Η σύγχρονη επεμβατική Καρδιολογία στην κλινική πρακτική του 2017

Ποιοι ασθενείς με ένδειξη βηματοδότησης πρέπει να λάβουν θεραπεία καρδιακού επανασυγχρονισμού;

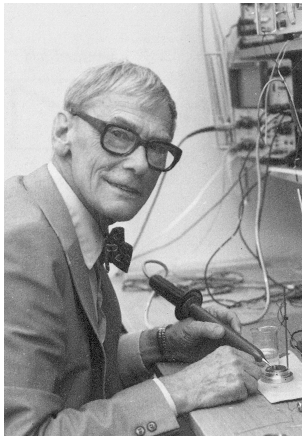
αρκεί το ΗΚΓράφημα;

Εμμ. Μ. Κανουπάκης *MD PhD FESC*

Πανεπιστημιακό Νοσοκομείο Ηρακλείου

1958: First implanted pacemaker

Engineer **Cardiologist** **Patient**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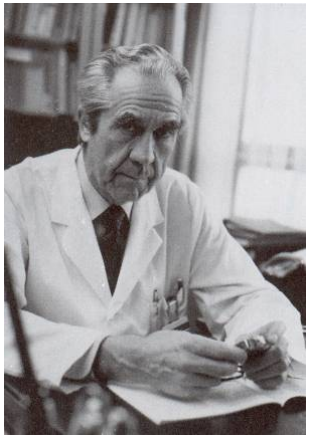
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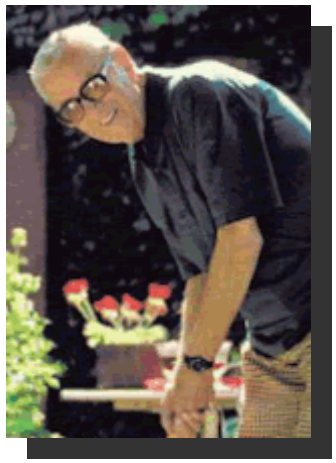
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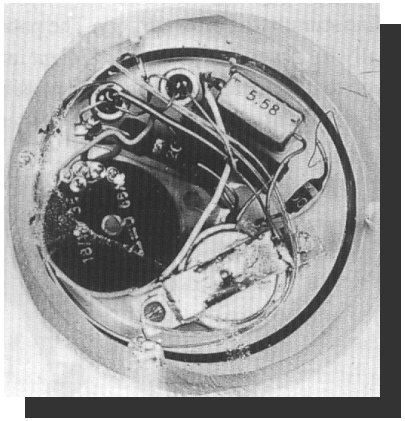


Elmquist Senning Larsson

59 years later…

…cardiac pacing is the only effective treatment for symptomatic bradycardia

- **in SSS improves quality of life**
- **in AV block not only improves quality of life but also prognosis**

Eur Heart J 2013; 34: 2281–2329

“Innocence questioning”

THE MUSCULAR REACTIONS OF THE MAMMALIAN VENTRICLES TO ARTIFICIAL SURFACE STIMULI

CARL J. WIGGERS

From the Physiological Laboratory, Western Reserve University, School of Medicine.

Received for publication April 20, 1925

ficial stimuli have not been studied with the degree of precision that the subject merits. This is due partly to the fact that, until recently, we have possessed no graphic appliances capable of recording the ventricular contractions in an accurate manner. The details of the premature contraction curve, the latent period, the extent of the refractory phase, the physiological conditions affecting it, the factors determining effectiveness or ineffectiveness of premature beats, etc., can be accurately analyzed only when a contraction curve is recorded on which the beginning and end of systole are clearly indicated and on which the separate phases of systole and diastole are clearly demarcated as well. Such a record is supplied by the optically recorded intraventricular pressure curve supplemented for special purposes by similar pressure curves from the auricle and aorta (Wiggers, 1921).

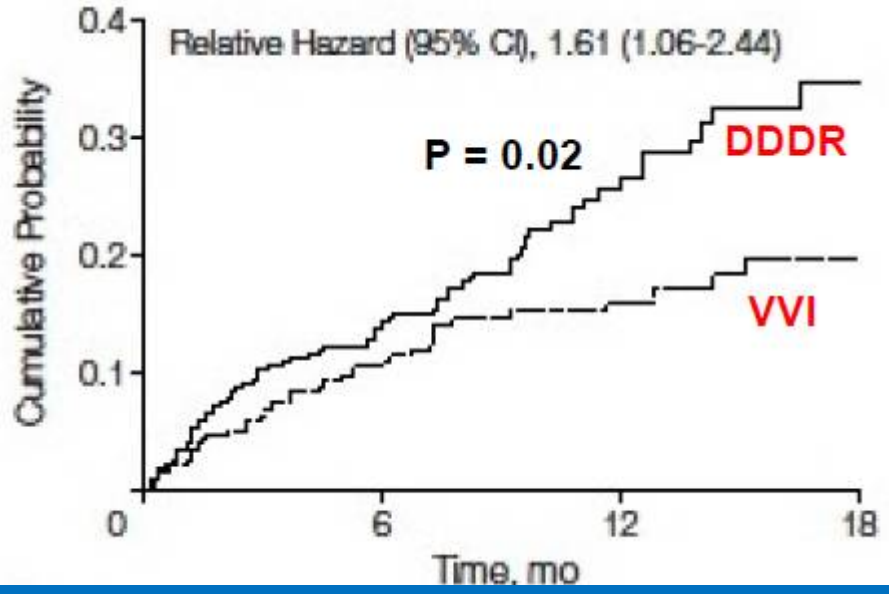
Experimental procedures. The heart was exposed in dogs under morphine and chloretone anesthesia and after the institution of artificial respiration. Whenever possible, the pericardium was left intact and small slits were made for the insertion of the optical manometer and the application of electrodes. One optical manometer was inserted into the left ventricle and another was introduced into the aorta so that the cannula was placed just outside of the semilunar valves. For special purposes, the experiments were varied by recording the second pressure curve from the other ventricle or from the left auricle. The theory, construction and application of these instruments as well as the nature of the optical curves recorded and the criteria that they contain for determining the consecutive phases of the heart cycle have been previously described (Wiggers, 1914, 1921 a, b, 1924). A reasonable familiarity with these communications is essential in order to follow the data and conclusions presented in this paper.

Induction shocks were applied to the left ventricle by means of two small hook-electrodes, well insulated except for their ends. These were

DAVID trial

Patients with indications for ICD implantation randomized to:

VVI (40/min) vs. DDDR (AV delay 180ms and lower rate 70/min)



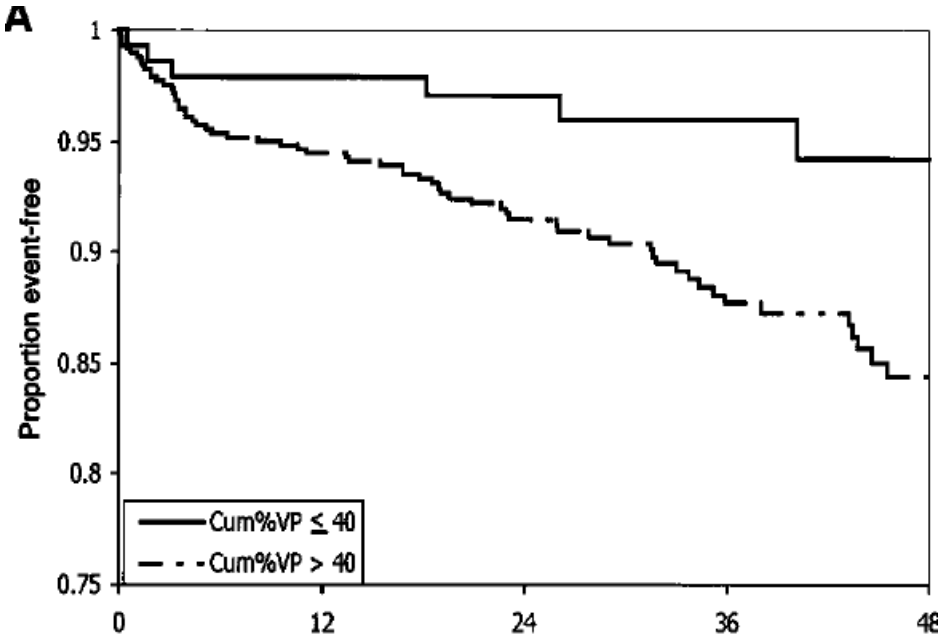
…more patients died or developed heart failure with prevention of bradycardia by DDDR-ICDs than with VVI-ICDs that basically did not pace

Wilkoff B et al, JAMA. 2002;288:3115-3123

The culprits…

…for worse outcomes were not the devices but the *physicians* who did not reprogramme dual-chamber ICDs and thus caused unnecessary RVP

MOST trial

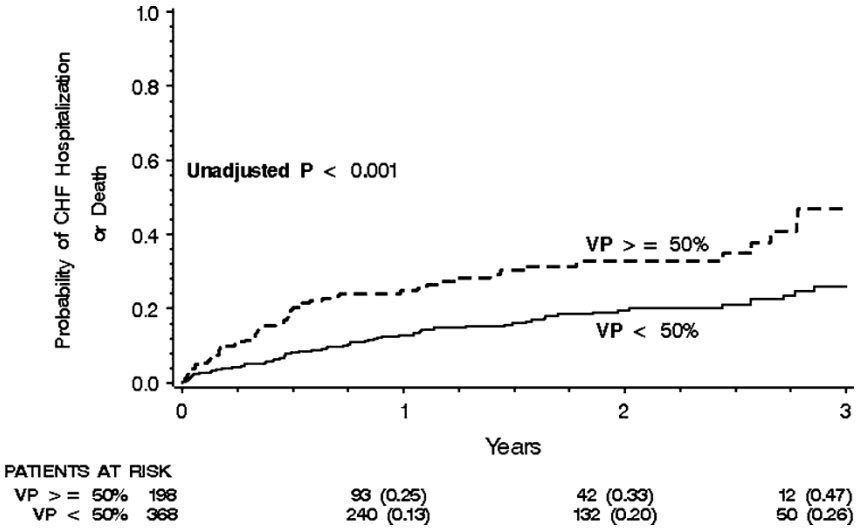


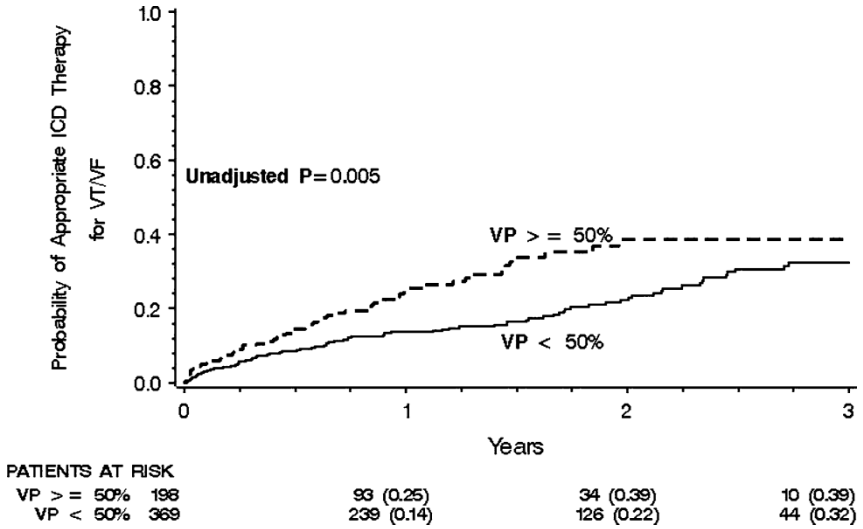
…in patients with sinus node disease and narrow QRS at baseline, unnecessary RVP (DDDR mode) increased the risk of HF hospitalization and AF compared to VVI mode

Patients without substrate (normal EF, no history of HF or MI, and normal baseline QRSd) had a correspondingly low risk of HFH

Sweeney M et al, Circulation. 2003;107:2932-2937

MADIT II study

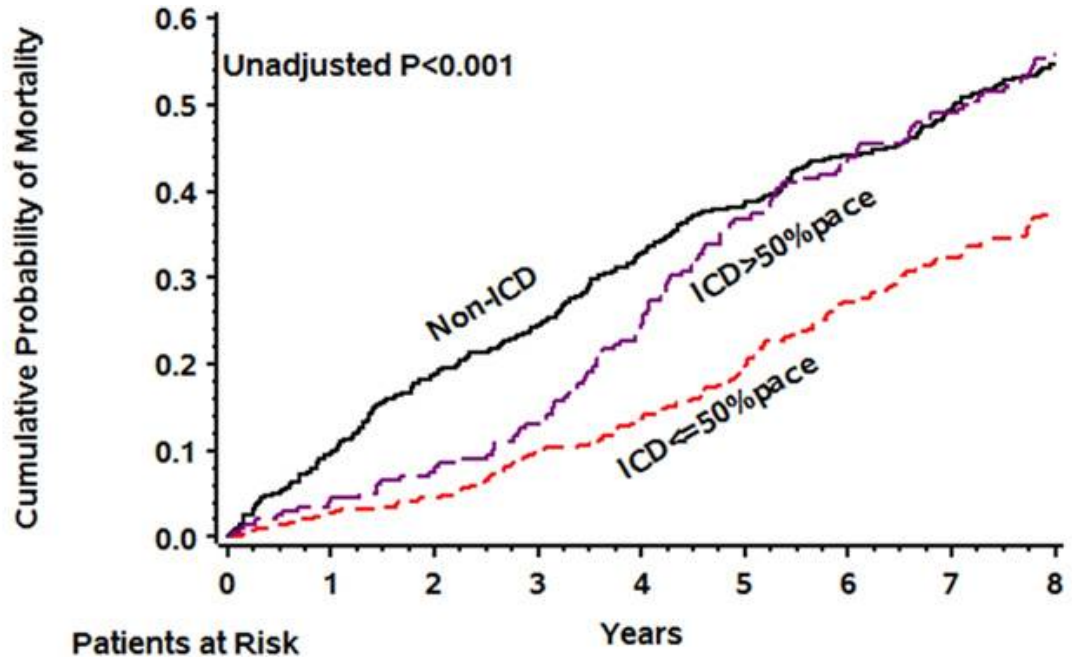




Patients who were predominantly paced had a higher rate of new or worsened heart failure and were more likely to receive therapy for VT/VF

Steinberg J et al, J Cardiovasc Electrophysiol 2005;16:359-365

MADIT II study – long-term f-up



Among ICD recipients, high RVP is associated with a significant increase in the risk of long-term mortality and with attenuated device efficacy

the detrimental effects is the result of years of large amount of RVA pacing

Barsheshet A et al, Heart Rhythm 2011;8:212–218

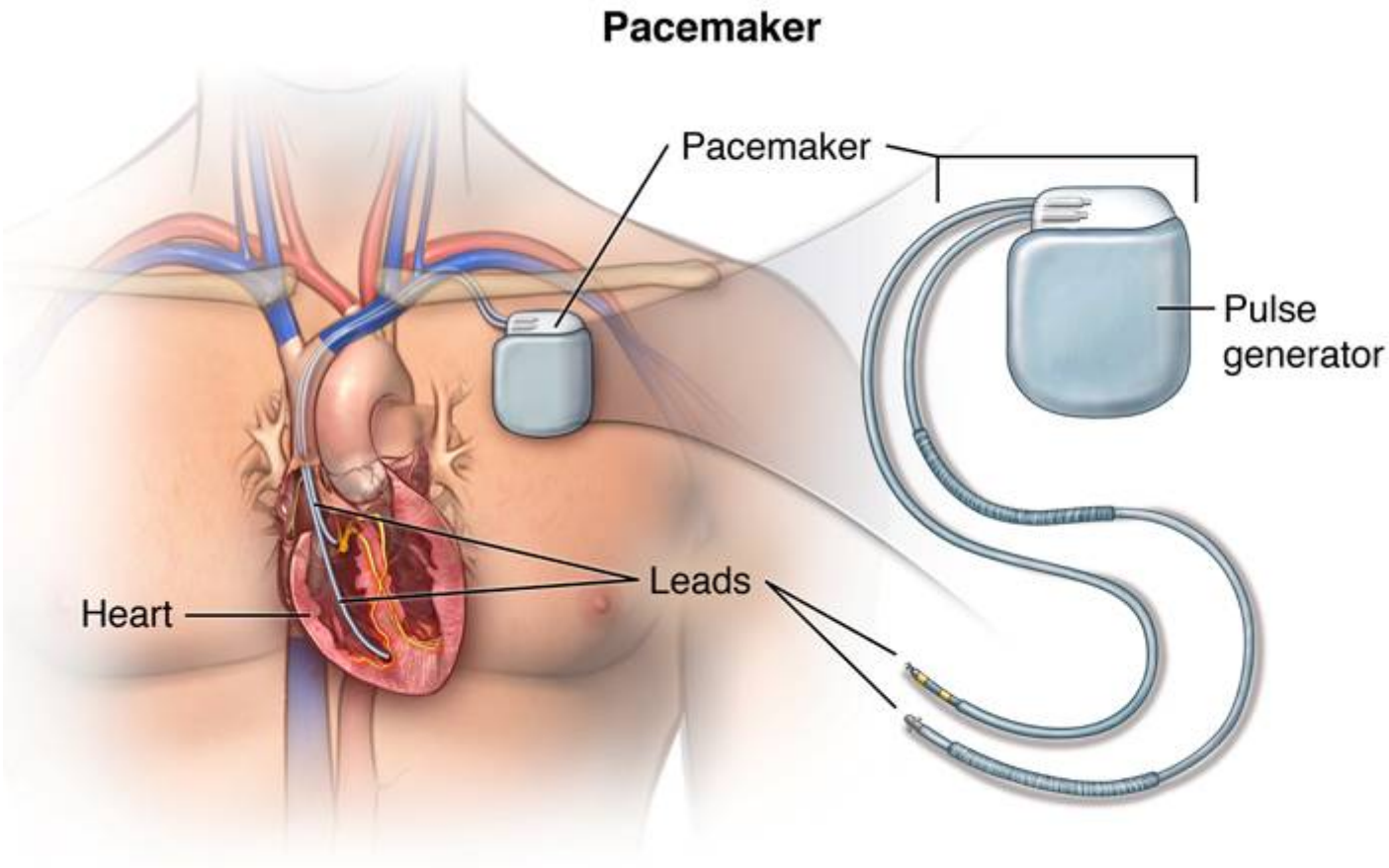
RV Pacing has adverse effects…

Trial	No. of Patients	Mean Age (y)	Mean FU (y)	LA Diameter	LV Function	CHF	AF
Tantengco et al.[28]	24	19.5	9.5	NA	↓	2 pts	NA
Karpawich et al.[29]	14	15.5	5.5	NA	Altered Histology	NA	NA
Thambo et al.[30]	23	24	10	NA	↓/DS	NA	NA
Tse et al.[31]	12	72	1.5	NA	↓/MPD	NA	NA
Hamdan et al.[32]	13	66	NA*	NA	↓/↑SNA	NA	NA
DAVID[36]	506	64	1	NA	NA	↑	NA
MADIT II[37,38] Substudy	567	64	1.7	NA	NA	↑	NA
Wonisch et al.[39]	17	59	0.25	NA	NA	**	NA
Thackray et al.[40]	307	72	5.2	NA	NA	↑	↑
MOST[41]	1,339	74	6	NA	NA	↑	↑
Nielsen et al.[43]	177	74	2.9	↑	↓	NA	↑
O'Keefe et al.[44]	59	69	1.5	NA	↓	NA	NA

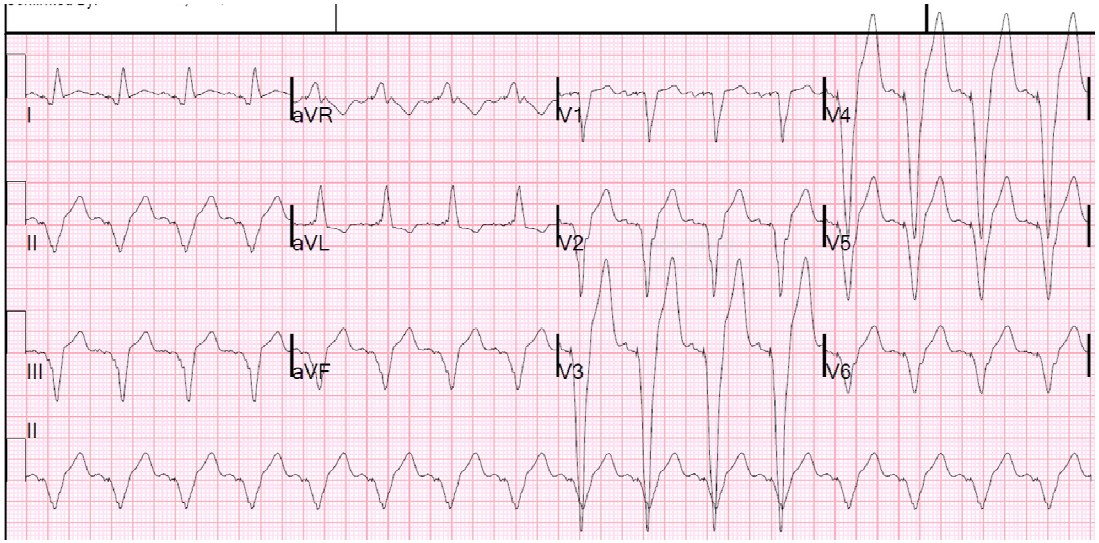
Manolis AS, PACE 2006; 29:298–315

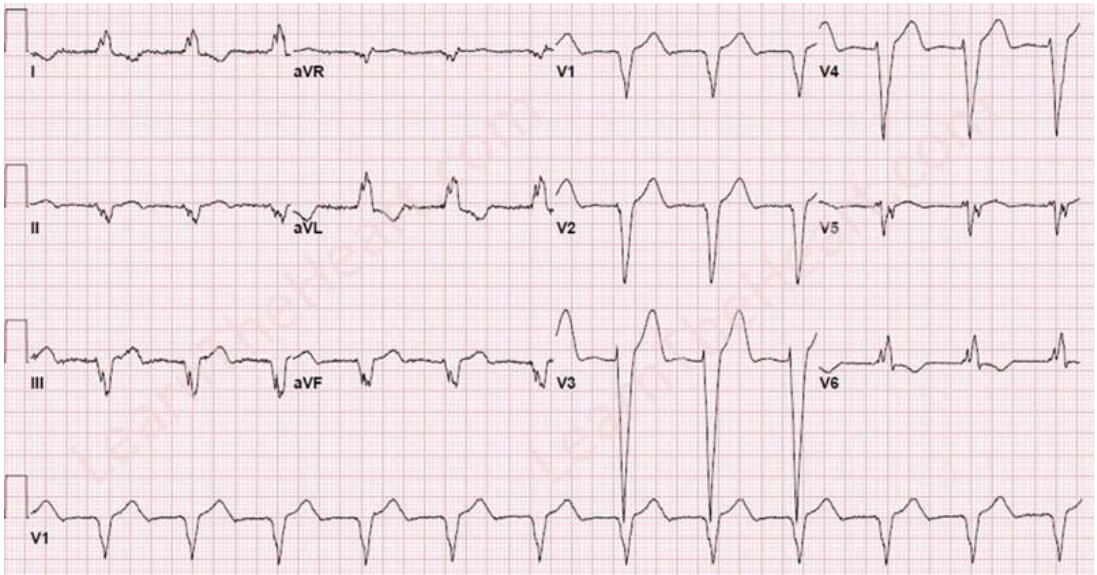
IS THERE PATHOPHYSIOLOGICAL EXPLANATION?

When we implant a pacemaker…

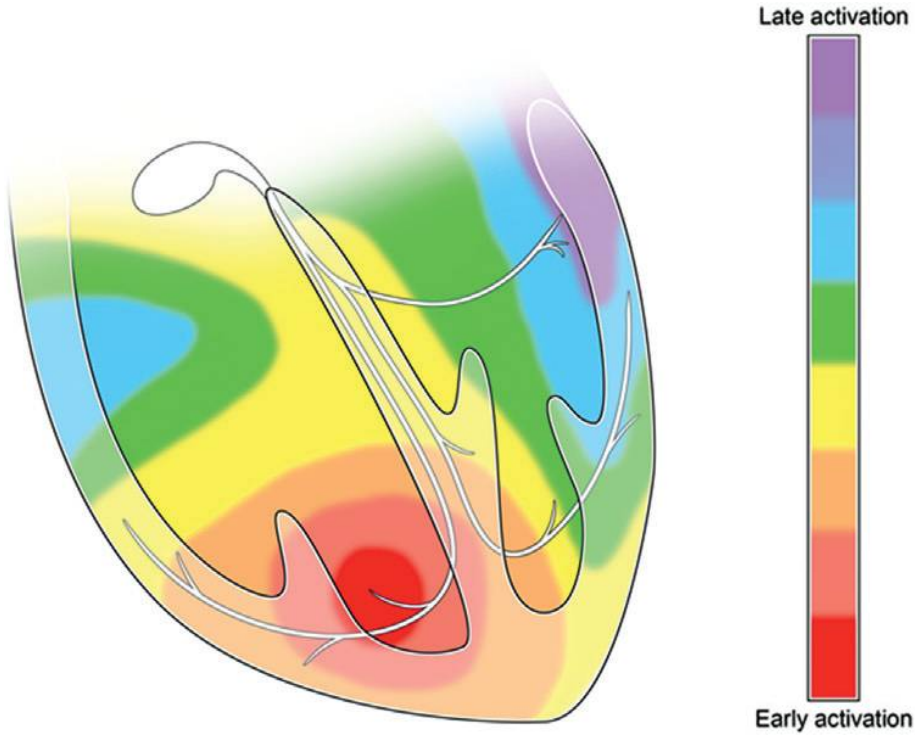


LBBB vs. RVA pacing ECG



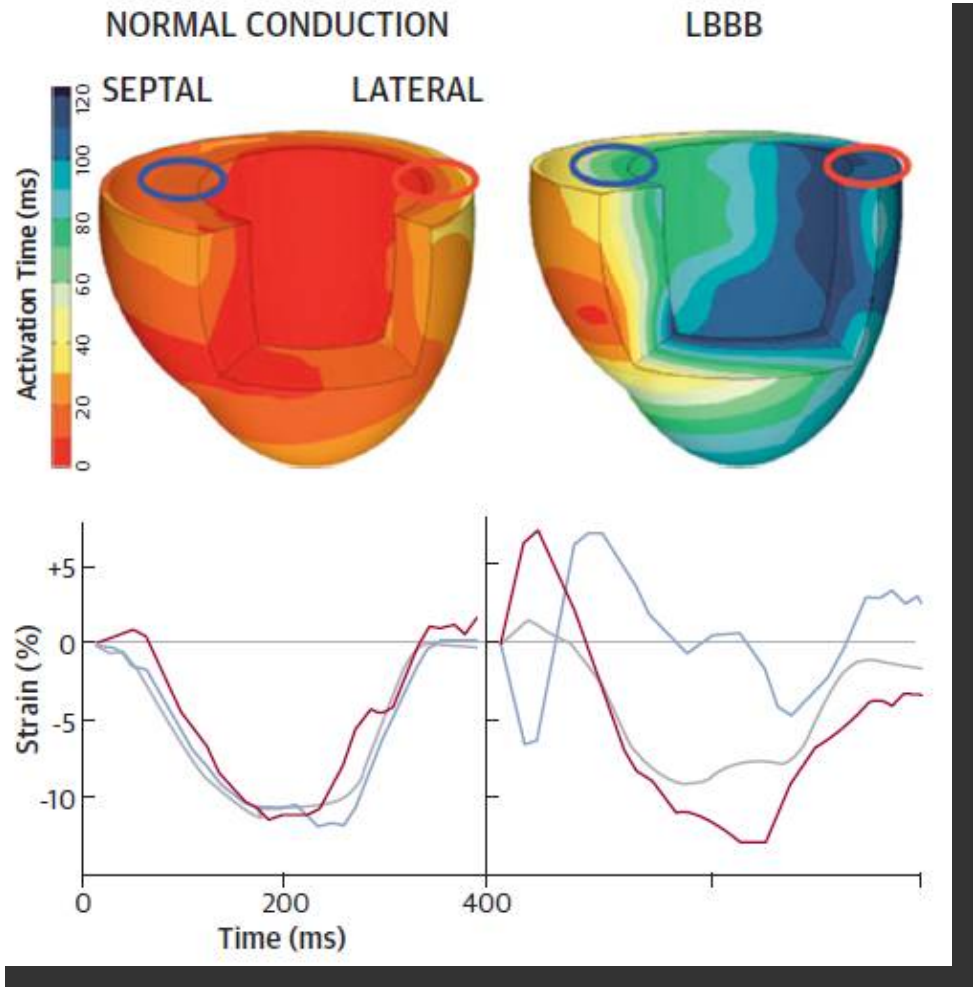


Heterogeneous electrical activation

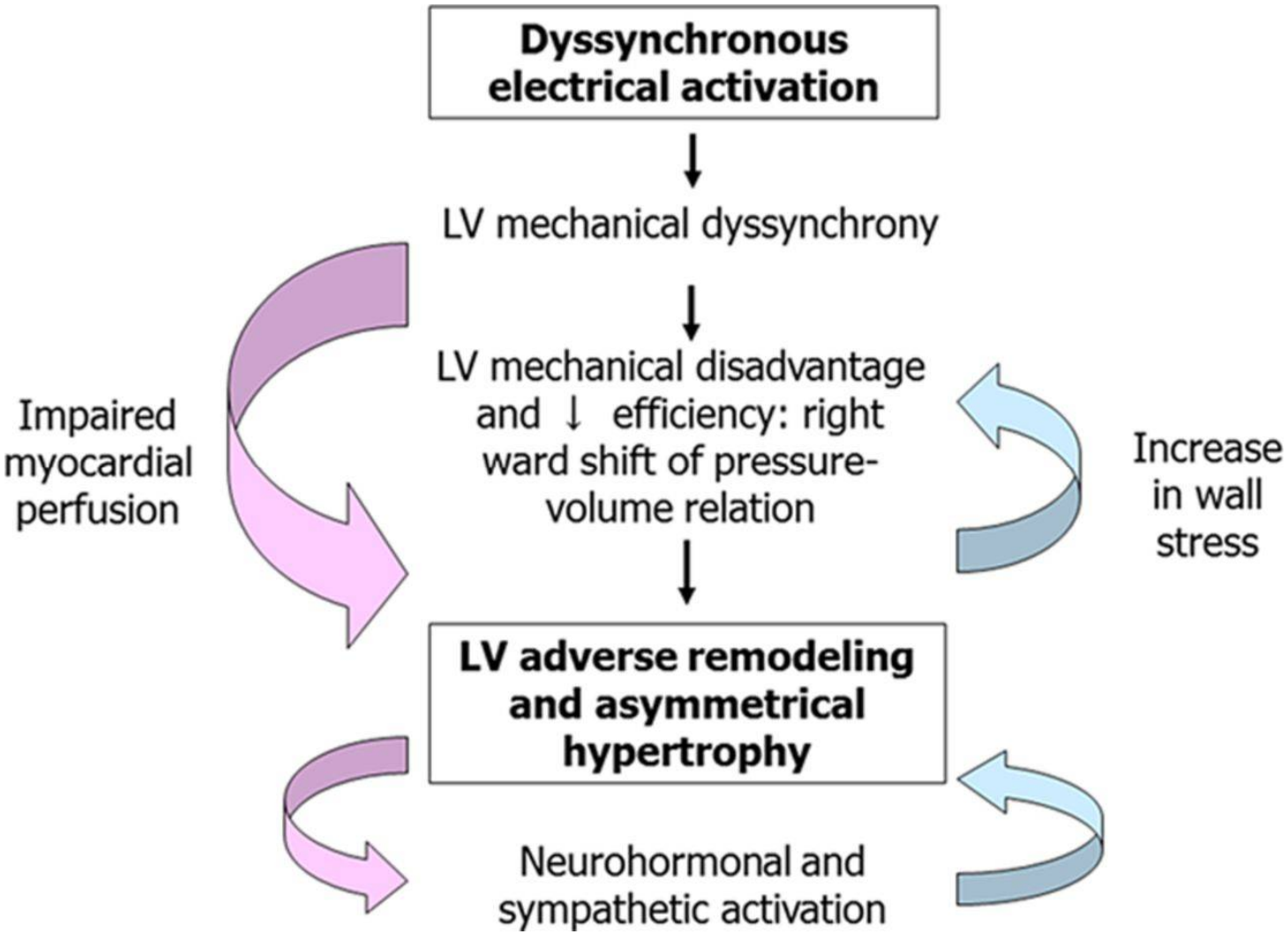


LBBB or a high percentage of RV apical pacing causes delayed electrical activation of the LV

Mechanical dyssynchrony

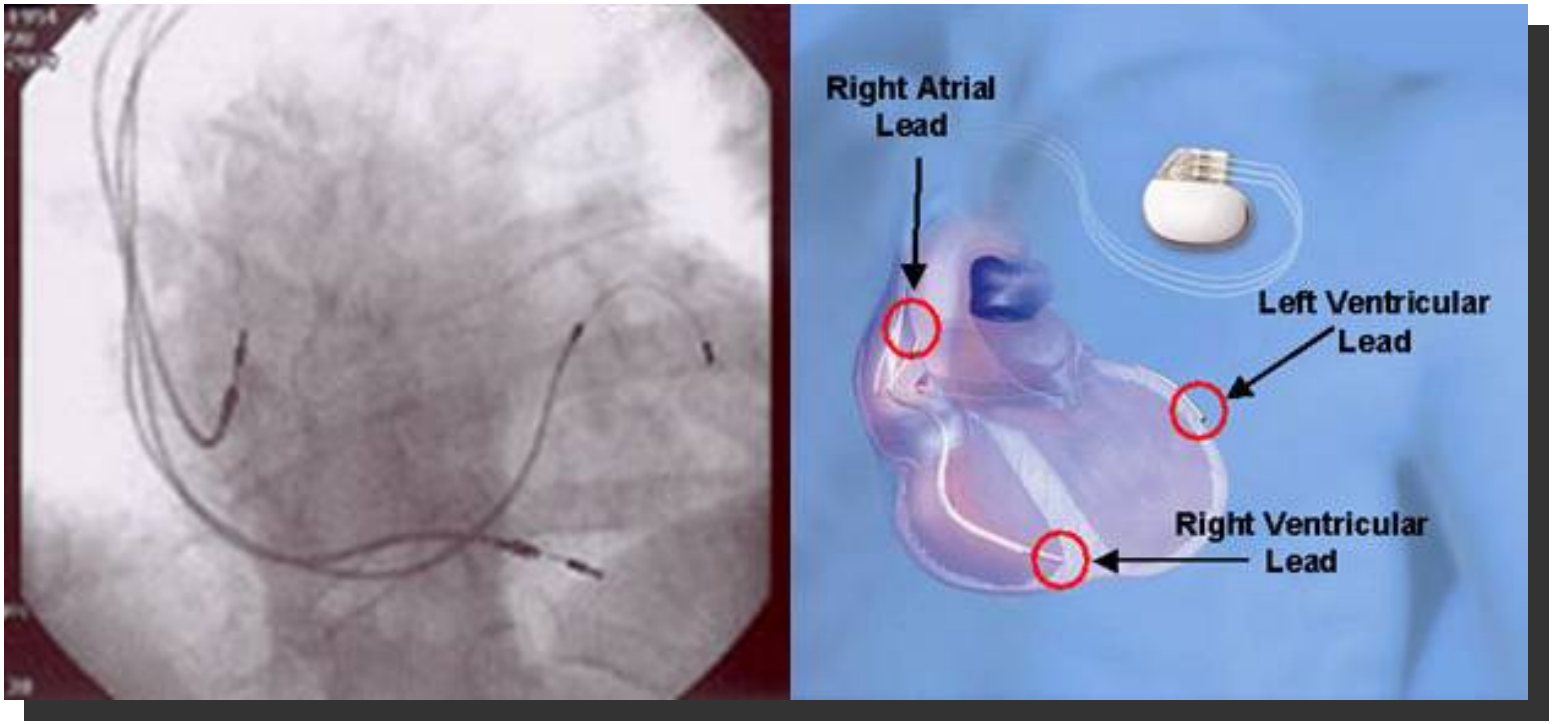


Detrimental effects of RV pacing



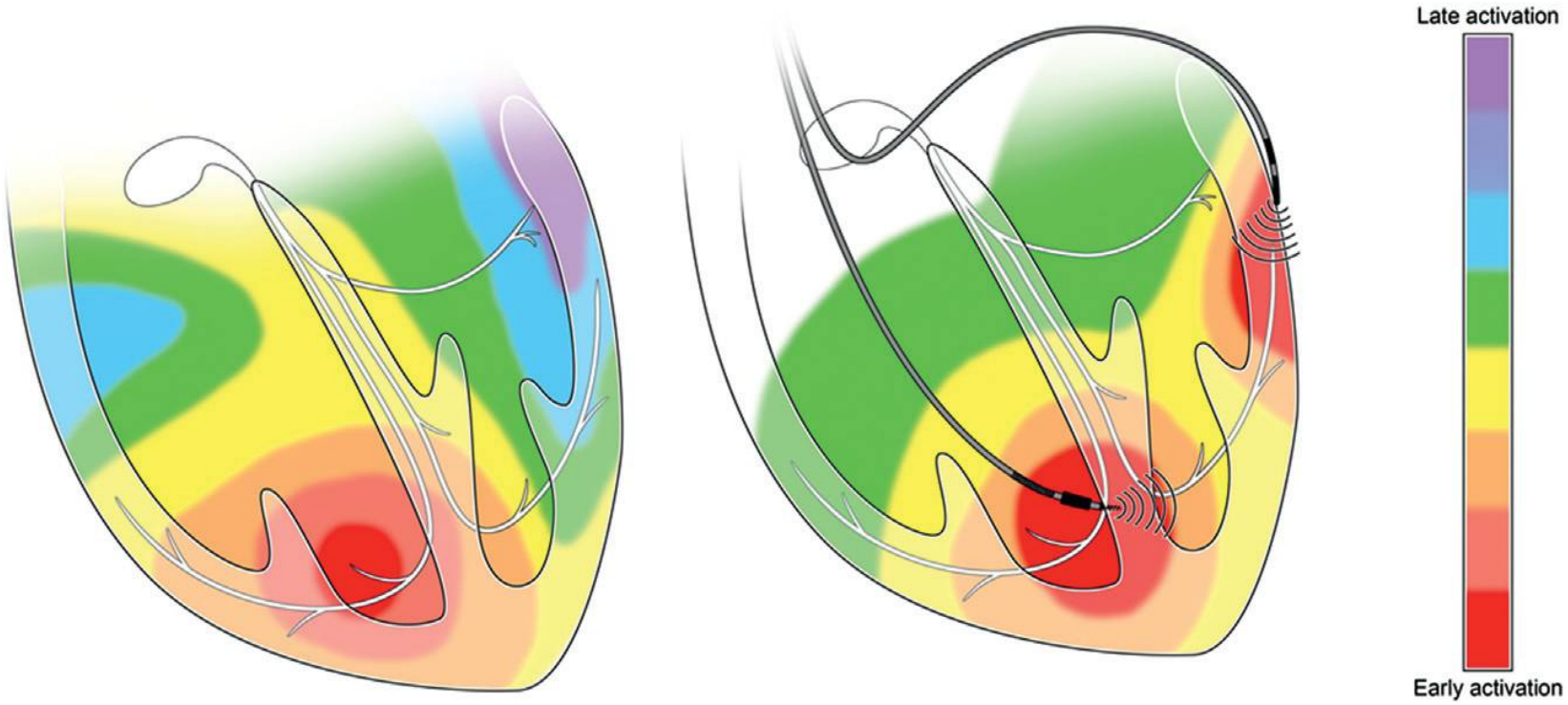
HOW TO AVOID THESE DETRIMENTAL EFFECTS?

23 years ago…



Cardiac Resynchronization Therapy

CRT: “pacing to correct dyssynchrony”



Trial (ref)	No.	Design	NYHA	LVEF	QRS	Primary endpoints	Secondary endpoints	Main Findings
MUSTIC-SR[52]	58	Single-blinded, crossover, randomized CRT vs. OMT, 6 months	III	<35%	≥150	6MWD	NYHA class, QoL, peak VO_2LV volumes, MR hospitalizations, mortality	CRT-P improved 6MWD, NYHA class, QoL, peak VO_2, reduced LV volumes and MR and reduced hospitalizations
PATH-CHF[51]	41	Single-blinded, crossover, randomized RV vs. LV vs. BiV, 12 months	III–IV	NA	≥150	Peak VO_2, 6MWD	NYHA class, QoL hospitalizations	CRT-P improved NYHA class, QoL and 6MWD and reduced hospitalizations
MIRACLE[49]	453	Double-blinded, randomized CRT vs. OMT, 6 months	III–IV	≤35%	≥130	NYHA class, 6MWD , QoL	Peak VO_2 LVEDD, LVEF, MR clinical composite response	CRT-P improved NYHA class, QoL and 6MWD and reduced LVEDD, MR and increased LVEF
MIRACLE-ICD[54]	369	Double-blinded, randomized CRT-D vs. ICD, 6 months	III–IV	≤35%	≥130	NYHA class, 6MWD , QoL	Peak VO_2 LVEDD, LVEF, MR clinical composite response	CRT-D improved NYHA class, QoL, peak VO_2
CONTAK-CD[53]	490	Double-blinded randomized	II–III–IV	≤35%	≥120	NYHA class, 6MWD , QoL	LV volume, LVEF composite of	CRT-D improved 6MWD, NYHA class, QoL,

Strong evidence that CRT reduces mortality and hospitalization, improves cardiac function and structure, in symptomatic chronic HF patients despite OMT, severely depressed LVEF (i.e.≤35%) and complete LBBB

CARE-HF[56]	813	Double-blinded randomized OMT vs. CRT-P 29.4 months	III–IV	≤35%	≥120	All-cause mortality or hospitalization	All-cause mortality, NYHA class, QoL	CRT-P reduced all-cause mortality and hospitalization and improved NYHA class and QoL
REVERSE[61]	610	Double-blinded, randomized CRT-ON vs. CRT-OFF, 12 months	I–II	≤40%	≥120	% worsened by clinical composite endpoint	LVESV index, heart failure hospitalizations and all-cause mortality	CRT-P/CRT-D did not change the primary endpoint and did not reduce all-cause mortality but reduced LVESV index and heart failure hospitalizations.
MADIT-CRT[50]	1820	Single-blinded, randomized CRT-D vs. ICD, 12 months	I–II	≤30%	≥130	All-cause mortality or heart failure hospitalizations	All-cause mortality and LVESV	CRT-D reduced the endpoint heart failure hospitalizations or all-cause mortality and LVESV. CRT-D did not reduced all-cause mortality
RAFT[62]	1798	Double-blinded, randomized CRT-D vs. ICD 40 months	II–III	≤30%	≥120	All-cause mortality or heart failure hospitalizations	All-cause mortality and cardiovascular death	CRT-D reduced the endpoint all-cause mortality or heart failure hospitalizations. In NYHA III, CRT-D only reduced significantly all-cause mortality

CRT… is now part of standard HF care

Recommendations	Class [a]	Level [b]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B

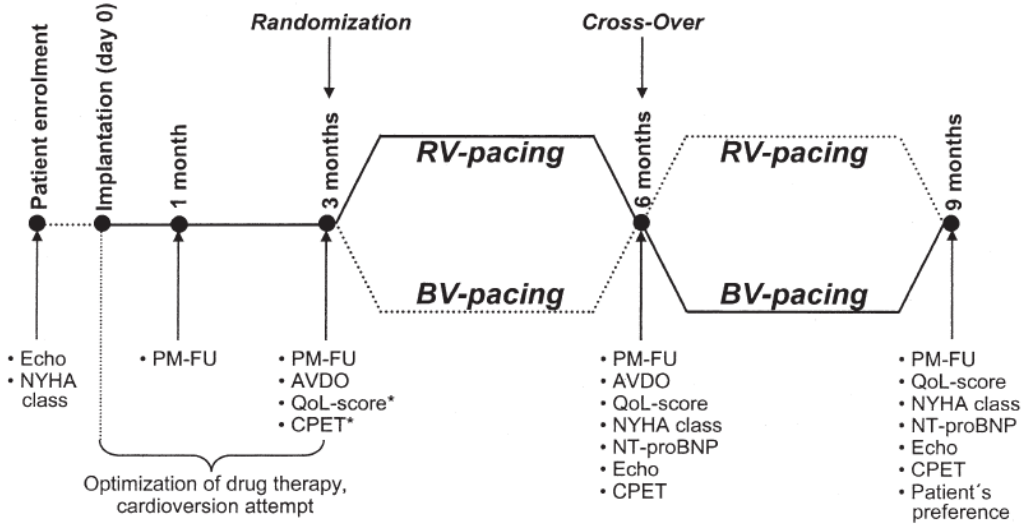
Ponikowski P et al, Eur Heart J. 2016;37:2129-200

The hypothesis

Should all patients with a pacemaker indication receive a CRT to avoid the detrimental effects of RV apical pacing?

WHAT IS THE EVIDENCE FOR PTS WITH REDUCED LVEF?

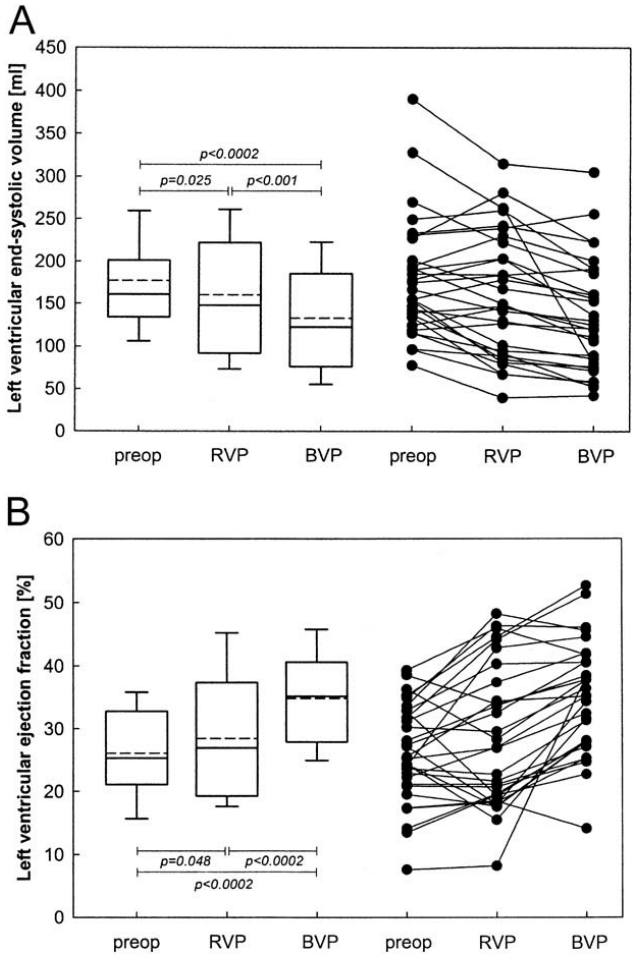
HOBIPACE

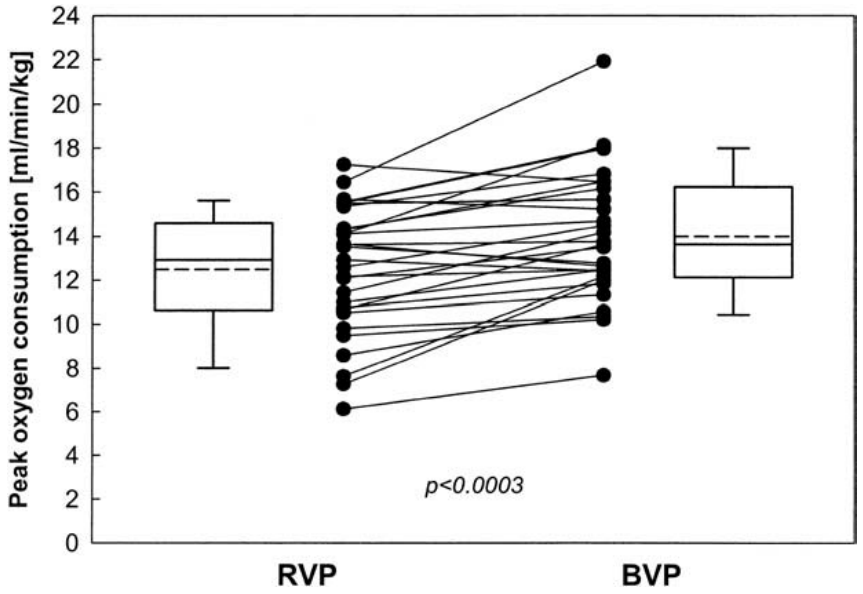


A small (30 pts) but the first RCT that compares BiV pacing with conventional RV pacing in pts with LV dysfunction and a standard indication for antibradycardia pacing

Kindermann et al, J Am Coll Cardiol 2006;47:1927–37

HOBIPACE

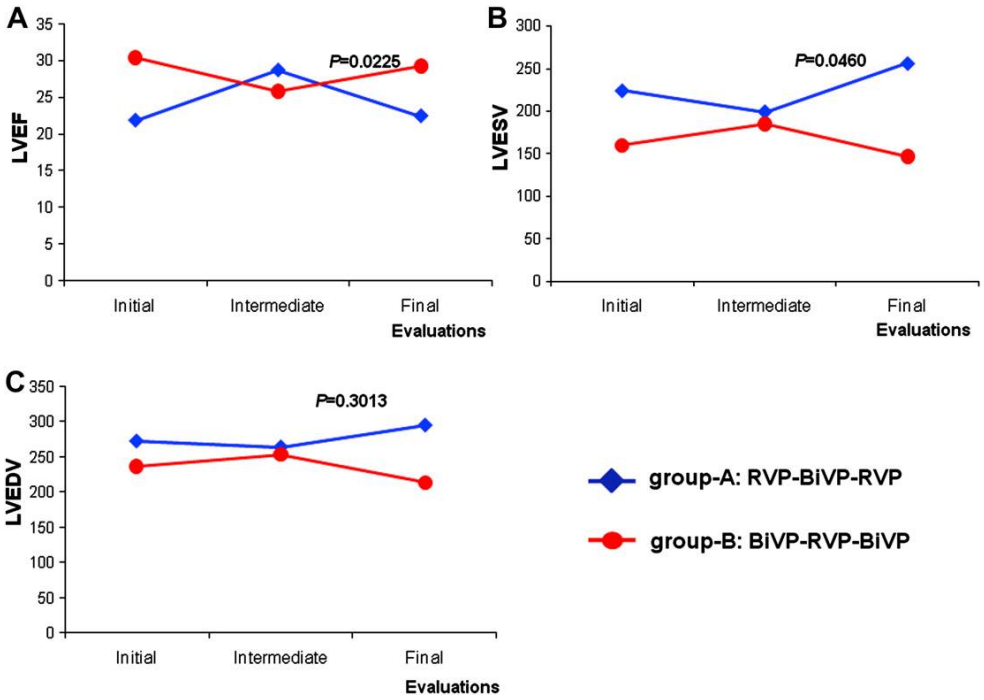




BiV pacing was superior in reduction of LV volumes, and improvement of LVEF, quality of life, maximal and submaximal exercise capacity

Kindermann et al, J Am Coll Cardiol 2006;47:1927–37

COMBAT



In 60 pts after a follow-up period of 17 mo there were significant improvements in QoL, FC, LVEF, and LV end-systolic volume with BiVP compared with RVP

Martinelli Filho et al, J Card Fail. 2010;16:293–300

The first large prospective RCT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

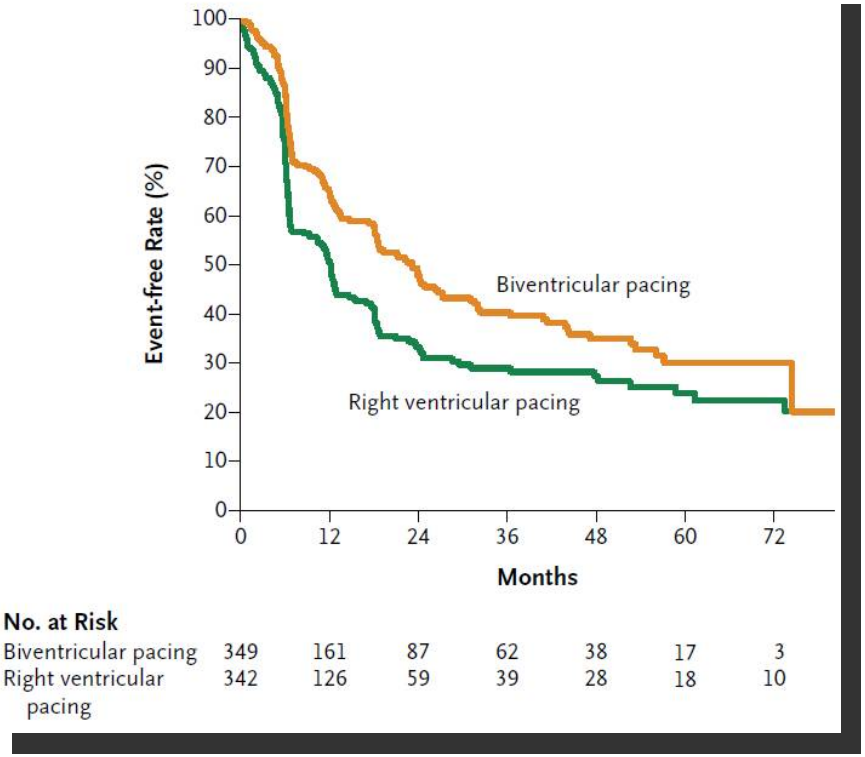
Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction

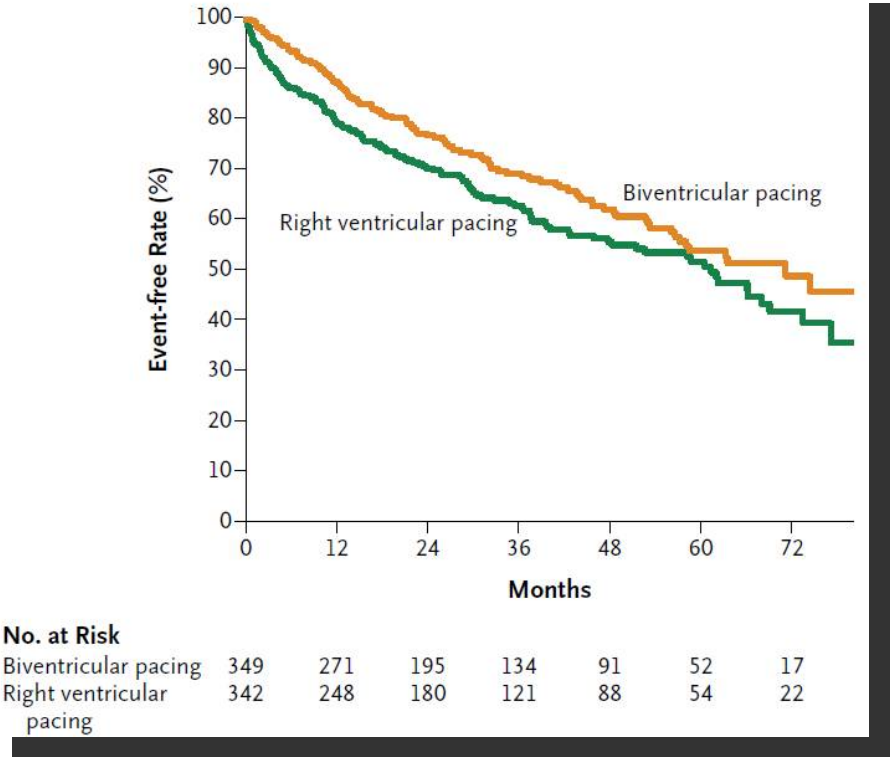
Anne B. Curtis, M.D., Seth J. Worley, M.D., Philip B. Adamson, M.D., Eugene S. Chung, M.D., Imran Niazi, M.D., Lou Sherfesee, Ph.D., Timothy Shinn, M.D., and Martin St. John Sutton, M.D., for the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators

BiV vs. conventional RV apical pacing among patients with AV block I–III, HF (NYHA I–III), and subnormal LVEF (≤50%)
691 pts, 37 mo follow-up, mean QRS 124 ms, mean LVEF 40 ± 8%, and most patients NYHA I–II

Curtis A et al, N Engl J Med 2013;368:1585-93

BLOCK-HF

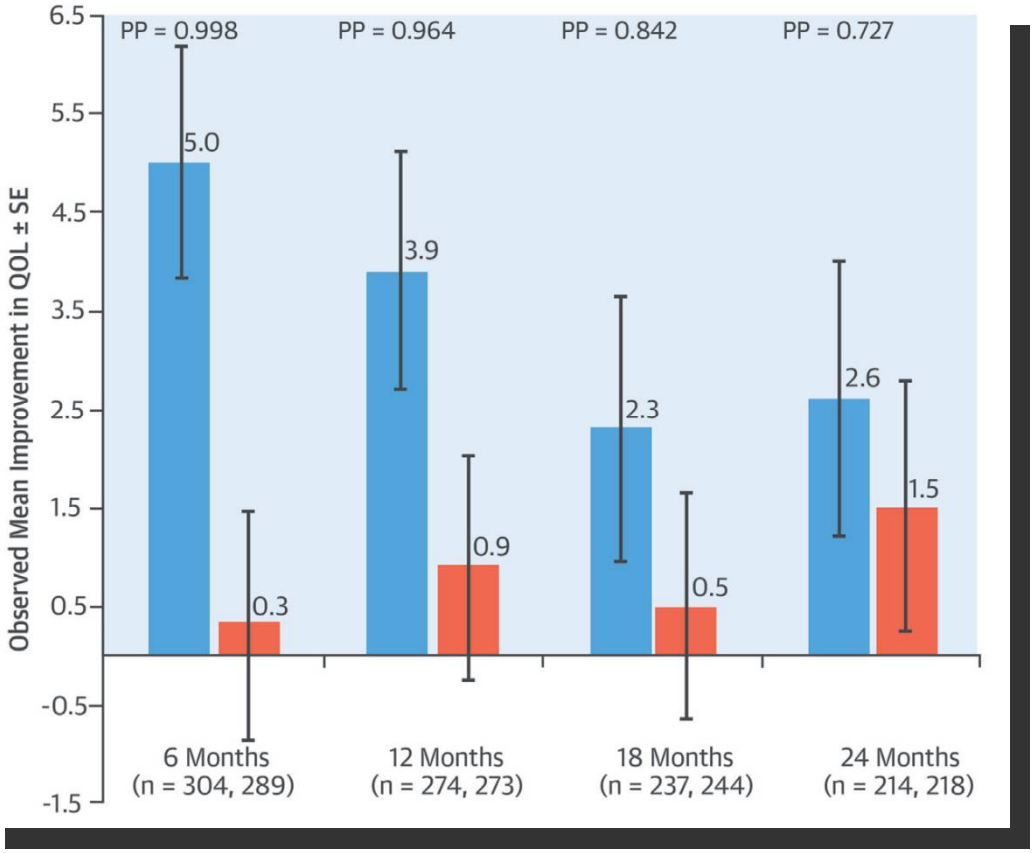




CRT was associated with a statistically significantly lower incidence (26% risk reduction) of the primary composite endpoint of all-cause death, HF-related urgent care visit, and >15% increase in LVESVi and a 27% risk reduction in all-cause mortality and HF-related urgent care

Curtis A et al, N Engl J Med 2013;368:1585-93

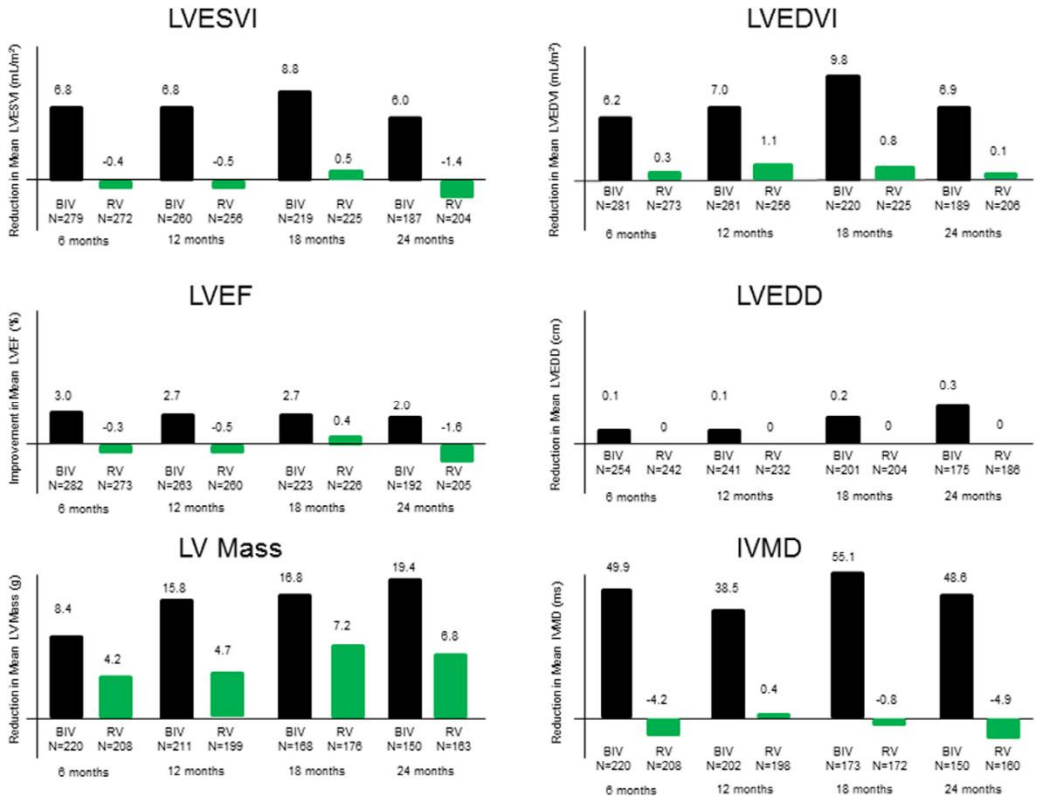
BLOCK-HF



CRT improved QOL and heart failure status, compared with RV pacing

Curtis A et al, J Am Coll Cardiol 2016;67:2148–57

BLOCK-HF – echo substudy



BiV pacing results in reverse structural and functional LV remodeling, whereas traditional RV pacing does not

Sutton M et al, Circ Heart Fail. 2015;8:510-518

BLOCK-HF message

For patients who require chronic RV pacing, treatment with CRT leads to:

- **significant improvement of LV function**
- **reduction of adverse clinical events**
  - ***even in patients with milder forms of HF and less severe LV dysfunction***

FDA approval

At the October 8, 2013 advisory meeting members voted that **the benefits** (as evidenced by a small reduction in occurrence of heart failure-related urgent care) **outweigh the risks** (LV lead-related complications as well as potentially more often pulse generator replacements**) in a population that is restricted to those who require a significant amount of RV pacing.**

Evidence for the guidelines…

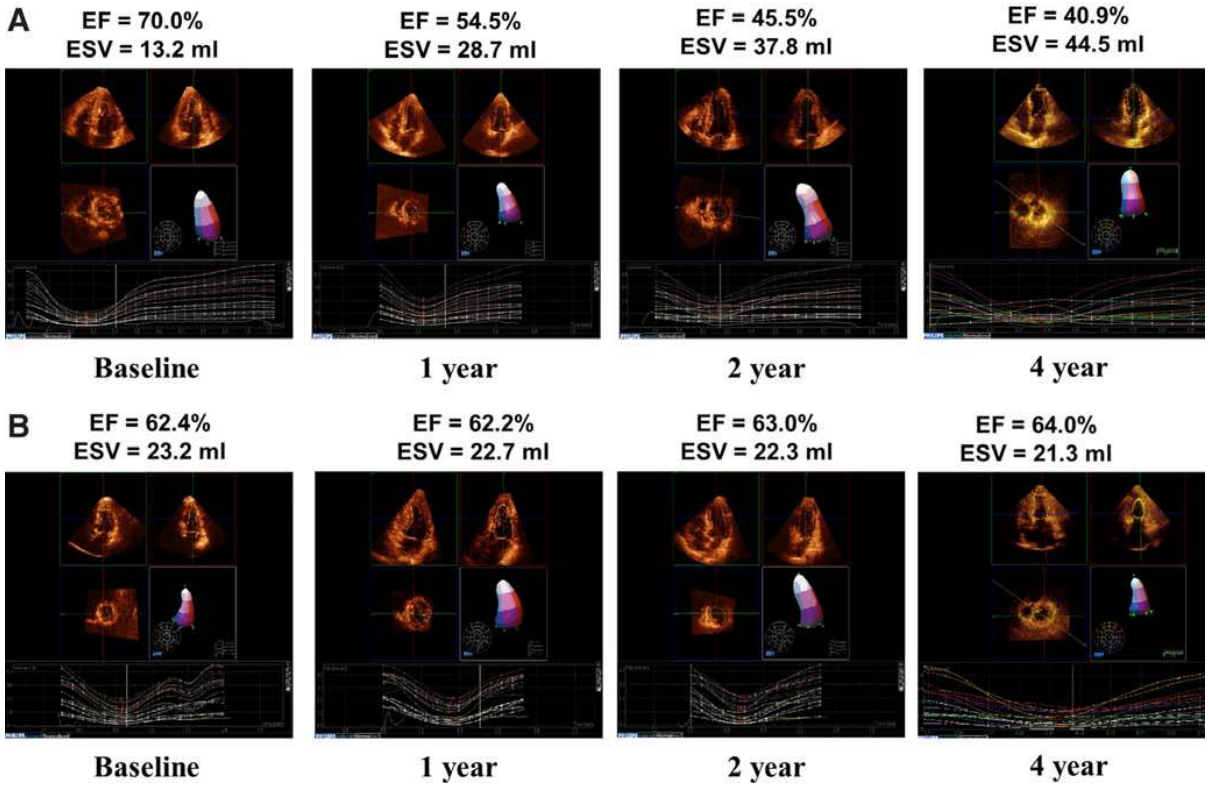
Studies	No. of patients	Echo, ESV (%)	Echo, EF (%)	QoL scores (%)	NYHA class (%)	Clinical outcome
Patients with moderate/severe systolic dysfunction, CRT vs RV						
HOBIPACE[127]	30	-9	+22	-19	-24	Patient's preference: 67% CRT, 7% RV (P = 0.0002)
COMBAT[128]	60	-24	-21	-47	-24	Worsening HF or hospitalization: 3 vs. 8 patients
BLOCK HF[125, 126]	691	-	-	-	-	Significant 28% reduction in the combined primary endpoint of mortality, heart-failure related urgent care, and increase in LV end-systolic volume

CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A

Brignole M et al, Eur Heart J. 2013; 34:2281–2329
Ponikowski P et al, Eur Heart J. 2016;37:2129-200

WHAT IS THE EVIDENCE FOR PTS WITH NORMAL EF?

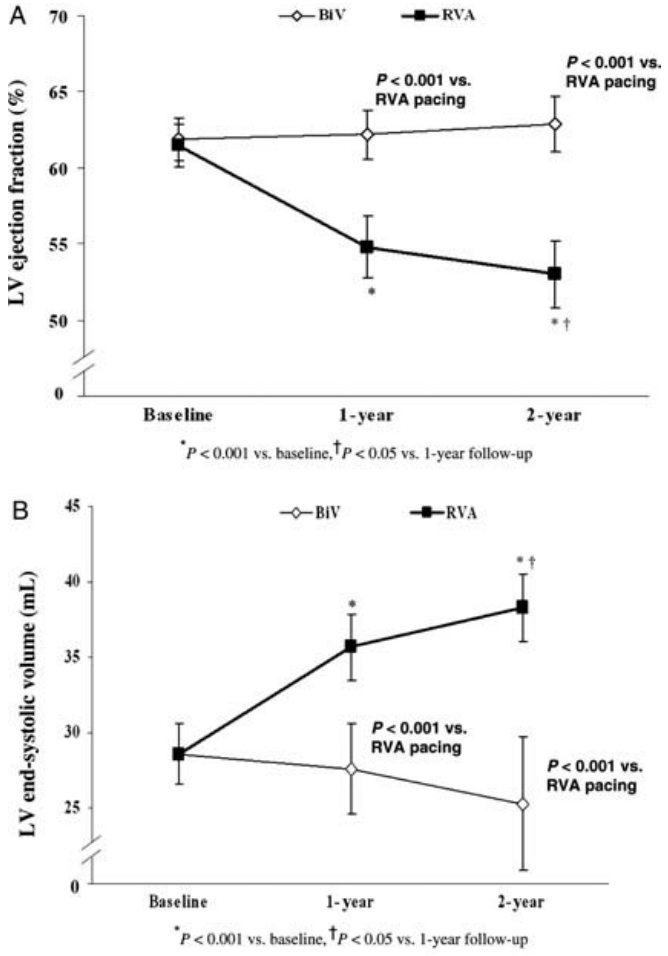
CRT for bradycardia and normal EF
PACE trial



In 177 pts at 1 year, conventional RVA pacing resulted in adverse LV remodeling and in a reduction in the LVEF, but these effects were prevented by BiV pacing

Yu CM et al, N Engl J Med 2009;361:2123-34

PACE trial at 2 years…

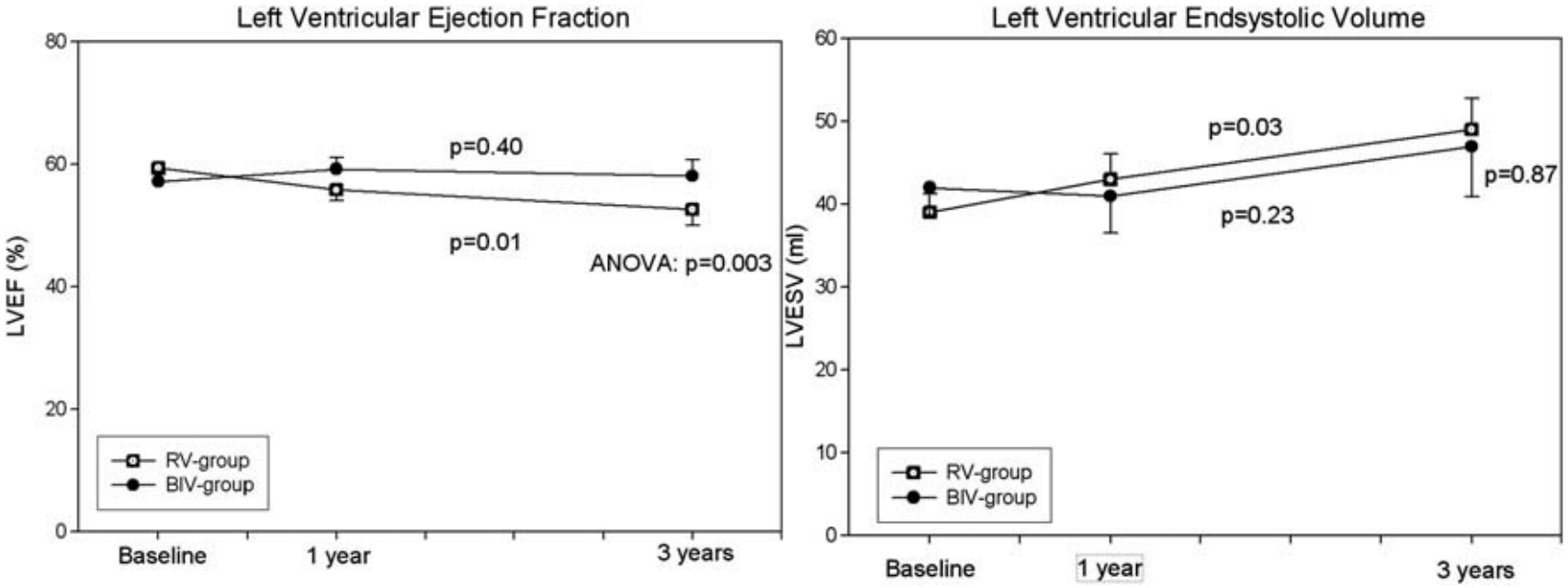


- *The adverse effect of RVA pacing on LV systolic function and remodeling observed at the first year <u>continue to progress</u> over the second year.*

- *On the contrary, the protective effect of BiV pacing <u>persists over time</u>*

Chan YS et al, Eur Heart J 2011;32:2533–40.

At 3 years…



Adverse remodeling observed during 3 years of RV pacing in 55 pts, was prevented by BIV pacing

Albertsen et al, Eur J Echocardiogr 2011;12:767–72.

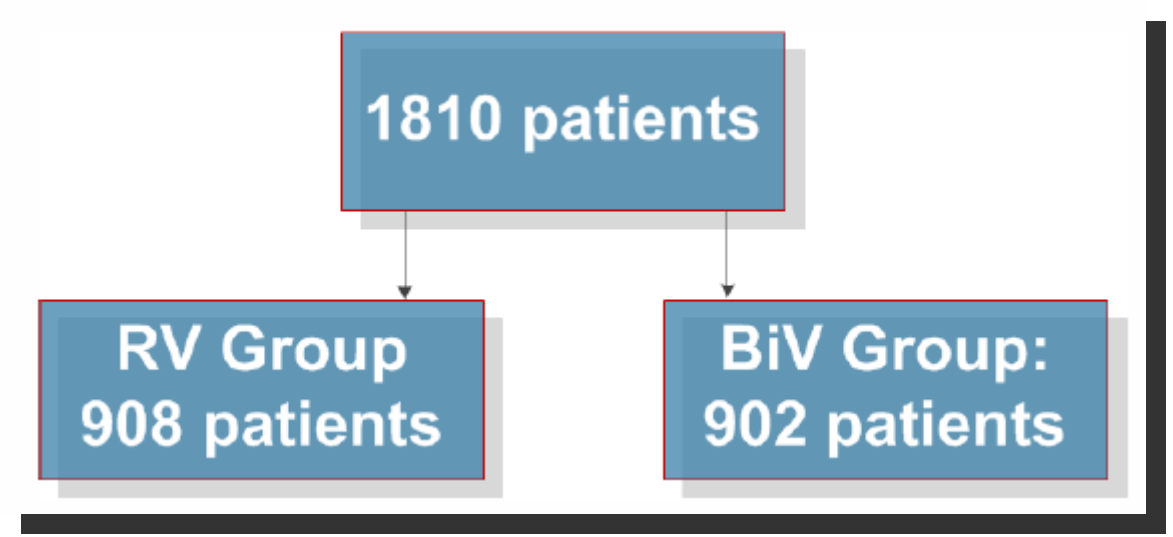
The evidence is not yet strong…

Patients with preserved systolic function, CRT vs RV						
Albertsen[123]	50	-	+5	-	-17	-
PACE[124, 130]	177	-22	+13	No difference	-	Hospitalization for HF: 6 vs. 7% (ns)
PREVENT-HF[129]	108	-5	+7	-	-	Worsening of HF: 6 vs. 14% (ns)

- **PACE trial and Albertsen et al. *failed to demonstrate a clinical benefit* of CRT in patients with preserved LVEF**

- **PREVENT-HF, another small multicenter study of 108 pts with AV block, NYHA I–II and normal LVEF, *failed to show LV volume differences* >12 mo between RV apical and BIV pacing**

BioPace study



Is BiV pacing superior to RV pacing in patients with AVB who require permanent ventricular pacing?

Blanc JJ, ESC Congress 2014

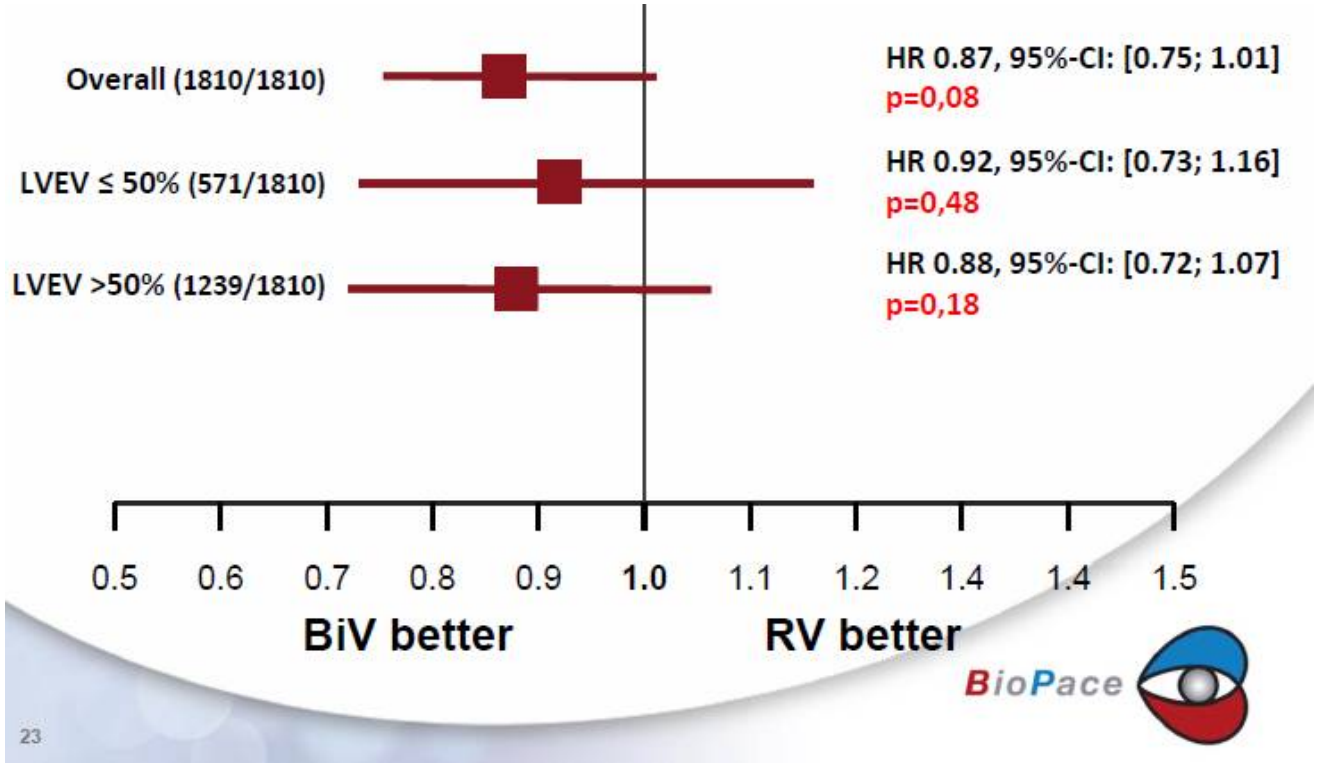
BioPace study

	TOTAL 1810	RV 908 (50.2%)	BiV 902 (49.8%)	p
• Age [year]	73.5±9.2	73.3±9.3	73.8±9.0	0.27
• Men	68.3%	67.4%	69.2%	0.42
• % Ventricular pacing at 1 month	88.2	86.3	90.1	0.07
• LVEF [%]	55.4±12.2	55.5±12.4	55.3±12.1	0.95
• QRS Duration [ms]	118.4±30.5	118.8±30.3	118.1±30.8	0.61
• Underlying Cardiac Disease	63.1%	63.0%	63.3%	0.92
• Atrial Fibrillation	24.9%	24.8%	24.9%	0.96
• LBBB	17.2%	18.3%	16.6%	0.39

the BioPace study cohort is quite different from the BLOCK-HF study population

Blanc JJ, ESC Congress 2014

BioPace study



After 5.6 yrs a non statistically significant trend in favor of BiV over RV pacing in combination of time-to-death or first hospitalization due HF

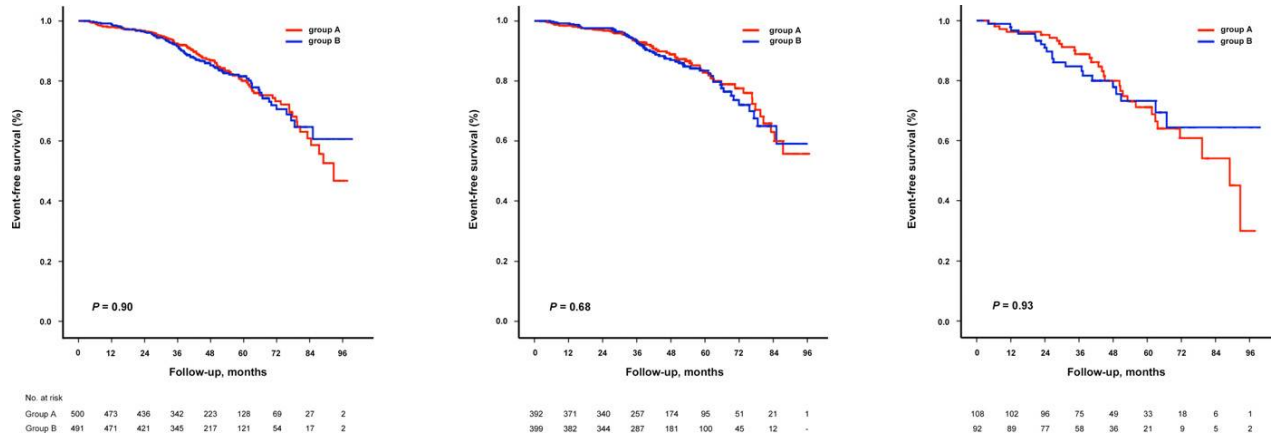
Blanc JJ, ESC Congress 2014

BLOCK-HF vs. BioPace

The discrepancy may be due at least in part to different patient characteristics:

- ***BLOCK HF appeared to have sicker patients with a lower average LVEF, more LBBB, and more AF***

If LV function is normal…



…development of clinically relevant LV systolic dysfunction is a rather infrequent event irrespective of pacing indication and cumulative percentage of RV pacing (only 6%)

…no significant difference in death from any cause and development of severe LV dysfunction requiring upgrade to BiV pacing between pts implanted for AVB and pts implanted for SND

Ebert M et al, J Am Heart Assoc. 2016;5:e003485

HOW TO APPROACH THE PATIENT WITH INDICATION FOR CARDIAC PACING?

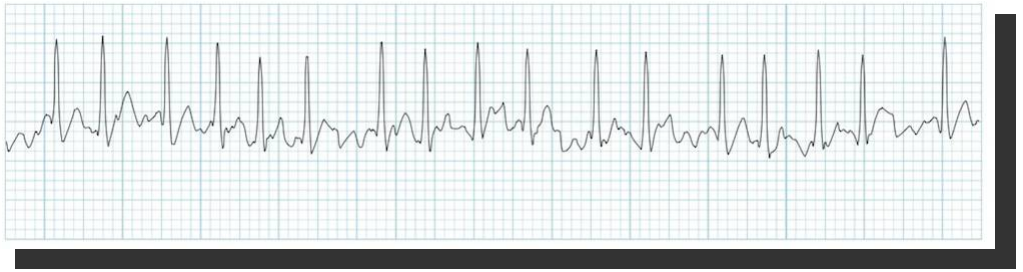
A practical approach

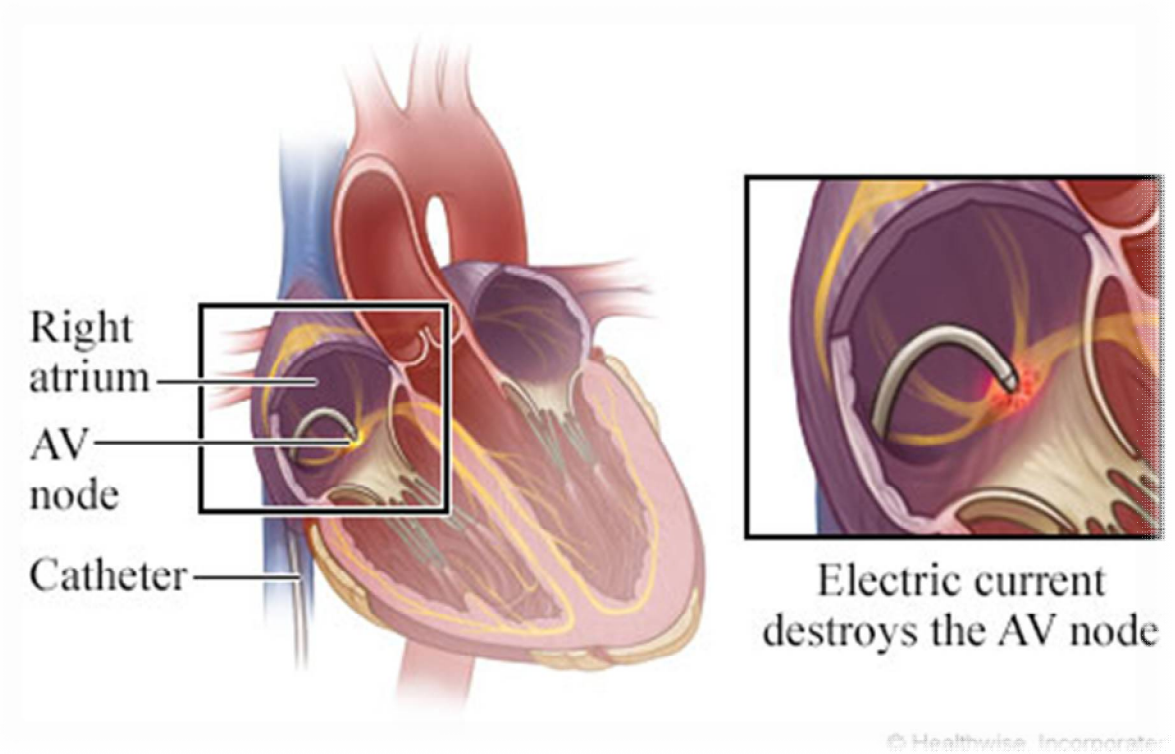
Consider BiV if:

- **Permanent AV block**
- **LVEF <40%**
- **Life expectancy >3 years**

- **Low LVEF and planned AV node ablation for AF**

AVJ ablation & pacing

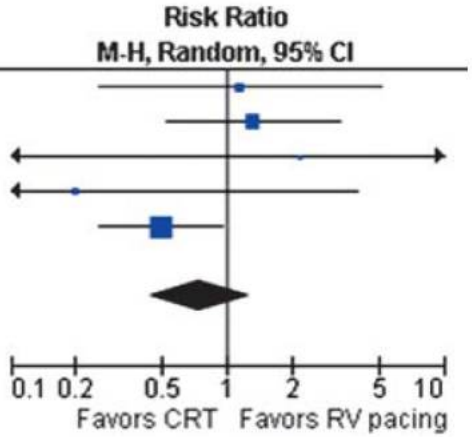




AVJ ablation & pacing

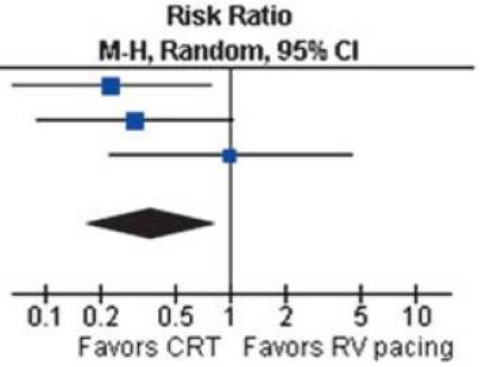
Study or Subgroup	CRT Events	CRT Total	RV pacing Events	RV pacing Total	Weight	Risk Ratio M-H, Random, 95% CI
AVAIL 2010	8	119	2	34	12.5%	1.14 [0.25, 5.13]
Eur Heart J 2011	10	97	7	89	30.0%	1.31 [0.52, 3.30]
MUSTIC-AF 2002	1	25	0	18	3.0%	2.19 [0.09, 50.93]
OPSITE 2005	0	26	2	26	3.3%	0.20 [0.01, 3.97]
PAVE 2005	13	146	19	106	51.1%	0.50 [0.26, 0.96]
Total (95% CI)		**413**		**273**	**100.0%**	**0.75 [0.43, 1.30]**
Total events	32		30			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 4.39$, df = 4 (P = 0.36); $I^2 = 9\%$
Test for overall effect: Z = 1.03 (P = 0.30)



Study or Subgroup	CRT Events	CRT Total	RV pacing Events	RV pacing Total	Weight	Risk Ratio M-H, Random, 95% CI
APAF 2011	3	97	12	89	36.7%	0.23 [0.07, 0.79]
MUSTIC-AF 2002	3	43	10	44	37.3%	0.31 [0.09, 1.04]
OPSITE 2005	3	26	3	26	26.0%	1.00 [0.22, 4.50]
Total (95% CI)		**166**		**159**	**100.0%**	**0.38 [0.17, 0.85]**
Total events	9		25			

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 2.36$, df = 2 (P = 0.31); $I^2 = 15\%$
Test for overall effect: Z = 2.34 (P = 0.02)



CRT resulted in a non-significant reduction in mortality and a significant reduction in hospitalizations for HF

Stavrakis S et al, Europace 2012;14:1490–1497

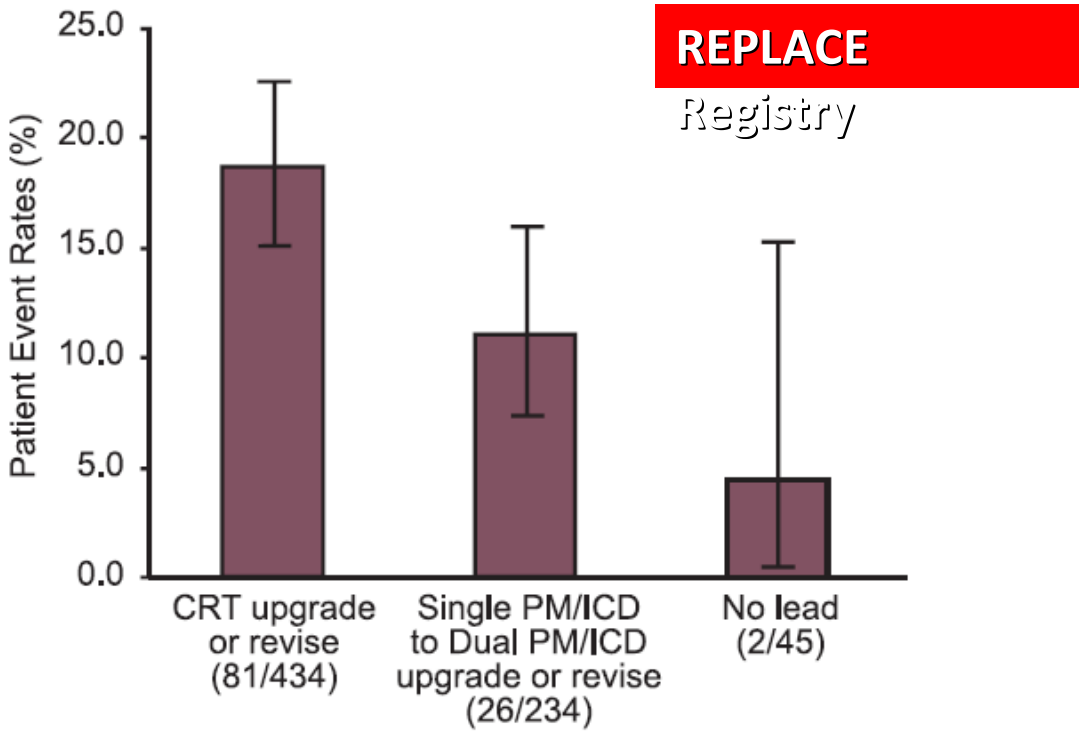
The challenge…

- **…is to *detect* progressive LV dysfunction even if patients remain asymptomatic, with regular echocardiographic follow-up**

- **…so that *upgrading* to BiV pacing can be implemented without delay if evidence of LV adverse remodeling and reduced LVEF is present**

CRT procedure

The risks…



major complication risks for CRT system upgrade have been reported to be as high as 19%

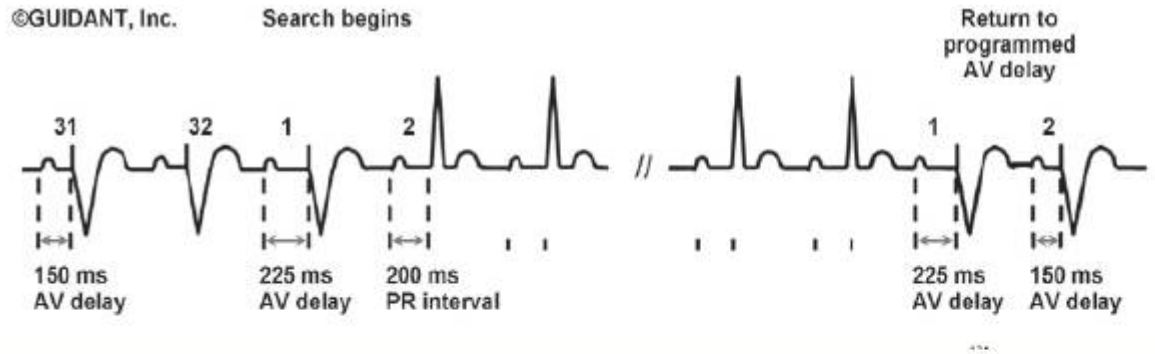
Poole et al, Circulation 2010;122:1553–61

Take home…

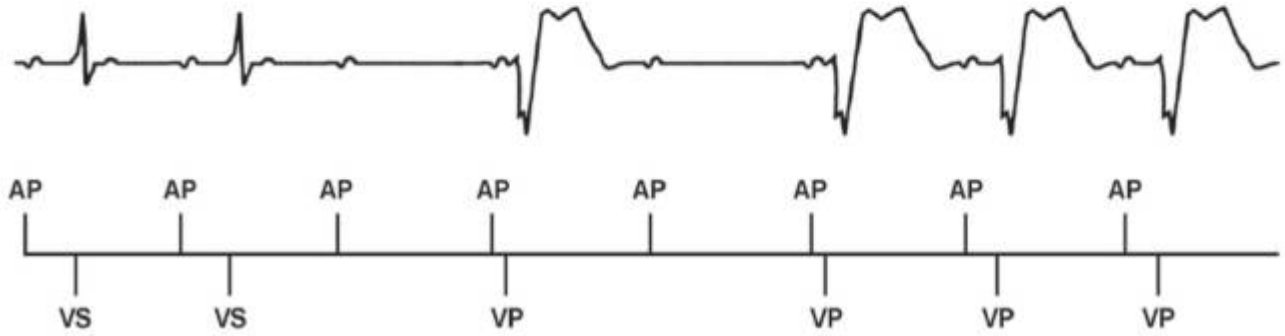
- In a ***limited*** number of patients CRT could be proposed as a first line option

- In patients with AV block and RV pacing do not ***follow*** only pacing parameters but also ***LV function*** and keep in mind that upgrading to CRT remains an option

Other options…



AV Search hysteresis



Managed ventricular pacing

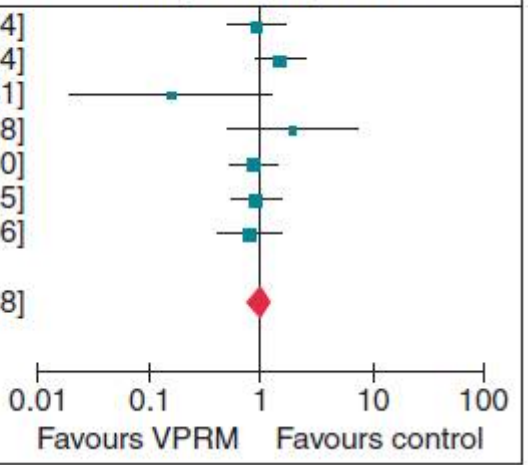
…pacemaker algorithms that reduce VP

Pacemaker algorithms…

Study or subgroup	VPRM Events	VPRM Total	Control Events	Control Total	Weight	Odds ratio M–H, random, 95% CI
Boriani	19	398	20	385	16.3%	0.91 [0.48, 1.74]
Botto	31	299	22	306	20.1%	1.49 [0.84, 2.64]
Chen	1	196	6	189	1.7%	0.16 [0.02, 1.31]
Davy	6	141	3	135	3.7%	1.96 [0.48, 7.98]
Stockburger	26	314	30	318	21.5%	0.87 [0.50, 1.50]
Sweeney	26	530	29	535	22.0%	0.90 [0.52, 1.55]
Thibault	17	191	20	182	14.7%	0.79 [0.40, 1.56]
Total (95% CI)		2069		2050	100.0%	0.97 [0.74, 1.28]
Total events	126		130			

Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 6.59$, df = 6 ($P = 0.36$); $I^2 = 9\%$

Test for overall effect: $Z = 0.20$ ($P = 0.84$)

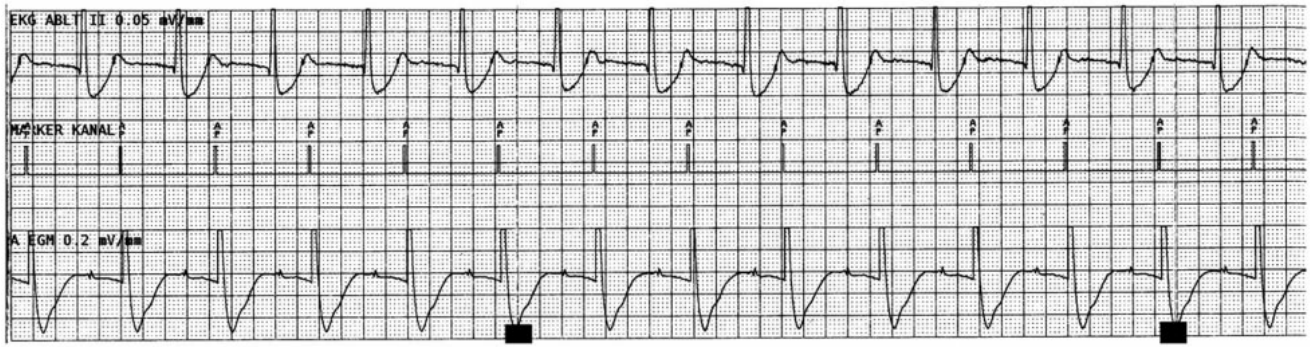


…did not improve clinical outcomes and were not superior to standard DDD programming in reducing incidence of persAF, all-cause hospitalization, and all-cause mortality in patients with preserved LV function

Shurrab et al, Europace 2017;19:282–288

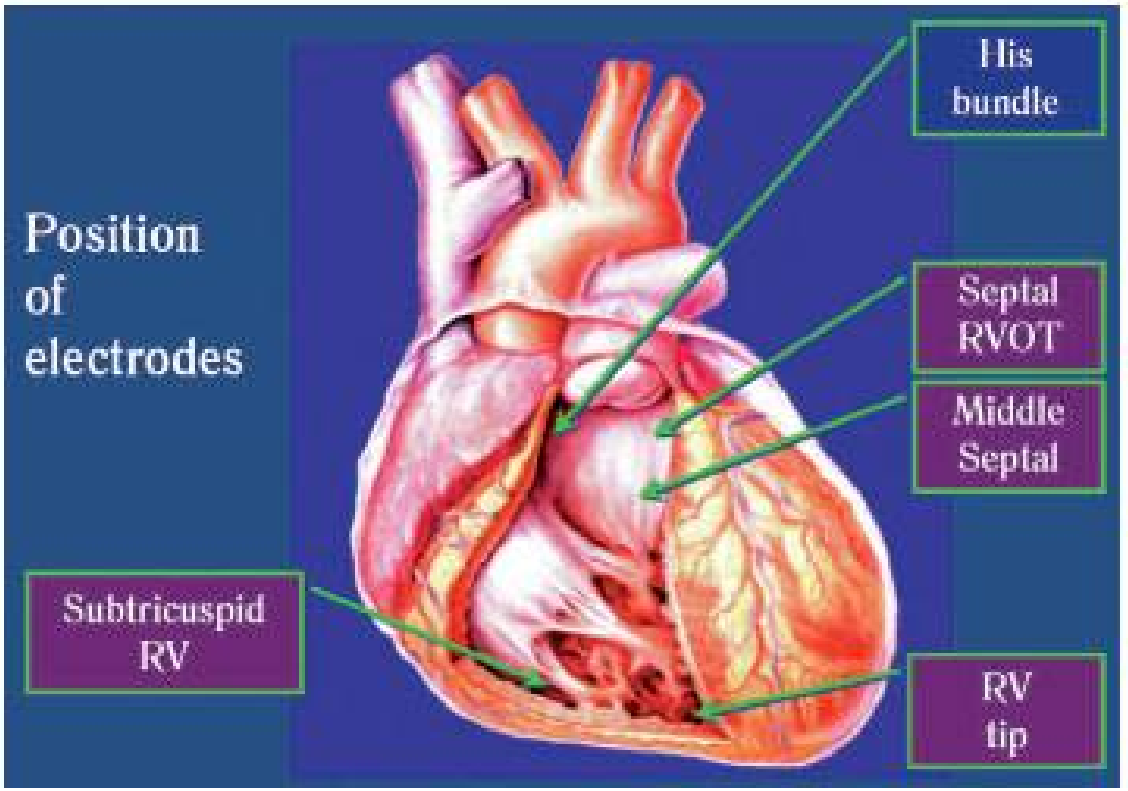
1st AV block

- **Intrinsic 1st AV block:**
  - *for PQ>230 ms, prevention of RVP likely not useful*
- **Paced 1st AV block:**
  - *for PQ>270 ms after atrial pacing, prevention of RVP likely not useful*

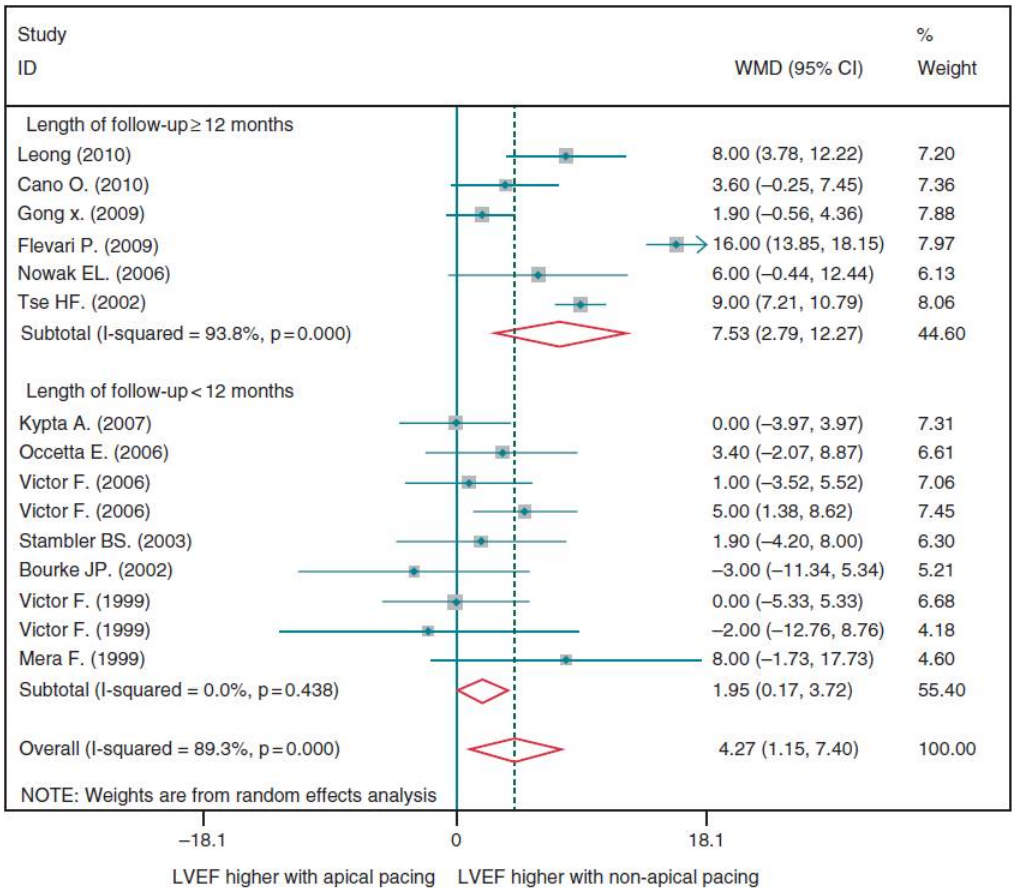


Functional atrial undersensing

Alternative RV pacing sites



Apical vs. Non-apical pacing

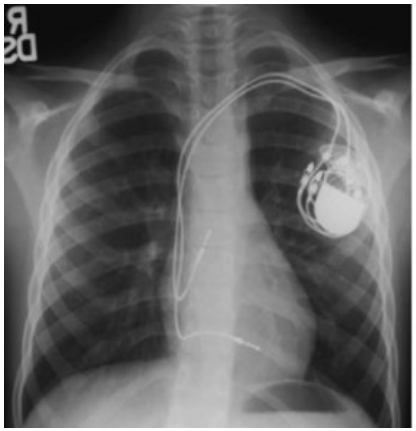


…data regarding exercise capacity, functional class, quality of life, and survival were limited and inconclusive

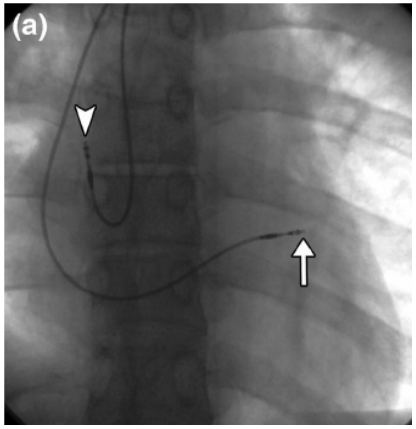
Shimony et al, Europace 2012;14: 81–91

Protect-Pace study

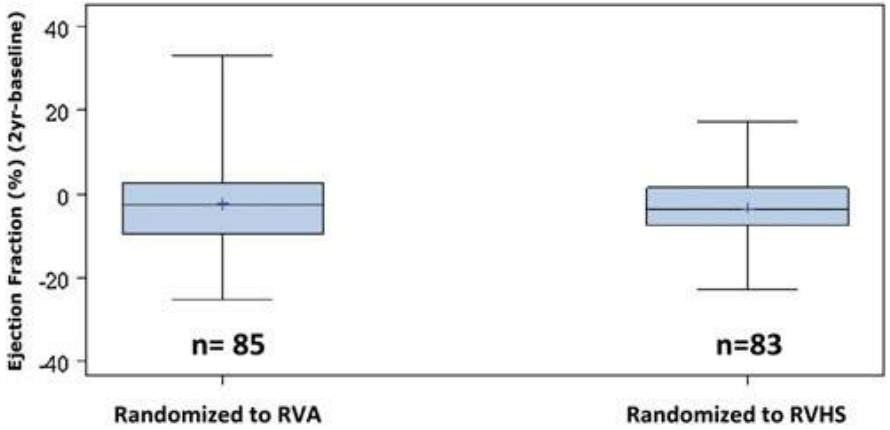
High-grade AV block & preserved EF >50%



RVA



Septal



- No significant change in individual patient's LVEF during follow-up
- No significant differences in HF hospitalizations, mortality, or BNP
- A significantly greater time to place the lead in the RV high septal with longer fluoroscopy times

Kaye et al , Eur Heart J. 2015;36:856–62