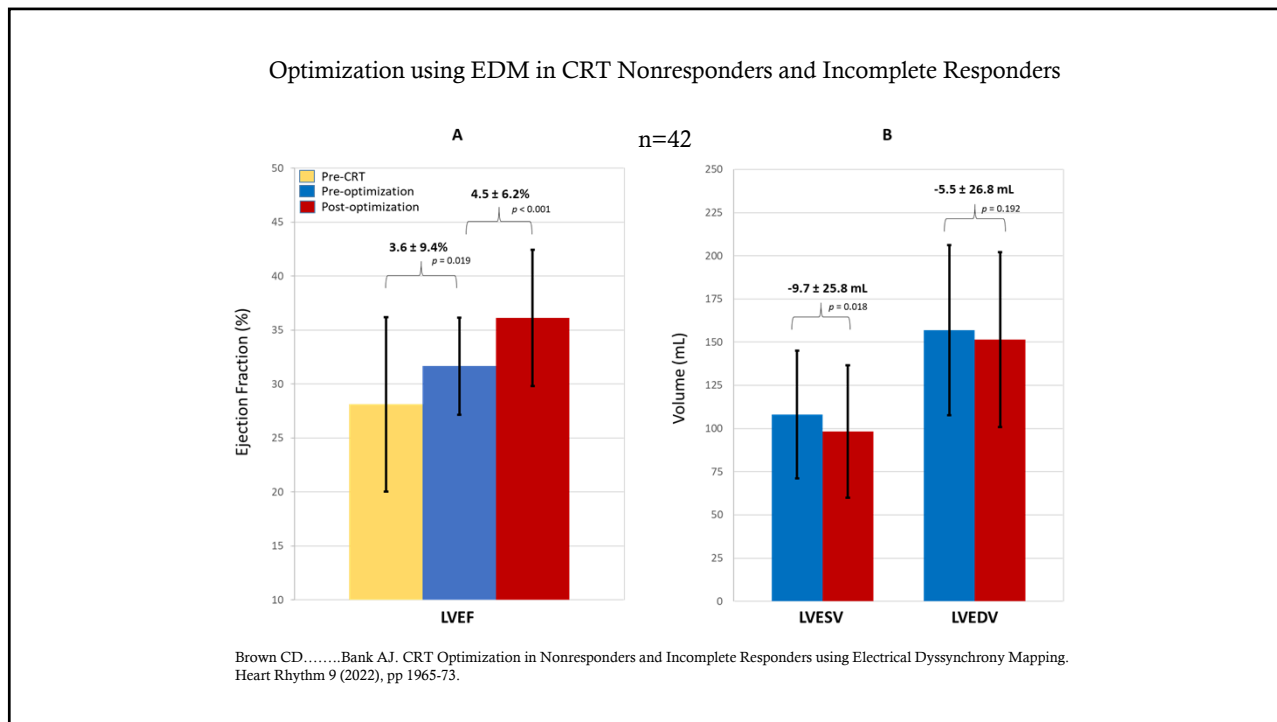
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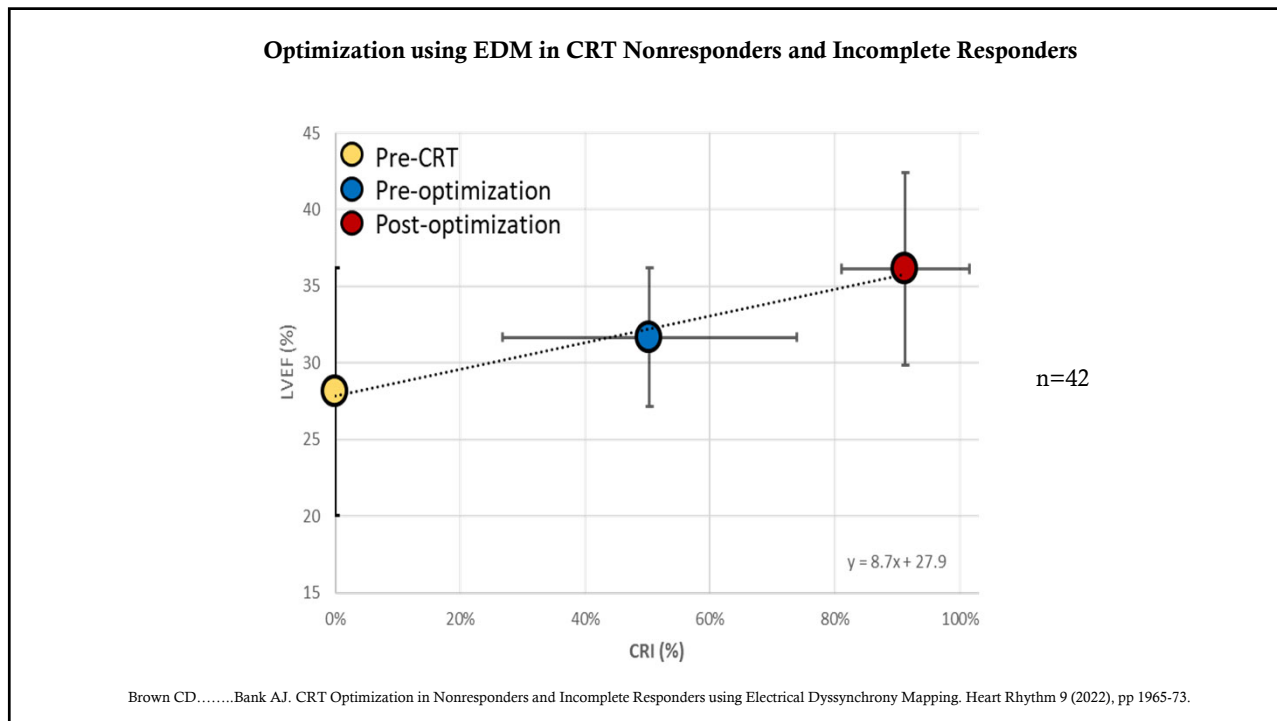
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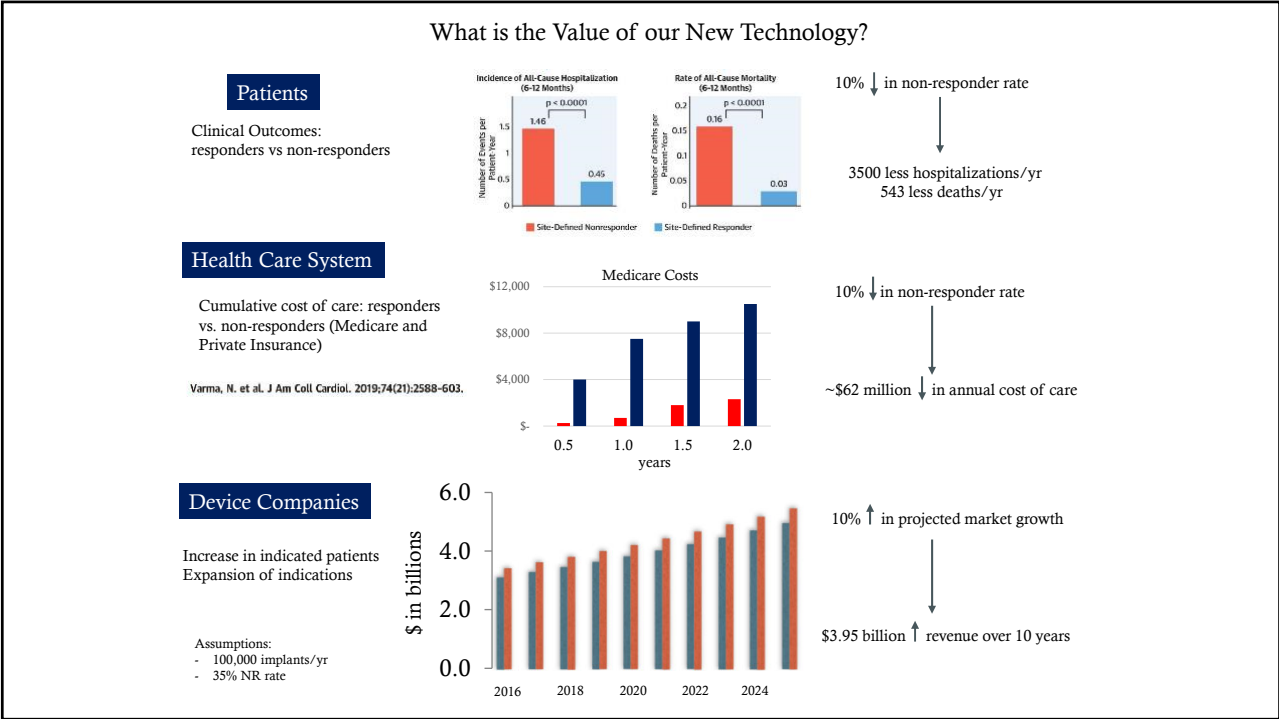
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# Conduction System Pacing: An Evolving Strategy for the Future of Ventricular Pacing

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## Ablate and Pace for Atrial Fibrillation

The earliest ablative strategy for managing AF

Pacemaker implantation followed by AV Node ablation has been performed for decades

Offers definitive non-pharmacologic rate control and has been associated with improved QOL, exercise tolerances, heart failure indices, and even mortality in certain scenarios

It has traditionally been viewed as the “last resort” for management of AF

With advancements in device therapy and pacing strategies we may need to revise our thinking about where the Ablate and Pace strategy fits into our AF management schema



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## Conduction System Pacing

- Much of the “Ablate and Pace” literature references RV apical pacing
- In the words of Bruce Stambler, MD – “There is no worse place to pace than the RV apex.”
- Pacing the RV is evolving rapidly:
  - RV septal pacing – RV septal myocardial activation
  - Selective His Bundle pacing – difficult and ultimately unreliable
  - Non-selective His Bundle pacing – difficult and risks compromise to the TV septal leaflet
  - Distal Purkinje system/ “Deep Septal” Pacing – nebulous QRS criteria and variable success rates
  - Left Bundle Branch Area Pacing (LBBAP) – simpler technique with good implant success rates
- These strategies have been combined with trans-venous LV pacing in patients with reduced LVEF previously creating super-responders to CRT
- Outcomes with conduction system pacing have been encouraging






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## Anatomic Correlates: RA/RV Purkinje System

Right side



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## Anatomic Correlates: LV Purkinje system

Left side



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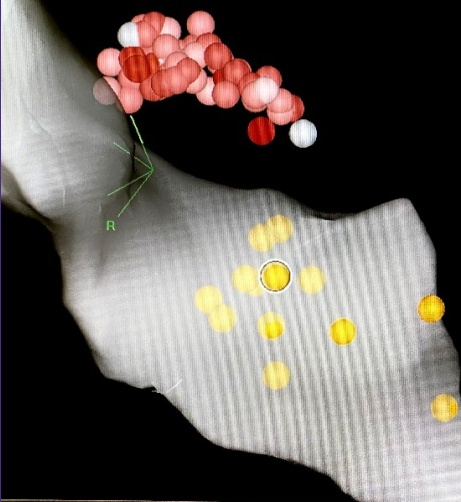

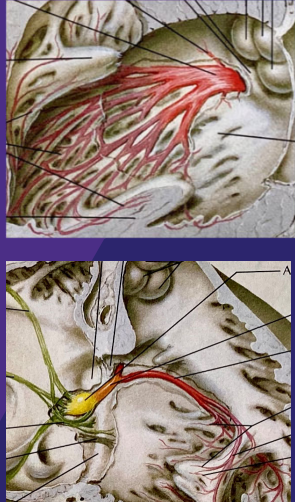




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## Anatomic Correlates: LA/LV electro-anatomic mapping


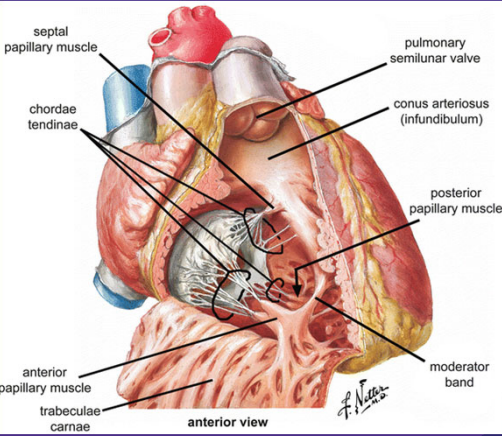
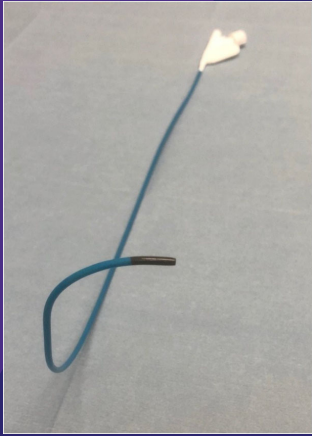














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## Implant Technique using a pre-formed guide

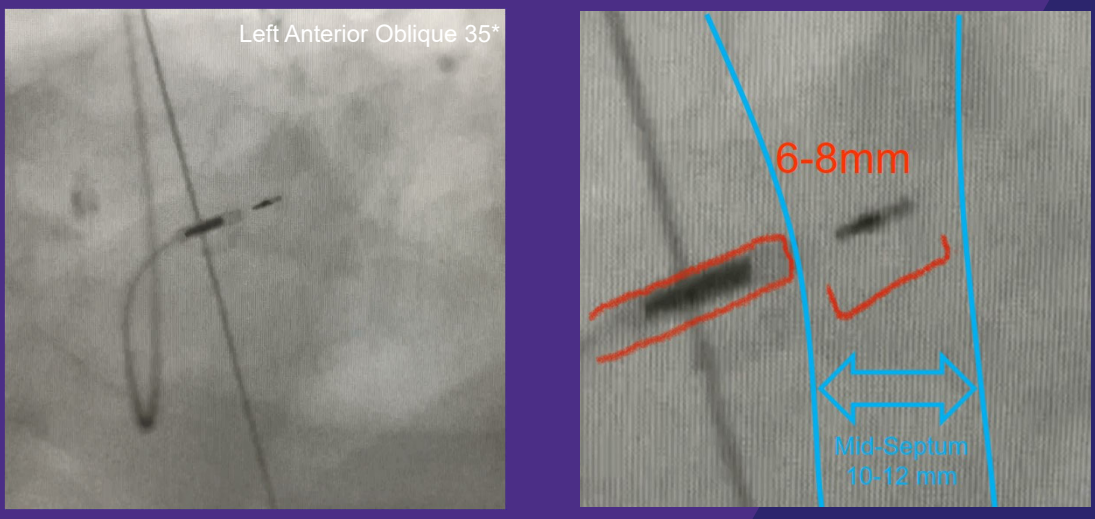




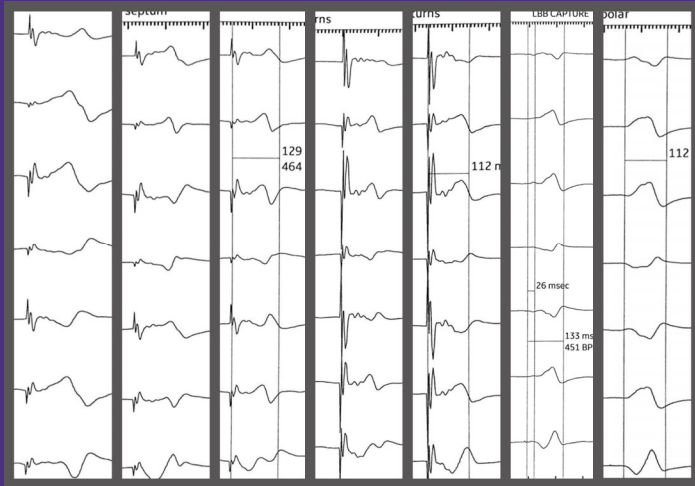
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The lead tip traverses the septum to recruit the LV sub-endocardial Purkinje system

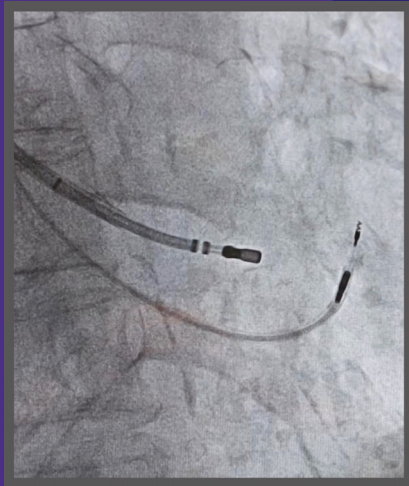


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Unipolar Pacing Complex as the helix advanced across the septum

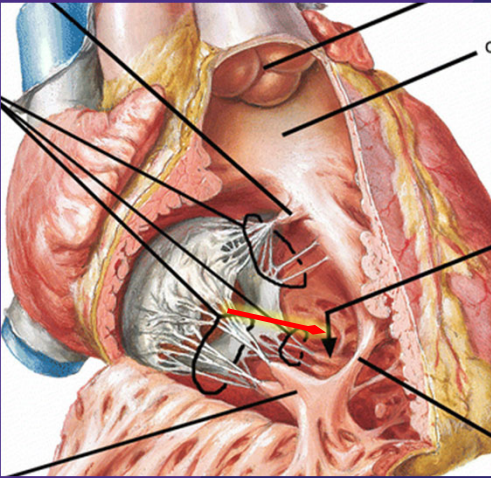
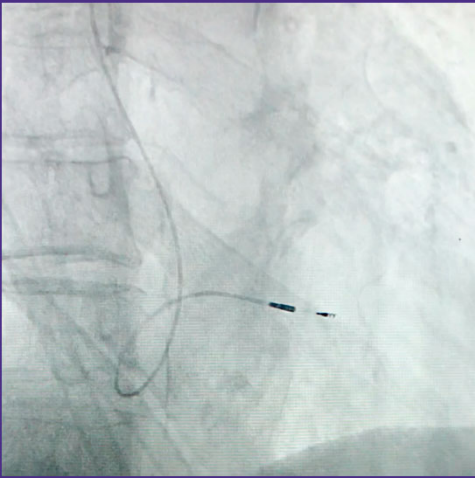


AV Node Ablation via the Axillary Vein



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### Final result after splitting away the guide

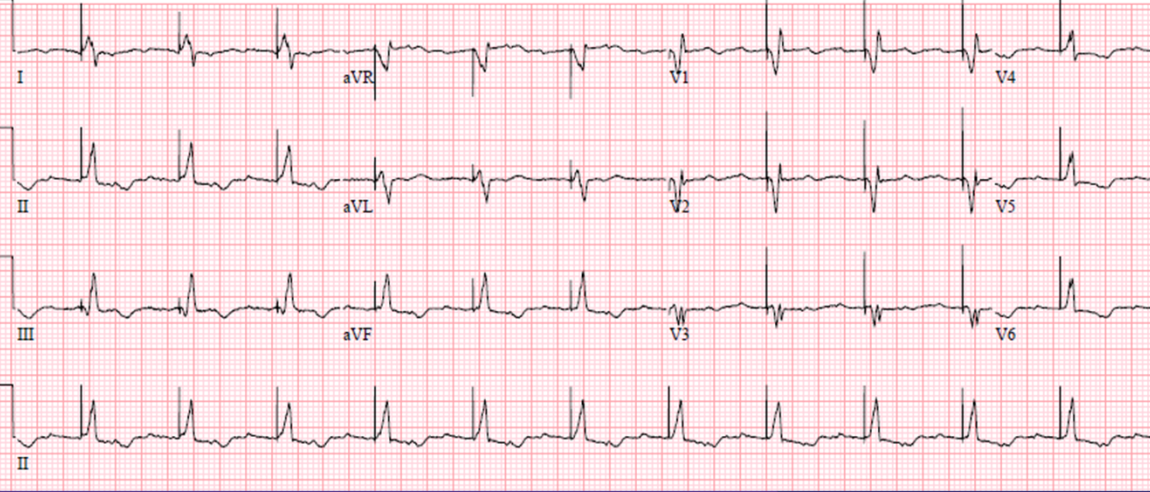


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### AF with CHB and LBBAP QRSD 112ms



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## Conduction System Pacing is the Future of Pacing

- Recruiting the Purkinje System improves LV activation dynamics
- CSP improves a variety of metrics including LV function in the setting of HFrEF
- CSP contributed to “Super Response” to CRT with combined with transvenous LV pacing
- Small robust pacing lead with deep septal implant:
  - low thresholds
  - Very low dislodgement rate
  - Simple implant procedure with minimal additional fluoroscopy and implant time
- When combined with AV Node ablation, CSP offers:
  - Definitive non-pharmacologic rate control
  - Physiologic pacing with a low risk of pacing mediated CM



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## Acknowledgements

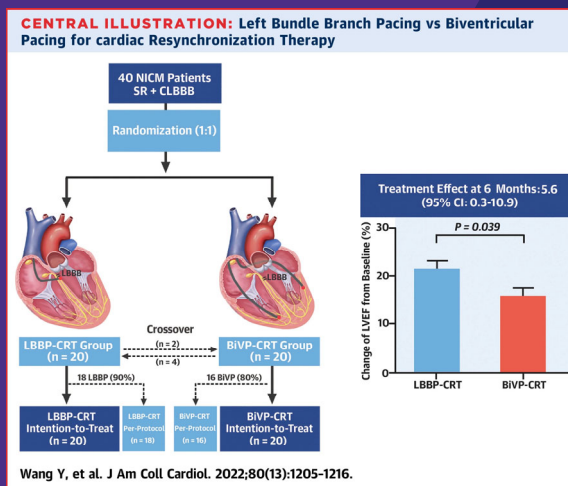
- We would like to acknowledge the Joseph F. Novogratz Family Heart Rhythm Center at the Minneapolis Heart Institute Foundation for their support on this study.



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## LBBP-RESYNC trial




- CRT-P versus LBBAP
- 40 patients NICM, EF 30%
- SR, LBBB
- 10% crossover, Intention To Treat
- Significant improvement in LVEF vs traditional CRT



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Comparative effects of left bundle branch area pacing, His bundle pacing, biventricular pacing in patients requiring cardiac resynchronization therapy:  
A network meta-analysis

- 6 studies
- 389 patients
- Comparison of outcomes in BVP, HBP, LBBAP
- HBP/LBBAP was superior to BVP in terms of improvement in EF and narrower QRS
- LBBAP resulted in lower thresholds than HBP




  

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85 year old female with history of heart failure and persistent atrial fibrillation with rapid ventricular rates has cardiomyopathy (mildly enlarged LV and LVEF 40-45%), moderate to severe mitral regurgitation, and ongoing fatigue with dyspnea on exertion.

In addition to maximally-tolerated GDMT for cardiomyopathy and HFrEF, what would be your next step?

- A. Optimize rate control and consultation to Valve clinic for MitraClip
- B. Cardioversion and trial of rhythm control with amiodarone
- C. Catheter ablation for persistent atrial fibrillation
- D. Implant of cardiac resynchronization therapy (CRT-P) and AVJ ablation
- E. Implant of left bundle pacing system and AVJ ablation
- F. Micra leadless pacemaker implant and medical therapy for rate control
- G. Ask GPT-4

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85 year old female with history of heart failure and persistent atrial fibrillation with rapid ventricular rates has cardiomyopathy (mildly enlarged LV and LVEF 40-45%), moderate to severe mitral regurgitation, and ongoing fatigue with dyspnea on exertion.

In addition to maximally-tolerated GDMT for cardiomyopathy and HFrEF, what would be your next step?

- A. **Optimize rate control and consultation to Valve clinic for MitraClip**
- B. **Cardioversion and trial of rhythm control with amiodarone**
- C. **Catheter ablation for persistent atrial fibrillation**  
Evidence builds for catheter ablation for atrial fibrillation and heart failure; safe and efficacious in octogenarians  
CASTLE-AF, EAST-AFNET 4, IIa recommendation in guidelines for improvement in symptoms, reduce hospitalization, improve LV function, and possibly reduce mortality
- D. **Implant of cardiac resynchronization therapy (CRT-P) and AVJ ablation**  
APAF-CRT superior to pharmacological rate control in reducing mortality with narrow QRS irrespective of baseline EF
- E. **Implant of left bundle pacing system and AVJ ablation**
- F. **Micra leadless pacemaker implant and medical therapy for rate control**
- G. Ask GPT-4



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## Acknowledgements

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## OCEANIC-AF

Phase 3 program of the Oral Factor XI Inhibitor Asundexian as Novel Antithrombotic – Atrial Fibrillation Study

**Enrolling!**  
 EPIC message: [MCHH EP OCEANIC-AF](#)

<b>CONDITION:</b> Atrial Fibrillation	<b>PI:</b> Nedaa Skeik, MD <b>Sub-I:</b> Manju Pai, MD Kris Krueger, MD, PhD	<b>RESEARCH CONTACT:</b> Jessie Whelan <a href="mailto:Jessica.whelan@allina.com">Jessica.whelan@allina.com</a>   612-863-1661	<b>SPONSOR:</b> Bayer AG
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**DESCRIPTION:**  
 OCEANIC-AF is a multicenter, international, randomized, active comparator-controlled, double-blind, double-dummy, parallel-group, phase 3 study. The purpose of the study is to investigate the efficacy of the oral FXIa inhibitor asundexian in prevention of stroke and systemic embolism and its safety (bleeding risk) compared with apixaban in adult participants with AF at risk for stroke. Asundexian is expected to have superior or at least similar efficacy while leading to less bleeding when compared with the NOAC apixaban. Expected to be conducted at 1100 sites, with 18,000 participants randomized over 2 years (already underway). Patients are expected to be on study drug 9-33 months.

**CRITERIA LIST/ QUALIFICATIONS:**

**Inclusion:**

- Documented AF with indication for indefinite treatment with oral AC
- CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥3 (male) or ≥4 (female) OR 2 (male) or 3 (female) with 1 of the following:
  - Age ≥70, previous stroke, TIA or SE, renal dysfunction with eGFR <50, prior non-traumatic major bleeding, current single agent antiplatelet therapy for 6+ months, ≤6 consecutive weeks of treatment with oral AC

**Exclusion:**

- Mechanical heart valve prosthesis (TAVR ok)
- Moderate-to-severe mitral stenosis
- AF only due to reversible cause
- Successful ablation, LAA occlusion, or plans for 1 in next 6 months
- Recent ischemic stroke
- Active non-trivial bleeding, chronic bleeding disorder, hx non-traumatic intracranial hemorrhage
- Significant liver disease or hepatic insufficiency
- eGFR < 25 at randomization
- Major surgery in last 30 days
- Chronic AC for non-AF reason, dual AP therapy
- VKA in past 10 days prior to randomization
- NSAIDs for +4 weeks during study period
- Combined P-gp and strong/mod CYP3A4 inducers

Duration of Treatment: ~9-33 months

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## AIM HIGHER

Assessment of Implantable CCM in the Heart Failure Group with Higher Ejection Fraction

**Enrolling!**  
 EPIC message: [MCHH EP Research Coordinator](#)

<b>CONDITION:</b> Heart Failure (pEF)	<b>PI:</b> Michael Samara, MD <b>Sub-I:</b> Jay Sengupta, MD	<b>RESEARCH CONTACT:</b> Jessie Whelan <a href="mailto:Jessica.whelan@allina.com">Jessica.whelan@allina.com</a>   612-863-1661	<b>SPONSOR:</b> Impulse Dynamics
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**DESCRIPTION:**  
 The AIM HIGHER study is multicenter, multi-national, randomized, double-blind, sham controlled, 2-part, embedded IDE clinical trial looking to evaluate the efficacy and safety of Cardiac Contractility Modulation, via the Optimizer Smart Mini System, in patients with symptomatic HF (EF 40%-60%, inclusive). The expected total study duration is approximately 5-6 years, with enrollment taking ~18 months. Subjects will all be implanted with Optimizer device, but 1/3 will be randomized to CCM OFF. After 18 month follow up, all patient devices will be programmed to CCM ON, and long-term follow up will likely last 5+ years. Expected to be conducted at 150 sites, with 1500 participants enrolled over 2 parts. Site enrollment is capped at 75 patients over Parts I and II.

**CRITERIA LIST/ QUALIFICATIONS:**

**Inclusion:**

- Diagnosed with symptomatic heart failure with EF 40-60% within past 12 months
- HF hospitalization within past 12 months OR urgent HF visit requiring IV therapy within past 6 months
- Elevated NT-proBNP, >200pg/ml without atrial tachyarrhythmia (AT), or >600 pg/ml for subjects in AT OR Elevated BNP levels, >75 pg/ml without AT or >225 pg/ml for subjects in AT
- No dose changes in cardiovascular medications for at least 14 days
- Stable, scheduled oral loop diuretic treatment (not only PRN) for at least 30 days

**Exclusion: (partial list)**

- Resting HR <50 or >110 bpm
- Resting systolic BP <110 or ≥160 mmHg
- BMI >40
- Any moderate or severe valvular stenotic disease or any severe valvular regurgitation
- Mechanical tricuspid valve
- Complex congenital heart disease
- Exercise tolerance limited by a condition other than HF
- Unable to walk at least 100 meters during a 6MWT
- A KCCQ CSS overall score higher than 85
- Hypertrophic, infiltration/restriction or inflammatory cardiomyopathy
- Unstable angina pectoris with 30 days, or MI within 90 days
- Acute, decompensated HF requiring IV therapy within 30 days
- Receiving CRT
- Expected lifespan of less than 18 months

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