Systematic Review for the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay

Data Supplements

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Abbreviations: 1° indicates primary; AF, atrial fibrillation; AV, atrioventricular; BIV, biventricular; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range; IVCD, interventricular conduction delay; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; N/A, not applicable; NYHA, New York Heart Association; NR, not reported; RBBB, right bundle branch block; RCT, randomized controlled trial; RR, relative risk; RV, right ventricular; and SD, standard deviation.

Data Supplement 1. Full PICO(TSS) Eligibility Criteria

#	Item	Details	
	Research Question and PICO(TSS) Framework		
1.	**Research question(s)**	For adult patients with LVEF >35% and having any degree of heart block, who require pacing, what are the benefits and harms of: • Dual chamber pacing vs. cardiac resynchronization therapy (CRT) pacing? • Dual chamber pacing vs. His-bundle pacing?	
2.	**Definitions**	**Dual chamber pacing:** Dual-chamber pacing referring to have one lead (wires) implemented in ventricle and one lead implemented in the Atrium. **Right ventricle (RV) pacing:** The pace maker has one lead implemented in the RV. So RV pacing can be dual chamber pacing if there is an extra lead also in the Atrium. **CRT** here includes both cardiac resynchronization therapy pacemaker (CRT-P) and cardiac resynchronization therapy defibrillator (CRT-D).	
3.	**Participants/population**	**Include:** 1. Adults age 18 y and older; 2. Any degree heart block (first, second or third degree); 3. Left ventricular (LV) ejection fraction >35%	**Exclude:**
		Additional information: a) Include mixed populations? Yes ☐ | No ☒ Include sub-groups or special populations? Yes ☒ | No ☐ • QRS morphology: LBBB, RBBB, IVCD, QRS duration • Patients with congenital complete heart block • Patients who undergo AV node ablation and PM implant for management of AF with rapid ventricular response rates, • Etiology of LV dysfunction (ischemic coronary artery disease, valvular disease, HTN, idiopathic), • HF functional class (NYHA functional class I, II, III or IV), • LVEF (36–40%, 40–50%, >50%) • Patients with AF • Indication for pacing, patients with a pre-existing single or dual chamber PM or ICD, sex (male/female), • Ethnicity (White, non-Hispanic, Black, Hispanic, Asian, and other if specified) • Co-morbidities (HTN, DM, CKD, valvular heart disease), • Percent physiologic ventricular pacing • Cardiac medications.	

		b) Restrict to specific line of therapy/prior treatment response criteria? Yes ☐ | No ☒ c) Restrict to specific severity? Yes ☒ | No ☒	
4.	**Intervention**	**Include:** • Dual chamber pacing	**Exclude:** • NA
		Additional information: a) Include studies of monotherapies? Yes ☒ | No ☐ b) Include studies of combination therapies? Yes ☒ | No ☐ i. Concurrent/concomitant ☒ ii. Add-on to background/maintenance ☒ iii. Combined with non-included/excluded intervention ☒ iv. Other(s)/describe: c) Include sequential therapy studies? Yes ☐| No ☒ d) Include studies of a dose or administration schedule not approved by the FDA and/or EMA? Yes ☒ | No ☐	
5.	**Comparator(s)**	**Include:** CRT pacing; OR His-bundle pacing	**Exclude:**
		Additional information: a) Include studies that compare different dosage/route/schedule/etc. for an intervention? Yes ☐ | No ☒	
6.	**Outcome(s): primary/critical**	**Include:** • Mortality; • Functional status (prefer change scores);	**Exclude:**

		• LVEF (prefer change);
		• HF symptoms (orthopnea, exercise capacity) (prefer change scores);
		• Length of hospital admission;
		• AF;
		• Health-related quality of life measurement;
		• Any adverse events resulting in an intervention (need to include but not limited to the following:
		  ○ Lead dislodgement;
		  ○ Phrenic nerve pacing;
		  ○ Emergency department visit;
		  ○ Reduced battery longevity;
		  ○ Infection)	

7.	**Timing**	a) Restrict included studies to minimum treatment duration or follow-up? Yes ☐ | No ☒ b) Restrict outcomes collected to certain time points? Yes ☐ | No ☒	
8.	**Setting/context**	• Restrict included studies to certain settings/context (e.g., ambulatory/outpatient vs. hospital/inpatient or specific geographical settings)? Yes ☒ | No ☒ • Ambulatory patients	
9.	**Study design**	**Include:** o Systematic review and/or meta-analyses to identify any additional RCTs and observational studies o Randomized controlled trials (RCTs) o Controlled observational studies	**Exclude:** • Case reports
		Additional information: a) For clinical trials, include phase: 1 ☐ | 2 ☐ | 3 ☒ | 4 ☐ b) Define a minimum sample size? Yes ☐ | No ☒	
	Literature Search		

10.	**Literature sources**	**Standard Databases:** • **Medline (via PubMed/OVID)** • **Embase (via OVID)** • **Cochrane Central Database of Controlled Trials (via CENTRAL)** **Conference Proceedings:** • **All (via Embase):** Yes ☐ | No ☒ **And** • **Specific conference/meeting:** a) Include manual search of specific conference, if not available through Embase? Yes ☐ | No ☒ ***Database Limits:*** • Language: English • Publication date (databases): 2002–current • Publication date (conferences): 2002–current • Subjects: humans
	Deliverables	
11.	**End use goals**	• This review is intended to support the AHA/ACC Clinical Practice Guideline
12.	**Description of any known analysis plan**	• Evidence synthesis
	Background and Existing Evidence	
13.	**Existing reviews or publications utilized or checked during the development of this protocol**	• https://www.ncbi.nlm.nih.gov/pubmed/25336367
14.	**Landmark/important studies**	• https://www.ncbi.nlm.nih.gov/pubmed/25446158

Data Supplement 2. Search Strategies

DATABASE: *PubMed*		
DATE SEARCHED: 5/26/17		
1	"Heart Block"[Mesh]	
2	heart block[tiab] OR Auriculo-Ventricular Dissociation[tiab] OR A-V Dissociation[tiab] OR AV Dissociation[tiab] OR AV block[tiab] OR A-V block OR Bundle-branch block[tiab] OR Mobitz[tiab] OR wenchebach*[tiab] OR LBBB[tiab] OR AVB[tiab] OR RBBB[tiab] OR BBB[tiab] OR Cardiac block[tiab] OR ventriculoatrial block[tiab] OR ventricular block[tiab] OR atrial-ventricular block[tiab] OR atrio-ventricular block[tiab] OR atrioventricular block[tiab] OR Left anterior fascicular block[tiab] OR LAFB[tiab] OR interatrial block[tiab] OR aIAB[tiab] OR IAB[tiab] OR sinoatrial block[tiab] OR cardiac conduction block[tiab] OR heart conduction block[tiab] OR NOP-LBBB[tiab]	
3	1 OR 2	
4	"Pacemaker, Artificial"[Mesh:noexp] OR "Cardiac Pacing, Artificial"[Mesh:noexp]	
5	((Dual chamber[tiab] OR double-chamber[tiab] OR physiologic*[tiab]) AND (pacing[tiab] OR pacemaker*[tiab] OR pace-maker*[tiab] OR paced[tiab]))	
6	DDDR[tiab] OR DDD*[tiab] OR DCP*[tiab] OR DOO*[tiab] OR DVI*[tiab] OR DDI*[tiab] OR AV pac*[tiab] OR A-V pac*[tiab] OR atrioventricular pac*[tiab] OR atrio-ventricular pac*[tiab]	
7	((rv[tiab] OR right ventricular[tiab] OR right ventricle[tiab] OR apical[tiab]) AND (pacing[tiab] OR pacemaker*[tiab] OR pace-maker*[tiab] OR paced[tiab])) OR RVP[tiab])	
8	4 OR 5 OR 6 OR 7	
9	"Cardiac Resynchronization Therapy"[Mesh] OR "Cardiac Resynchronization Therapy Devices"[Mesh]	
10	Cardiac resynchronization therapy[tiab] OR Cardiac resynchronisation therapy[tiab] OR CRT[tiab] OR ((Biventricular[tiab] OR biv[tiab]) AND (pacing[tiab] OR pacemaker*[tiab] OR pace-maker*[tiab] OR paced[tiab])) OR bivp[tiab]	
11	(("Bundle of His"[Mesh] OR His-bundle[tiab] OR HB[tiab] OR bundle of his[tiab]) AND (pacing[tiab] OR pacemaker*[tiab] OR pace-maker*[tiab] OR paced[tiab])) OR HBP[tiab]	
12	9 OR 10 OR 11	
13	3 AND 8 AND 12 AND eng[la] NOT (animals[mh] NOT humans[mh]) AND 2002+	704
EMBASE SEARCH		

DATE SEARCHED: 5/26/17		
EMBASE SEGMENT USED 1974 to 2017 May 25		
#	Searches	Results
	1 exp *heart block/ (22191)	
	2 (heart block or Auriculo-Ventricular Dissociation or A-V Dissociation or AV Dissociation or AV block or A-V block or Bundle-branch block or Mobitz or wenchebach$ or LBBB or AVB or RBBB or BBB or Cardiac block or ventriculoatrial block or ventricular block or atrial-ventricular block or atrio-ventricular block or atrioventricular block or Left anterior fascicular block or LAFB or interatrial block or aIAB or IAB or sinoatrial block or cardiac conduction block or heart conduction block or NOP-LBBB).ab,kw,ti. (51439)	
	3 1 or 2 (60556)	
	4 dual chamber pacemaker/ or heart pacing/ or heart atrium pacing/ or heart ventricle pacing/ (23917)	
	5 (((Dual chamber or double-chamber or physiologic$) and (pacing or pacemaker$ or pace-maker$ or paced)) or DDDR or DDD$ or DCP$ or DOO$ or DVI$ or DDI$ or AV pac$ or A-V pac$ or atrioventricular pac$ or atrio-ventricular pac$ or ((rv or right ventricular or right ventricle or apical) and (pacing or pacemaker$ or pace-maker$ or paced)) or RVP).ab,kw,ti. (58833)	
	6 4 or 5 (77017)	
	7 3 and 6 (6094)	
	8 cardiac resynchronization therapy/ or cardiac resynchronization therapy device/ (24429)	
	9 (Cardiac resynchronization therapy or Cardiac resynchronisation therapy or CRT or ((Biventricular or biv) and (pacing or pacemaker$ or pace-maker$ or paced)) or bivp).ab,kw,ti. (28965)	
	10 His bundle/ (3410)	
	11 (pacing or pacemaker$ or pace-maker$ or paced).ab,kw,ti. (86138)	
	12 10 and 11 (910)	
	13 (((His-bundle or HB or bundle of his) and (pacing or pacemaker$ or pace-maker$ or paced)) or HBP).ab,kw,ti. (3924)	
	14 8 or 9 or 12 or 13 (46236)	
	15 7 and 14 (1453)	
	16 limit 15 to (english language and yr="2002 -Current") (1194)	
	17 remove duplicates from 16 (1174)	

	18 17 not ((exp animal/ or nonhuman/) not exp human/) (1091)	1,091
	We excluded 458 meeting abstracts from the 1091 (line 18)	633

The Cochrane Library (Wiley)		
Date of search: 5/23/17		
#	Searches	Results
ID	Search	Hits
#1	[mh "Heart Block"]	498
#2	heart block or Auriculo-Ventricular Dissociation or A-V Dissociation or AV Dissociation or AV block or A-V block or Bundle-branch block or Mobitz or wenchebach* or LBBB or AVB or RBBB or BBB or Cardiac block or ventriculoatrial block or ventricular block or atrial-ventricular block or atrio-ventricular block or atrioventricular block or Left anterior fascicular block or LAFB or interatrial block or aIAB or IAB or sinoatrial block or cardiac conduction block or heart conduction block or NOP-LBBB:ti,ab,kw (Word variations have been searched)	8,585
#3	#1 or #2	8,650
#4	[mh ^"Pacemaker, Artificial"] or [mh ^"Cardiac Pacing, Artificial"]	1471
#5	DDDR or DDD* or DCP* or DOO* or DVI* or DDI* or AV pac* or A-V pac* or atrioventricular pac* or atrio-ventricular pac* or RVP:ti,ab,kw (Word variations have been searched)	2,810
#6	Dual chamber or double-chamber or physiologic* or rv or right ventricular or right ventricle or apical:ti,ab,kw (Word variations have been searched)	28,891
#7	pacing or pacemaker* or pace-maker* or paced:ti,ab,kw (Word variations have been searched)	4,675
#8	#6 and #7	1,227
#9	#5 or #8	3,537
#10	#3 and #9 Publication Year from 2002	412
#11	#10 not (pubmed or embase):an	19
	1 in trials	

Data Supplement 3. Dual Chamber vs. His-Bundle or CRT Pacing for Bradycardia: Cochrane Risk of Bias Assessment

	Sequence Generation	Allocation Concealment	Blinding of Study Participants and Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
Study, Year	**Was the randomization sequence adequately generated?**	**Was allocation adequately concealed?**	**Were study participants and personnel adequately blinded to participants' allocated intervention?**	**Were outcome assessors adequately blinded to participants' allocated intervention?**	**Were incomplete outcome data adequately addressed?**	**Is the study free of selective outcome reporting?**	**Was the study free of other potential sources of bias?**
Albertsen et al. 2011 (27)	No (high risk)	No (high risk)	No (high risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)
Stockburger et al. 2011 (30)	Yes (low risk)	No (high risk)	Yes (low risk)	Yes (low risk)	No (high risk)	Yes (low risk)	No (high risk)
Yu et al. 2009 {Yu, 2009 #792}	Yes (low risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)	No (high risk)
Kronborg et al. 2014 (31)	Yes (low risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)
Occhetta et al. 2006 (33)	Yes (low risk)	No (high risk)	No (high risk)	Yes (low risk)	Yes (low risk)	Yes (low risk)	No (high risk)

Data Supplement 4. Newcastle- Ottawa Scale Assessments for Cohort Studies

Study, Year	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study?	Study controls for X (most important factor)?	Study controls for any additional factor?	Assessment of outcome	Follow-up long enough for outcome to occur?	Adequacy of follow-up of cohorts (i.e., missing participants)	Selection Score (maximum score is 4)	**Comparability Score (maximum score is 2)**	**Outcome Score (maximum score is 3)**	**Total Score (maximum score is 9)**
Sharma et al. 2015 (32)	1	1	1	1	1	0	0	1	1	4	1	2	7

Note: '1' means response is "Yes" OR if criteria is acceptable otherwise '0'

Data Supplement 5. RCTs and Randomized Crossovers

Study Acronym; Author; Year Published; PMID	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Albertsen AE, et al. 2011 (1) 21857020	**Aim:** To investigate whether BIV pacing preserves LVEF and reduces LV dyssynchrony when compared with standard dual-chamber RV pacing in consecutive patients with high-grade AV during 3 y of pacing. **Study type:** RCT **Size:** 50	**Inclusion criteria:** Patients with permanent or paroxysmal high-grade AV block **Exclusion criteria:** N/A	**Intervention:** RV pacing (N = 25) **Comparator:** BIV pacing (N = 25)	**1° endpoint:** **RV pacing:** Dyssynchrony index - 1 y - 25.3 ms (SD ± 21.5) (SE ± 4.3) Dyssynchrony index - 3 y - 32 ms (SD ± 17) LV volume, end-diastolic - 3 y - 102 mL (SD ± 26) LV volume, end-systolic - 3 y - 49 mL (SD ± 17) LVEF - 1 y - 55.8% (SD ± 8) (SE ± 1.6) LVEF - 3 y - 53% (IQR difference ± 11) – (median, IQR) LVEF - 3 y - 52.7% (SD ± 12.5) (SE ± 2.5) – (mean, SD, SE) NT-pro-BNP - 1 y - 3.46 µg/L (SD ± 1.3) (SE ± 0.26)	• N/A • The study randomized patients regardless of their pre-implant intrinsic QRS duration and there were significant differences in QRS duration between the 2 groups after randomization. The study also used Vingmed Vivid Five (GE Medical) instead of a modern echocardiography; therefore, 2-dimensional recordings were assessed instead of 3-dimensional. • N/A

				NT-pro-BNP - 3 y - 3.93 µg/L (SD ± 1.65) (SE ± 0.33) NYHA class I - 3 y - 12 (48%) NYHA class II - 3 y - 8 (32%) NYHA class III - 3 y - 0 (0%) NYHA class IV - 3 y - 0 (0%) 6-min walk test - 1 y - 477.13 m (SD ± 118.35) (SE ± 23.67) 6-min walk test - 3 y - 488 m (SD ± 80.5) (SE ± 16.1) **BIV pacing:** Dyssynchrony index - 1 y - 17.8 ms (SD ± 28) (SE ± 5.6) Dyssynchrony index - 3 y - 22.7 ms (SD ± 17) LV volume, end-diastolic - 3 y - 109 mL (SD ± 27) LV volume, end-systolic - 3 y - 47 mL (SD ± 24) LVEF - 1 y - 59.3% (SD ± 8) (SE ± 1.6) LVEF - 3 y - 58% (IQR difference ± 10) – (median, IQR) LVEF - 3 y - 58.2% (SD ± 13.5) (SE ± 2.7) – (mean, SD, SE) NT-pro-BNP - 1 y - 3.85 µg/L (SD ± 1.95) (SE ± 0.39) NT-pro-BNP - 3 y - 3.41 µg/L (SD ± 1.5) (SE ± 0.3) NYHA class I - 3 y - 13 (52%) NYHA class II - 3 y - 3 (12%) NYHA class III - 3 y - 0 (0%) NYHA class IV - 3 y - 0 (0%) 6-min walk test - 1 y - 472.4 m (SD ± 132.55) (SE ± 26.51) 6-min walk test - 3 y - 512 m (SD ± 94.5) (SE ± 18.9) **<u>Safety endpoint</u>:** N/A	

PACE Chan JY, et al. 2011 (2) 21875860	**Aim:** To report the extended 2-y follow-up results for changes in LV function and remodeling of the PACE trial. **Study type:** RCT **Size:** 177	**Inclusion criteria:** - Normal ejection fraction (≥45%) - Standard indications for pacing - SND and bradycardia due to advanced AV block **Exclusion criteria:** - Persistent AF - Unstable angina - Acute coronary syndrome - Undergone percutaneous coronary intervention or coronary-artery bypass surgery within the previous 3 mo - Life expectancy of <6 mo - Received a heart transplant - Pregnant - Patients who fulfilled the eligibility criteria but in whom implantation of a BIV system was unsuccessful	**Intervention:** RV apical pacing – (N = 88) RV apical pacing, age, <70 y – (N = NR) RV apical pacing, age, ≥ 70 y – (N = NR) RV apical pacing, coronary heart disease, No – (N = NR) RV apical pacing, coronary heart disease, Yes – (N = NR) RV apical pacing, DM, type unspecified, No – (N = NR) RV apical pacing, DM, type unspecified, Yes – (N = NR) RV apical pacing, diastolic dysfunction, No – (N = NR) RV apical pacing, diastolic dysfunction, Yes – (N = NR) RV apical pacing, heart block RV apical pacing, HTN, No – (N = NR)	**1° endpoint:** **RV apical pacing:** Dyssynchrony index - 1 y - 36.3 ms (SD ± 14.3) Dyssynchrony index - 2 y - 42.2 ms (SD ± 13.3) LV volume, end-systolic, % change - baseline – 1 y - 25% LV volume, end-systolic, % change - baseline – 2 y - 34% LV volume, end-systolic, change - baseline – 1 y - 7.3 mL LV volume, end-systolic, change - 1 y – 2 y - 2.6 mL LV volume, end-systolic - 1 y - 35.7 mL (SD ± 16.2) [95% CI: 33.4–37.8] – (intent to treat) LV volume, end-systolic - 1 y - 33.3 mL (SD ± 13.3) - (N = 86) – (per protocol) LV volume, end-systolic - 2 y - 38.3 mL (SD ± 20.3) [95% CI: 36–40.4] – (intent to treat) LV volume, end-systolic - 2 y - 35.6 mL (SD ± 16.7) - (N = 81) – (per protocol) LVEF < 45% - 2 y - 15 (17%) LVEF, change - baseline – 1 y - -6.7% LVEF, change - 1 y – 2 y - -1.8% LVEF, decrease ≥ 5% - 2 y - 55 (62.5%) LVEF - 1 y - 56.2% (SD ± 9.4) - (N = 86) – (per protocol) LVEF - 1 y - 54.8% (SD ± 9.2) [95% CI: 52.8–56.9] – (intent to treat) LVEF - 2 y - 53.3% (SD ± 10.1) - (N = 81) – (per protocol) LVEF - 2 y - 53% (SD ± 10.1) [95% CI: 50.7 – 55.1] – (intent to treat) SF-36, bodily pain - 1 y - 72 units (SD ± 26) SF-36, bodily pain - 2 y - 73 units (SD ± 27)	• N/A • The sample size was relatively small and not powered to detect any difference in clinical events. A longer follow-up is needed to examine change in LVESV over time and clinical events such as HF hospitalization and mortality. • N/A

			RV apical pacing, HTN, Yes – (N = NR) RV apical pacing, SND – (N = NR) **<u>Comparator</u>:** BIV pacing – (N = 89) BIV pacing, age, < 70 y – (N = NR) BIV pacing, age, ≥ 70 y – (N = NR) BIV pacing, coronary heart disease, No – (N = NR) BIV pacing, coronary heart disease, Yes – (N = NR) BIV pacing, DM, type unspecified, No – (N = NR) BIV pacing, DM, type unspecified, Yes – (N = NR) BIV pacing, diastolic dysfunction, No – (N = NR) BIV pacing, diastolic dysfunction, Yes – (N = NR)	SF-36, general health, change - baseline – 1 y - 2 units (SD ± 35) – (adjusted for correlation coefficient = 0) SF-36, general health, change - baseline – 1 y - 2 units (SD ± 25) – (adjusted for correlation coefficient = 0.5) SF-36, general health, change - baseline – 2 y - 1 units (SD ± 33) – (adjusted for correlation coefficient = 0) SF-36, general health, change - baseline – 2 y - 1 units (SD ± 24) - (adjusted for correlation coefficient = 0.5) SF-36, general health - 1 y - 45 units (SD ± 27) SF-36, general health - 2 y - 44 units (SD ± 24) SF-36, mental health - 1 y - 76 units (SD ± 19) SF-36, mental health - 2 y - 76 units (SD ± 20) SF-36, physical functioning - 1 y - 67 units (SD ± 22) SF-36, physical functioning - 2 y - 68 units (SD ± 28) SF-36, role emotional - 1 y - 67 units (SD ± 42) SF-36, role emotional - 2 y - 68 units (SD ± 42) SF-36, role physical - 1 y - 62 units (SD ± 43) SF-36, role physical - 2 y - 64 units (SD ± 43) SF-36, social functioning - 1 y - 50 units (SD ± 6) SF-36, social functioning - 2 y - 48 units (SD ± 11) SF-36, vitality - 1 y - 65 units (SD ± 22) SF-36, vitality - 2 y - 64 units (SD ± 24) 6-min walk test - 1 y - 374 m (SD ± 106) 6-min walk test - 2 y - 363 m (SD ± 117)	

			BIV pacing, heart block – (N = NR) BIV pacing, HTN, No – (N = NR) BIV pacing, HTN, Yes – (N = NR) BIV pacing, SND – (N = NR)	ventricular pacing - 1 y–2 y - 97.9% (SD ± 11.8) **RV apical pacing, age, <70 y:** LV volume, end-systolic - 2 y - 38.8 mL LVEF - 2 y - 53.4% **RV apical pacing, age, ≥70 y:** LV volume, end-systolic - 2 y - 34.1 mL LVEF - 2 y - 53.7% **RV apical pacing, coronary heart disease, No:** LV volume, end-systolic - 2 y - 35.1 mL LVEF - 2 y - 53.4% **RV apical pacing, coronary heart disease, Yes:** LV volume, end-systolic - 2 y - 40.5 mL LVEF - 2 y - 53.7% **RV apical pacing, DM, Type Unspecified, No:** LV volume, end-systolic - 2 y - 34.5 mL LVEF - 2 y - 53.8% **RV apical pacing, DM, type unspecified, Yes:** LV volume, end-systolic - 2 y - 41.1 mL LVEF - 2 y - 53.3% **RV apical pacing, diastolic dysfunction, No:** LV volume, end-systolic - 2 y - 37 mL LVEF - 2 y - 52.1% **RV apical pacing, diastolic dysfunction, Yes:** LV volume, end-systolic - 2 y - 35.9 mL LVEF - 2 y - 54.5%	

				RV apical pacing, heart block: LV volume, end-systolic - 2 y - 39.3 mL LVEF - 2 y - 53.7% **RV apical pacing, HTN, No:** LV volume, end-systolic - 2 y - 34 mL LVEF - 2 y - 54.3% **RV apical pacing, HTN, Yes:** LV volume, end-systolic - 2 y - 37.7 mL LVEF - 2 y - 53.2% **RV apical pacing, SND:** LV volume, end-systolic - 2 y - 37.4 mL LVEF - 2 y - 53.4% **BIV pacing:** Dyssynchrony index - 1 y - 27.4 ms (SD ± 8.9) Dyssynchrony index - 2 y - 29.3 ms (SD ± 13.5) LV volume, end-systolic - 1 y - 27.6 mL (SD ± 10.2) [95% CI: 24.6–30.6] – (intent to treat) LV volume, end-systolic - 1 y - 26.5 mL (SD ± 10.4) - (N = 87) – (per protocol) LV volume, end-systolic - 2 y - 25.3 mL (SD ± 10.2) [95% CI: NR – 29.7] – (intent to treat) LV volume, end-systolic - 2 y - 25.5 mL (SD ± 10.7) - (N = 82) – (per protocol) LVEF < 45% - 2 y - 4 (4.5%) LVEF, decrease ≥5% - 2 y - 18 (20.2%) LVEF - 1 y - 63.5% (SD ± 7.1) - (N = 87) – (per protocol) LVEF - 1 y - 62.2% (SD ± 7) [95% CI: 60.5–63.7] – (intent to treat) LVEF - 2 y - 62.9% (SD ± 9) - (N = 82) – (per protocol)	

				LVEF - 2 y - 62.9% (SD ± 8.8) [95% CI: 61.1–64.7] – (intent to treat) SF-36, bodily pain - 1 y - 77 units (SD ± 26) SF-36, bodily pain - 2 y - 76 units (SD ± 29) SF-36, general health, change - baseline – 1 y - 3 units (SD ± 34) – (adjusted for correlation coefficient = 0) SF-36, general health, change - baseline – 1 y - 3 units (SD ± 24) – (adjusted for correlation coefficient = 0.5) SF-36, general health, change - baseline – 2 y - 1 units (SD ± 33) – (adjusted for correlation coefficient = 0) SF-36, general health, change - baseline – 2 y - 1 units (SD ± 24) – (adjusted for correlation coefficient = 0.5) SF-36, general health - 1 y - 51 units (SD ± 25) SF-36, general health - 2 y - 49 units (SD ± 24) SF-36, mental health - 1 y - 77 units (SD ± 20) SF-36, mental health - 2 y - 79 units (SD ± 18) SF-36, physical functioning - 1 y - 71 units (SD ± 27) SF-36, physical functioning - 2 y - 66 units (SD ± 27) SF-36, role emotional - 1 y - 71 units (SD ± 39) SF-36, role emotional - 2 y - 71 units (SD ± 38) SF-36, role physical - 1 y - 70 units (SD ± 40) SF-36, role physical - 2 y - 60 units (SD ± 43) SF-36, social functioning - 1 y - 50 units (SD ± 10) SF-36, social functioning - 2 y - 49 units (SD ± 8)	

				SF-36, vitality - 1 y - 64 units (SD ± 24) SF-36, vitality - 2 y - 66 units (SD ± 21) 6-min walk test - 1 y - 375 m (SD ± 100) 6-min walk test - 2 y - 361 m (SD ± 105) ventricular pacing - 1 y–2 y - 92.9% (SD ± 22.6) **BIV pacing, age, < 70 y – (N = NR):** LV volume, end-systolic - 2 y - 27.7 mL LVEF - 2 y - 61.2% **BIV pacing, age, ≥ 70 y – (N = NR):** LV volume, end-systolic - 2 y - 23.1 mL LVEF - 2 y - 64.4% **BIV pacing, coronary heart disease, No:** LV volume, end-systolic - 2 y - 25.1 mL LVEF - 2 y - 62.5% **BIV pacing, coronary heart disease, Yes:** LV volume, end-systolic - 2 y - 26.2 mL LVEF - 2 y - 62.9% **BIV pacing, DM, type unspecified, No:** LV volume, end-systolic - 2 y - 25.4 mL LVEF - 2 y - 62.4% **BIV pacing, DM, type unspecified, Yes:** LV volume, end-systolic - 2 y - 25.1 mL LVEF - 2 y - 64.2% **BIV pacing, diastolic dysfunction, No:** LV volume, end-systolic - 2 y - 25.2 mL LVEF - 2 y - 64.2% **BIV pacing, diastolic dysfunction, Yes:** LV volume, end-systolic - 2 y - 25.4 mL LVEF - 2 y - 62% **BIV pacing, heart block:**	

				LV volume, end-systolic - 2 y - 26.5 mL LVEF - 2 y - 63.7% **BIV pacing, HTN, No:** LV volume, end-systolic - 2 y - 21.5 mL LVEF - 2 y - 63.2% **BIV pacing, HTN, Yes:** LV volume, end-systolic - 2 y - 25.3 mL LVEF - 2 y - 62.9% **BIV pacing, SND:** LV volume, end-systolic - 2 y - 23.9 mL LVEF - 2 y - 61.9% **<u>Safety endpoint</u>:** **RV apical pacing:** Hospitalization, HF - baseline – 2 y - 10 (11.36%) Mortality, all-cause - baseline – 1 y - 1 (1.14%) Mortality, all-cause - baseline – 2 y - 4 (4.55%) Mortality, all-cause - 1 y–2 y - 3 (3.41%) Mortality, procedure-related - baseline – 2 y - 0 (0%) **BIV pacing:** Hospitalization, HF - baseline – 2 y - 8 (8.99%) Mortality, all-cause - baseline – 1 y - 0 (0%) Mortality, all-cause - baseline – 2 y - 3 (3.37%) Mortality, all-cause - 1 y–2 y - 3 (3.37%) Mortality, procedure-related - baseline – 2 y - 0 (0%)	

PACE Fang F, et al. 2013 (3) 22944596	**Aim:** To assess the role of early pacing-induced systolic dyssynchrony to predict adverse LV remodeling. **Study type:** RCT **Size:** 177	**Inclusion criteria:** - Normal ejection fraction (≥45%) - Standard indications for pacing - SND and bradycardia due to advanced AV block **Exclusion criteria:** - Persistent AF - Unstable angina - Acute coronary syndrome - Undergone percutaneous coronary intervention or coronary-artery bypass surgery within the previous 3 mo - Life expectancy of <6 mo - Received a heart transplant - Pregnant - Patients who fulfilled the eligibility criteria but in whom implantation of a BIV system was unsuccessful	**Intervention:** RV apical pacing (N = 88) **Comparator:** BIV pacing (N = 89)	**1° endpoint:** **RV apical pacing:** Dyssynchrony index - 1 mo - 34 ms (SD ± 14) Dyssynchrony index - 12 mo - 37 ms (SD ± 14) **BIV pacing:** Dyssynchrony index - 1 mo - 24 ms (SD ± 12) Dyssynchrony index - 12 mo - 27 ms (SD ± 9) **Safety endpoint:** **RV apical pacing:** Mortality, all-cause - baseline – 12 mo - 1 (1.14%) **BIV pacing:** Mortality, all-cause - baseline – 12 mo - 0 (0%)	• N/A • This study had a couple limitations: most patients with SND received continuous ventricular pacing; volumetric change was assessed with 3-dimensional echocardiography, but dyssynchrony was assessed by tissue Doppler imaging; dyssynchrony was assessed at 1 month, but not at the time of implantation; and relatively small sample size. • N/A
Kronborg MB, et al. 2014 (4) 24509688	**Aim:** To compare LV function after a long-term His or para-His pacing and RV septal pacing in patients with AV block. **Study type:** Randomized crossover	**Inclusion criteria:** - Patients with high-grade AV block - QRS complex <120 ms **Exclusion criteria:** - Permanent AF - Life expectancy of <2 y - Expecting heart surgery within 2 y	**Intervention:** RV septal pacing (pooled) - (N = 38) RV septal pacing (pooled), HTN, arterial - (N = 14) RV septal pacing (pooled), HTN, none - (N = 14)	**1° endpoint:** **RV septal pacing (pooled):** HF and LVEF, reduction, significant - 12 mo duration - 3 (8.82%) - (N = 34) LV volume, end-diastolic - 12 mo duration - 95 mL (SD ± 36) - (N = 34) LV volume, end-systolic - 12 mo duration - 49 mL (SD ± 26) - (N = 34) LVEF < 50% - during RV septal pacing - 15 (53.57%) - (N = 28)	• N/A • The limitations in this study were sample size and the follow-up period was limited to 12 mo. • N/A

	Size: 38	- Implantable cardioverter-defibrillator or CRT indications - LVEF <0.40 - Recent myocardial infarction - History of AV node ablation - Pregnancy	RV septal pacing (pooled), LVEF <50% - (N = 15) RV septal pacing (pooled), LVEF >50% - (N = 13) RV septal pacing × His/Para-His pacing - (N = 19) **Comparator:** His/Para-His pacing (pooled) - (N = 38) His/Para-His pacing (pooled), HTN, arterial - (N = 14) His/Para-His pacing (pooled), HTN, none - (N = 14) His/Para-His pacing (pooled), LVEF <50% - (N = 15) His/Para-His pacing (pooled), LVEF >50% - (N = 13) His/Para-His pacing × RV septal pacing - (N = 19)	LVEF > 50% - during RV septal pacing - 13 (46.43%) - (N = 28) LVEF - 12 mo duration - 50% (SD ± 11) - (N = 34) – (intent to treat) LVEF - 12 mo duration - 48% (SD ± 10) - (N = 28) – (on-treatment) NYHA class I - 12 mo duration - 21 (61.76%) - (N = 34) NYHA class II - 12 mo duration - 6 (17.65%) - (N = 34) NYHA class III - 12 mo duration - 7 (20.59%) - (N = 34) NYHA class IV - 12 mo duration - 0 (0%) - (N = 34) NYHA class - 12 mo duration - 1.6 - (N = 34) SF-36, bodily pain - 12 mo duration - 73 units (SD ± 25) - (N = 28) SF-36, general health - 12 mo duration - 58 units (SD ± 24) - (N = 28) SF-36, mental health - 12 mo duration - 75 units (SD ± 19) - (N = 28) SF-36, physical functioning - 12 mo duration - 69 units (SD ± 30) - (N = 28) SF-36, role emotional - 12 mo duration - 69 units (SD ± 42) - (N = 28) SF-36, role physical - 12 mo duration - 59 units (SD ± 43) - (N = 28) SF-36, social functioning - 12 mo duration - 85 units (SD ± 21) - (N = 28) SF-36, vitality - 12 mo duration - 55 units (SD ± 23) - (N = 28) 6-min walk test - 12 mo duration - 558 m (SD ± 109) - (N = 25) **RV septal pacing (pooled), HTN, arterial:** LVEF - 12 mo duration - 46% (SD ± 10) **RV septal pacing (pooled), HTN, none:** LVEF - 12 mo duration - 50% (SD ± 9)	

				RV septal pacing (pooled), LVEF <50%: LVEF - 12 mo duration - 41% (SD ± 6) **RV septal pacing (pooled), LVEF >50%:** LVEF - 12 mo duration - 56% (SD ± 5) **His/Para-His pacing (pooled):** LV volume, end-diastolic - 12 mo duration - 91 mL (SD ± 31) - (N = 34) LV volume, end-systolic - 12 mo duration - 42 mL (SD ± 21) - (N = 34) LVEF < 50% - during RV septal pacing - 15 (53.57%) - (N = 28) LVEF > 50% - during RV septal pacing - 13 (46.43%) - (N = 28) LVEF - 12 mo duration - 55% (SD ± 10) - (N = 34) – (intent to treat) LVEF - 12 mo duration - 54% (SD ± 10) - (N = 28) – (on-treatment) NYHA class I - 12 mo duration - 24 (70.59%) - (N = 34) NYHA class II - 12 mo duration - 6 (17.65%) - (N = 34) NYHA class III - 12 mo duration - 4 (11.76%) - (N = 34) NYHA class IV - 12 mo duration - 0 (0%) - (N = 34) NYHA class - 12 mo duration - 1.4 - (N = 34) SF-36, bodily pain - 12 mo duration - 74 units (SD ± 26) - (N = 28) SF-36, general health - 12 mo duration - 65 units (SD ± 24) - (N = 28) SF-36, mental health - 12 mo duration - 78 units (SD ± 16) - (N = 28) SF-36, physical functioning - 12 mo duration - 74 units (SD ± 27) - (N = 28) SF-36, role emotional - 12 mo duration - 65 units (SD ± 28) - (N = 28)	

				SF-36, role physical - 12 mo duration - 58 units (SD ± 45) - (N = 28) SF-36, social functioning - 12 mo duration - 84 units (SD ± 24) - (N = 28) SF-36, vitality - 12 mo duration - 63 units (SD ± 28) - (N = 28) 6-min walk test - 12 mo duration - 560 m (SD ± 97) - (N = 25) **His/Para-His pacing (pooled), HTN, arterial:** LVEF - 12 mo duration - 54% (SD ± 11) **His/Para-His pacing (pooled), HTN, none:** LVEF - 12 mo duration - 55% (SD ± 9) **His/Para-His pacing (pooled), LVEF <50%:** LVEF - 12 mo duration - 50% (SD ± 9) **His/Para-His pacing 12mo (pooled), LVEF >50%:** LVEF - 12 mo duration - 60% (SD ± 8) **<u>Safety endpoint</u>:** **RV septal pacing (pooled):** AF, persistent - 12 mo duration - 3 (7.89%) Mortality, all-cause - 12 mo duration - 2 (5.26%) **RV septal pacing × His/Para-His pacing:** Mortality, all-cause - baseline – 12 mo - 1 (5.26%) Mortality, all-cause - baseline – 24 mo - 1 (5.26%) **His/Para-His pacing (pooled):** AF, persistent - 12 mo duration - 0 (0%) Mortality, all-cause - 12 mo duration - 1 (2.63%)	

				His/Para-His pacing × RV septal pacing: Mortality, all-cause - baseline – 12 mo - 0 (0%) Mortality, all-cause - baseline – 24 mo - 1 (5.26%)	
Occhetta E, et al. 2007 (5) 17538702	**Aim:** N/A **Study type:** Randomized crossover and non-randomized controlled trial **Size:** 68	**Inclusion criteria:** Indication for ablation of the AV node for chronic AF with high ventricular rate, not controlled by pharmacological therapy (digoxin, beta-blockers, diltiazem, in monotherapy or in association - Concomitant structural cardiopathy - Narrow spontaneous QRS complexes, even during the tachyarrhythmia phases, documented with Holter recording **Exclusion criteria:** N/A	**Intervention:** Right apical pacing 6 mo (pooled) - (N = 17) **Comparator:** Para-Hisian pacing 6 mo (pooled) - (N = 17) Para-Hisian pacing average 21 mo (pooled) - (N = 57)	**1° endpoint:** **Right apical pacing 6 mo (pooled):** LV volume, end-diastolic – 6 mo duration - 99.4 mL (SD ± 33.1) - (N = 16) LV volume, end-systolic - 6 mo duration - 50.9 mL (SD ± 23.2) - (N = 16) LVEF - 6 mo duration - 50% (SD ± 7.9) - (N = 16) Minnesota Living with HF Questionnaire - 6 mo duration - 20.6 units (SD ± 8.5) - (N = 16) NYHA class - 6 mo duration - 2.5 (SD ± 0.4) - (N = 16) 6-min walk test - 6 mo duration - 360 m (SD ± 71) - (N = 16) **Para-Hisian pacing 6 mo (pooled):** LV volume, end-diastolic - 6 mo duration - 93.2 mL (SD ± 26.6) - (N = 16) LV volume, end-systolic - 6 mo duration - 44.7 mL (SD ± 17.6) - (N = 16) LVEF - 6 mo duration - 53.4% (SD ± 7.9) - (N = 16) Minnesota Living with HF Questionnaire - 6 mo duration - 16.2 units (SD ± 8.7) - (N = 16) NYHA class - 6 mo duration - 1.75 (SD ± 0.4) - (N = 16) 6-min walk test - 6 mo duration - 431 m (SD ± 73) - (N = 16) **Para-Hisian pacing average 21 mo (pooled):** LVEF – mean 21 mo - 51.1% (SD ± 9.9)	• N/A

				Minnesota Living with HF Questionnaire - mean 21 mo - 16.2 units (SD ± 8.7) NYHA class - mean 21 mo - 1.7 (SD ± 0.7) 6-min walk test - mean 21 mo - 374 m (SD ± 79.2) **Safety endpoint:** N/A	
Occhetta E, et al. 2006 (6) 16697308	**Aim:** To evaluate the feasibility, the safety, and hemodynamic improvements induced by permanent para-Hisian pacing in patients with chronic AF and narrow QRS who underwent AV node ablation. **Study type:** Randomized crossover **Size:** 18	**Inclusion criteria:** - Indication for AV node ablation for chronic AF - Fast ventricular rate not controlled pharmacologically (digoxin, beta-blocker, or diltiazem, alone or in association) - Concomitant heart disease - Narrow QRS complexes even at high ventricular rates (during 24-h Holter monitoring) **Exclusion criteria:** - Already been implanted with a pacemaker or an implantable cardioverter-defibrillator - Absence of escape rhythm after radiofrequency ablation - Poor clinical condition and not suitable for adequate clinical follow-up	**Intervention:** Right apical pacing (pooled) - (N = 18) Right apical pacing (pooled), LVEF > 52% - (N = NR) Right apical pacing (pooled), LVEF ≤52% - (N = NR) **Comparator:** Para-Hisian pacing (pooled) - (N = 18) Para-Hisian pacing (pooled), LVEF > 52% - (N = NR) Para-Hisian pacing (pooled), LVEF ≤52% - (N = NR)	**1° endpoint:** **Right apical pacing (pooled):** Dyssynchrony, mechanical delay, Interventricular - 6 mo duration - 34 ms (SD ± 18) - (N = 16) LV volume, end-diastolic - 6 mo duration - 99.4 mL (SD ± 33.1) - (N = 16) LV volume, end-systolic - 6 mo duration - 50.9 mL (SD ± 23.2) - (N = 16) LVEF - 6 mo duration - 50% (SD ± 7.9) - (N = 16) Minnesota Living with HF Questionnaire - 6 mo duration - 20.6 units (SD ± 8.5) - (N = 16) NYHA class - 6 mo duration - 2.5 (SD ± 0.4) - (N = 16) 6-min walk test - 6 mo duration - 360 m (SD ± 71) - (N = 16) **Right apical pacing (pooled), LVEF >52%:** LV volume, change - 6 mo duration - 35 mL (SD ± 58) **Right apical pacing (pooled), LVEF ≤52%:** LV volume, change - 6 mo duration - -5 mL (SD ± 21) **Para-Hisian pacing (pooled):** Dyssynchrony, mechanical delay, Interventricular - 6 mo duration - 47 ms (SD ± 19) - (N = 16)	• N/A

				LV volume, end-diastolic - 6 mo duration - 93.2 mL (SD ± 26.6) - (N = 16) LV volume, end-systolic - 6 mo duration - 44.7 mL (SD ± 17.6) - (N = 16) LVEF - 6 mo duration - 53.4% (SD ± 7.9) - (N = 16) Minnesota Living with HF Questionnaire - 6 mo duration - 16.2 units (SD ± 8.7) - (N = 16) NYHA class - 6 mo duration - 1.75 (SD ± 0.4) - (N = 16) 6-min walk test - 6 mo duration - 431 m (SD ± 73) - (N = 16) **Para-Hisian pacing 6 mo (pooled), LVEF >52%:** LV volume, change - 6 mo duration - 26 mL (SD ± 66) **Para-Hisian pacing 6 mo (pooled), LVEF ≤52%:** LV volume, change - 6 mo duration - -13 mL (SD ± 20) **Safety endpoint:** N/A	
PREVENT-HF Stockburger M, et al. 2011 (7) 21613427	**Aim:** To explore the differences in LV remodeling during RV apical vs. BIV pacing in patients with AV block. **Study type:** RCT **Size:** 108	**Inclusion criteria:** - Age ≥18 y - Met Class I or IIa implantation criteria for pacemaker stimulation according to the guidelines of the American College of Cardiology/American Heart Association - The need for future ventricular pacing had to be >80% (estimated by the enrolling	**Intervention:** RV apical pacing - (N = 58) **Comparator:** BIV pacing - (N = 50)	**1° endpoint:** **RV apical pacing:** LV volume, end-diastolic - 12 mo - 104.4 mL (SD ± 36.39) - (N = 40) - (according to assigned treatment) LV volume, end-diastolic - 12 mo - 104.33 mL (SD ± 35.1) - (N = 46) - (on-treatment) LV volume, end-diastolic - discharge - 101.5 mL (SD ± 41.7) - (N = 40) - (according to assigned treatment) LV volume, end-diastolic - discharge - 100.93 mL (SD ± 40.34) - (N = 46) - (on-treatment)	• N/A • The limitations in this study were sample size and the follow-up period was limited to 12 mo. • N/A

		investigator) prior to inclusion **<u>Exclusion criteria</u>:** - Advanced HF (NYHA class III or IV) prior to the development of the pacing indication - Myocardial infarction or cardiac surgery during the preceding 3 mo - Future need for revascularization within 3 mo - Hypertrophic cardiomyopathy - Constrictive pericarditis - Aortic stenosis - Poor echocardiographic window - Previously implanted pacemaker or defibrillator - Pregnancy - Life expectancy <1 year - No signed informed consent		LV volume, end-systolic - 12 mo - 44.69 mL (SD ± 25.29) - (N = 40) - (according to assigned treatment) LV volume, end-systolic - 12 mo - 45.9 mL (SD ± 27.64) - (N = 46) - (on-treatment) LV volume, end-systolic - discharge - 44.65 mL (SD ± 25.13) - (N = 40) - (according to assigned treatment) LV volume, end-systolic - discharge - 42.72 mL (SD ± 24.34) - (N = 46) - (on-treatment) LVEF - 12 mo - 56.24% (SD ± 14.5) - (N = 40) - (according to assigned treatment) LVEF - 12 mo - 57.25% (SD ± 13.87) - (N = 46) - (on-treatment) LVEF - discharge - 55.58% (SD ± 14.03) - (N = 40) - (according to assigned treatment) LVEF - discharge - 57.65% (SD ± 14.35) - (N = 46) - (on-treatment) **BIV pacing:** LV volume, end-diastolic - 12 mo - 99.43 mL (SD ± 30.21) - (N = 35) - (according to assigned treatment) LV volume, end-diastolic - 12 mo - 98.52 mL (SD ± 30.95) - (N = 29) - (on-treatment) LV volume, end-diastolic - discharge - 97.2 mL (SD ± 49.43) - (N = 35) - (according to assigned treatment) LV volume, end-diastolic - discharge - 97.21 mL (SD ± 52.69) - (N = 29) - (on-treatment) LV volume, end-systolic - 12 mo - 42.2 mL (SD ± 23.65) - (N = 35) - (according to assigned treatment) LV volume, end-systolic - 12 mo - 39.76 mL (SD ± 17.95) - (N = 29) - (on-treatment) LV volume, end-systolic - discharge - 41.26 mL (SD ± 27.83) - (N = 35) - (according to assigned treatment)	

				LV volume, end-systolic - discharge - 43.62 mL (SD ± 29.57) - (N = 29) - (on-treatment) LVEF - 12 mo - 60.08% (SD ± 9.61) - (N = 35) - (according to assigned treatment) LVEF - 12 mo - 59.27% (SD ± 10.15) - (N = 29) - (on-treatment) LVEF - discharge - 59.65% (SD ± 12.25) - (N = 35) - (according to assigned treatment) LVEF - discharge - 57.2% (SD ± 11.67) - (N = 29) - (on-treatment) **Safety endpoint:** **RV apical pacing:** Adverse events, procedure-related - baseline – 12 mo - 1 (2.17%) - (N = 46) Adverse events, Related to LV Leads - baseline – 12 mo - 1 (2.17%) - (N = 46) Adverse events, Related to RV Leads - baseline – 12 mo - 1 (2.17%) - (N = 46) Arrhythmia - baseline – 12 mo - 1 (2.17%) - (N = 46) Mortality, all-cause - baseline – 12 mo - 1 (2.17%) - (N = 46) **BIV pacing:** Adverse events, procedure-related - baseline – 12 mo - 1 (3.45%) - (N = 29) Adverse events, related to atrial leads - baseline – 12 mo - 1 (3.45%) - (N = 29) Adverse events, Related to RV Leads - baseline – 12 mo - 0 (0%) - (N = 29) Mortality, all-cause - baseline – 12 mo - 0 (0%) - (N = 29)	
PACE Yu CM, et al. 2009 (8) 19915220	**Aim:** To examine whether BIV pacing is superior to RV apical pacing in preventing deterioration of LV systolic function and	**Inclusion criteria:** - Normal ejection fraction (≥45%) - Standard indications for pacing	**Intervention:** RV apical pacing - (N = 88) RV apical pacing, age, < 70 y - (N = NR)	**1° endpoint:** **RV apical pacing:** LV volume, end-diastolic - 12 mo - 76.7 mL (SD ± 22.5) - (N = 86) LV volume, end-systolic - 12 mo - 35.7 mL (SD ± 16.3) - (N = 86)	● N/A ● The limitations to this study were the small sample size and the study was not powered to detect significant differences in clinical events.

	cardiac remodeling in patients with bradycardia and a normal ejection fraction. **Study type:** RCT **Size:** 177	- SND and bradycardia due to advanced AV block **Exclusion criteria:** - Persistent AF - Unstable angina - Acute coronary syndrome - Undergone percutaneous coronary intervention or coronary-artery bypass surgery within the previous 3 mo - Life expectancy of <6 mo - Received a heart transplant - Pregnant - Patients who fulfilled the eligibility criteria but in whom implantation of a BIV system was unsuccessful	RV apical pacing, age, ≥ 70 y - (N = NR) RV apical pacing, coronary heart disease, No - (N = NR) RV apical pacing, coronary heart disease, Yes - (N = NR) RV apical pacing, DM, No - (N = NR) RV apical pacing, DM, Yes - (N = NR) RV apical pacing, heart block, advanced AV block - (N = NR) RV apical pacing, HTN, No - (N = NR) RV apical pacing, HTN, Yes - (N = NR) RV apical pacing, SND - (N = NR) **Comparator:** BIV pacing - (N = 89) BIV pacing, age, < 70 y - (N = NR) BIV pacing, age, ≥ 70 y - (N = NR)	LV volume, end-systolic, change - baseline – 12 mo - 7.1 mL - (N = 86) LV volume, end-systolic, % change - baseline – 12 mo - 26% LVEF - 12 mo - 54.8% (SD ± 9.1) - (N = 86) LVEF, change - baseline – 12 mo - -6.7% - (N = 86) LVEF < 45% - 12 mo - 8 (9%) SF-36, bodily pain - 12 mo - 72 units (SD ± 26) - (N = 86) SF-36, general health - 12 mo - 45 units (SD ± 28) - (N = 86) SF-36, general health, change - baseline – 12 mo - 3 units (SD ± 36) – (adjusted for correlation coefficient = 0) SF-36, general health, change - baseline – 12 mo - 3 units (SD ± 26) – (adjusted for correlation coefficient = 0.5) SF-36, mental health - 12 mo - 77 units (SD ± 18) - (N = 86) SF-36, physical functioning - 12 mo - 71 units (SD ± 23) - (N = 86) SF-36, role emotional - 12 mo - 67 units (SD ± 42) - (N = 86) SF-36, role physical - 12 mo - 61 units (SD ± 43) - (N = 86) SF-36, social functioning - 12 mo - 49 units (SD ± 6) - (N = 86) SF-36, vitality - 12 mo - 66 units (SD ± 21) - (N = 86) 6-min walk test - 12 mo - 374 m (SD ± 112) - (N = 86) **RV apical pacing, age, <70 y:** LV volume, end-systolic - 12 mo - 37.4 mL LVEF - 12 mo - 54.8% **RV apical pacing, age, ≥ 70 y:** LV volume, end-systolic - 12 mo - 33.8 mL LVEF - 12 mo - 54.8%	● N/A

			BIV pacing, coronary heart disease, No - (N = NR) BIV pacing, coronary heart disease, Yes - (N = NR) BIV pacing, DM, No - (N = NR) BIV pacing, DM, Yes - (N = NR) BIV pacing, heart block, advanced AV block - (N = NR) BIV pacing, HTN, No - (N = NR) BIV pacing, HTN, Yes - (N = NR) BIV pacing, SND - (N = NR)	**RV apical pacing, coronary heath disease, No:** LV volume, end-systolic - 12 mo - 34 mL LVEF - 12 mo - 55.4% **RV apical pacing, coronary heath disease, Yes:** LV volume, end-systolic - 12 mo - 40.1 mL LVEF - 12 mo - 53.1 **RV apical pacing, DM, No:** LV volume, end-systolic - 12 mo - 33.5 mL LVEF - 12 mo - 56.3% **RV apical pacing, DM, Yes:** LV volume, end-systolic - 12 mo - 40.8 mL LVEF - 12 mo - 51.2% **RV apical pacing, heart block, advanced AV block:** LV volume, end-systolic - 12 mo - 38.6 mL LVEF - 12 mo - 54.5% **RV apical pacing, HTN, No:** LV volume, end-systolic - 12 mo - 32.2 mL LVEF - 12 mo - 56.1% **RV apical pacing, HTN, Yes:** LV volume, end-systolic - 12 mo - 37.7 mL LVEF - 12 mo - 54% **RV apical pacing, SND:** LV volume, end-systolic - 12 mo - 31.2 mL LVEF - 12 mo - 55.3% **BIV pacing:** LV volume, end-diastolic - 12 mo - 71.5 mL (SD ± 17.8) - (N = 87)	

				LV volume, end-systolic - 12 mo - 27.6 mL (SD ± 10.4) - (N = 87) LVEF - 12 mo - 62.2% (SD ± 7) - (N = 87) LVEF < 45% - 12 mo - 1 (1%) SF-36, bodily pain - 12 mo - 77 units (SD ± 26) - (N = 87) SF-36, general health - 12 mo - 53 units (SD ± 24) - (N = 87) SF-36, general health, change - baseline – 12 mo - 3 units (SD ± 34) – (adjusted for correlation coefficient = 0) SF-36, general health, change - baseline – 12 mo - 3 units (SD ± 24) – (adjusted for correlation coefficient = 0.5) SF-36, mental health - 12 mo - 78 units (SD ± 20) - (N = 87) SF-36, physical functioning - 12 mo - 70 units (SD ± 28) - (N = 87) SF-36, role emotional - 12 mo - 73 units (SD ± 38) - (N = 87) SF-36, role physical - 12 mo - 72 units (SD ± 40) - (N = 87) SF-36, social functioning - 12 mo - 50 units (SD ± 9) - (N = 87) SF-36, vitality - 12 mo - 64 units (SD ± 24) - (N = 87) 6-min walk test - 12 mo - 380 m (SD ± 110) - (N = 87) **BIV pacing, age, <70 y:** LV volume, end-systolic - 12 mo - 31.8 mL LVEF - 12 mo - 60.4% **BIV pacing, age, ≥70 y:** LV volume, end-systolic - 12 mo - 23.4 mL LVEF - 12 mo - 63.9% **BIV pacing, coronary heart disease, No:** LV volume, end-systolic - 12 mo - 27 mL LVEF - 12 mo - 62.6%	

				BIV pacing, coronary heart disease, Yes: LV volume, end-systolic - 12 mo - 29.6 mL LVEF - 12 mo - 60.6% **BIV pacing, DM, No:** LV volume, end-systolic - 12 mo - 26.6 mL LVEF - 12 mo - 62.5% **BIV pacing, DM, Yes:** LV volume, end-systolic - 12 mo - 30.6 mL LVEF - 12 mo - 61% **BIV pacing, heart block, advanced AV block:** LV volume, end-systolic - 12 mo - 28 mL LVEF - 12 mo - 62.6% **BIV pacing, HTN, No:** LV volume, end-systolic - 12 mo - 29.4 mL LVEF - 12 mo - 62.3% **BIV pacing, HTN, Yes:** LV volume, end-systolic - 12 mo - 26.8 mL LVEF - 12 mo - 62.1% **BIV pacing, SND:** LV volume, end-systolic - 12 mo - 27.1 mL LVEF - 12 mo - 61.7% **<u>Safety endpoint</u>:** **RV apical pacing:** Hospitalization, acute coronary syndrome - baseline – 12 mo - 3 (3%) Hospitalization, congestive HF - baseline – 12 mo - 6 (7%) Hospitalization, stroke - baseline – 12 mo - 2 (2%)	

				Mortality, periprocedural - baseline – 12 mo - 0 (0%) Mortality, septicemia and mortality, urinary tract infection - baseline – 12 mo - 1 (1.14%) **BIV pacing:** Hospitalization, congestive HF - baseline – 12 mo - 5 (6%) Mortality, periprocedural - baseline – 12 mo - 0 (0%)	
PACE Yu CM, et al. 2014 (9) 25179592	**Aim:** To report the long-term results of the PACE trial. **Study type:** RCT **Size:** 177	**Inclusion criteria:** - Normal ejection fraction (≥45%) - Standard indications for pacing - SND and bradycardia due to advanced AV block **Exclusion criteria:** - Persistent AF - Unstable angina - Acute coronary syndrome - Undergone percutaneous coronary intervention or coronary-artery bypass surgery within the previous 3 mo - Life expectancy of <6 mo - Received a heart transplant - Pregnant - Patients who fulfilled the eligibility criteria but in whom implantation of a BIV system was unsuccessful	**Intervention:** RV pacing - (N = 88) RV pacing, age, < 70 y – (N = NR) RV pacing, age, ≥ 70 y – (N = NR) RV pacing, DM, No – (N = NR) RV pacing, DM, Yes – (N = NR) RV pacing, diastolic dysfunction, No – (N = NR) RV pacing, diastolic dysfunction, Yes – (N = NR) RV pacing, sex, female – (N = NR) RV pacing, sex, male – (N = NR)	**1° endpoint:** **RV pacing - (N = 88)** LV volume, end-diastolic – 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 81 mL (SD ± 30.4) - (N = 74) LV volume, end-diastolic - 1 y - 76.2 mL (SD ± 21.3) - (N = 86) LV volume, end-diastolic - 2 y - 73.6 mL (SD ± 26.2) - (N = 81) LV volume, end-systolic, change - baseline – 1 y - 5.1 mL - (N = 75) LV volume, end-systolic, change - 1 y–2 y - 2 mL - (N = 75) LV volume, end-systolic, change - 2 y – end of follow-up - 3.5 mL - (N = 75) LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 39.2 mL (SD ± 21.2) [95% CI: 36.9–41.2] - (N = 74) LV volume, end-systolic - 1 y - 33.8 mL (SD ± 15.2) [95% CI: 31.6–35.99] - (N = 86) LV volume, end-systolic - 2 y - 35.7 mL (SD ± 19.6) [95% CI: 33.3–37.8] - (N = 81) LVEF < 45% - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 12 (16.2%) - (N = 74) LVEF, change - baseline – 1 y - -5.5% - (N = 75) LVEF, change - 1 y – 2 y - -2.3% - (N = 75) LVEF, change - 2 y – end of follow-up - -1.5% - (N = 75)	• N/A • This study had a relatively small sample size to detect a difference in the clinical event rate. In this study, those with SND required a high percentage of ventricular pacing while approximately 30% of patients with bradycardia required ventricular pacing >40% of the time. This study did not explore whether the benefits of BIV pacing outweighs the risks of complications nor the effect of LV lead position on LV remodeling and LVEF. • N/A

			RV pacing, heart block – (N = NR) RV pacing, HTN, No – (N = NR) RV pacing, HTN, Yes – (N = NR) RV pacing, SND - (N = 27) – (N = NR) **<u>Comparator</u>:** BIV pacing - (N = 89) BIV pacing, age, < 70 y – (N = NR) BIV pacing, age, ≥ 70 y – (N = NR) BIV pacing, DM, No – (N = NR) BIV pacing, DM, Yes – (N = NR) BIV pacing, diastolic dysfunction, No – (N = NR) BIV pacing, diastolic dysfunction, Yes – (N = NR) BIV pacing, sex, female – (N = NR)	LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 53.2% (SD ± 8.2) [95% CI: 51.3–55] - (N = 74) LVEF - 1 y - 56.3% (SD ± 9.2) [95% CI: 54.8–59] - (N = 86) LVEF - 2 y - 54.7% (SD ± 8.9) [95% CI: 52.6–56.6] - (N = 81) SF-36, bodily pain - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 72 units (SD ± 30) - (N = 74) SF-36, bodily pain - 1 y - 71 units (SD ± 26) - (N = 74) SF-36, bodily pain - 2 y - 72 units (SD ± 27) - (N = 74) SF-36, general health - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 50 units (SD ± 22) - (N = 74) SF-36, general health - 1 y - 44 units (SD ± 28) - (N = 74) SF-36, general health - 2 y - 45 units (SD ± 25) - (N = 74) SF-36, mental health - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 79 units (SD ± 17) - (N = 74) SF-36, mental health - 1 y - 76 units (SD ± 20) - (N = 74) SF-36, mental health - 2 y - 75 units (SD ± 20) - (N = 74) SF-36, physical functioning - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 67 units (SD ± 26) - (N = 74) SF-36, physical functioning - 1 y - 71 units (SD ± 22) - (N = 74) SF-36, physical functioning - 2 y - 69 units (SD ± 27) - (N = 74) SF-36, role emotional - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 65 units (SD ± 46) - (N = 74) SF-36, role emotional - 1 y - 64 units (SD ± 43) - (N = 74)	

			BIV pacing, sex, male – (N = NR) BIV pacing, heart block – (N = NR) BIV pacing, HTN, No – (N = NR) BIV pacing, HTN, Yes – (N = NR) BIV pacing, SND - (N = 32)	SF-36, role emotional - 2 y - 67 units (SD ± 42) - (N = 74) SF-36, role physical - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 69 units (SD ± 44) - (N = 74) SF-36, role physical - 1 y - 62 units (SD ± 43) - (N = 74) SF-36, role physical - 2 y - 63 units (SD ± 44) - (N = 74) SF-36, social functioning - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 52 units (SD ± 18) - (N = 74) SF-36, social functioning - 1 y - 50 units (SD ± 6) - (N = 74) SF-36, social functioning - 2 y - 48 units (SD ± 11) - (N = 74) SF-36, vitality - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 63 units (SD ± 20) - (N = 74) SF-36, vitality - 1 y - 66 units (SD ± 22) - (N = 74) SF-36, vitality - 2 y - 64 units (SD ± 23) - (N = 74) 6-min walk test - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 354 m (SD ± 80) - (N = 74) 6-min walk test - 1 y - 367 m (SD ± 108) - (N = 74) 6-min walk test - 2 y - 359 m (SD ± 118) - (N = 74) **RV pacing, age, <70 y – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 41.8 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 52.9% **RV pacing, age, ≥70 y – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 36.7 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 53.4%	

				RV pacing, DM, No – (N = NR) LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 36 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 54.2% **RV pacing, DM, Yes – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 47.8 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 50.5% **RV pacing, diastolic dysfunction, No – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 39.8 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 53% **RV pacing, diastolic dysfunction, Yes – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 38.8 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 53.3% **RV pacing, sex, female – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 33.4 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 55.5% **RV pacing, sex, male – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 43.6 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 51.6% **RV pacing, heart block – (N = NR)**	

				LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 42.2 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 53% **RV pacing, HTN, No – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 35 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 53.8% **RV pacing, HTN, Yes – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 41.7 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 52.8% **RV pacing, SND - (N = 27) – (N = NR)** LV volume, end-systolic - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 34 mL LVEF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 53.3% **BIV pacing - (N = 89)** LV volume, end-diastolic – 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 71.2 mL (SD ± 18.6) - (N = 72) LV volume, end-diastolic - 1 y - 71 mL (SD ± 16.5) - (N = 87) LV volume, end-diastolic - 2 y - 70.8 mL (SD ± 15.2) - (N = 82) LV volume, end-systolic, change - baseline – 1 y - -1.7 mL - (N = 74) LV volume, end-systolic, change - 1 y – 2 y - -0.6 mL - (N = 74) LV volume, end-systolic, change - 2 y – end of follow-up - -0.2 mL - (N = 74) LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 26.1 mL (SD ± 10.6) [95% CI: 21.2 – 30.9] - (N = 72)	

				LV volume, end-systolic - 1 y - 26.5 mL (SD ± 9.8) [95% CI: 22.95 – 29.98] - (N = 87) LV volume, end-systolic - 2 y - 25.9 mL (SD ± 8.8) [95% CI: 21.5 – 30.2] - (N = 82) LVEF < 45% - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 2 (2.8%) - (N = 72) LVEF, change - baseline – 1 y - 0.9% - (N = 74) LVEF, change - 1 y – 2 y - 0.6% - (N = 74) LVEF, change - 2 y – end of follow-up - 0.1% - (N = 74) LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 63.9% (SD ± 6.7) [95% CI: 62.3 – 65.4] - (N = 72) LVEF - 1 y - 63.3% (SD ± 7.1) [95% CI: 61.7 – 64.9] - (N = 87) LVEF - 2 y - 63.9% (SD ± 6.3) [95% CI: 62.4 – 65.3] - (N = 82) SF-36, bodily pain - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 74 units (SD ± 29) - (N = 72) SF-36, bodily pain - 1 y - 77 units (SD ± 26) - (N = 72) SF-36, bodily pain - 2 y - 75 units (SD ± 29) - (N = 72) SF-36, general health - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 53 units (SD ± 33) - (N = 72) SF-36, general health - 1 y - 53 units (SD ± 24) - (N = 72) SF-36, general health - 2 y - 51 units (SD ± 26) - (N = 72) SF-36, mental health - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 78 units (SD ± 17) - (N = 72) SF-36, mental health - 1 y - 80 units (SD ± 17) - (N = 72) SF-36, mental health - 2 y - 80 units (SD ± 16) - (N = 72)	

				SF-36, physical functioning - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 67 units (SD ± 27) - (N = 72) SF-36, physical functioning - 1 y - 74 units (SD ± 24) - (N = 72) SF-36, physical functioning - 2 y - 70 units (SD ± 27) - (N = 72) SF-36, role emotional - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 67 units (SD ± 43) - (N = 72) SF-36, role emotional - 1 y - 72 units (SD ± 40) - (N = 72) SF-36, role emotional - 2 y - 71 units (SD ± 35) - (N = 72) SF-36, role physical - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 57 units (SD ± 44) - (N = 72) SF-36, role physical - 1 y - 72 units (SD ± 40) - (N = 74) SF-36, role physical - 2 y - 65 units (SD ± 41) - (N = 72) SF-36, social functioning - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 49 units (SD ± 13) - (N = 72) SF-36, social functioning - 1 y - 50 units (SD ± 10) - (N = 72) SF-36, social functioning - 2 y - 49 units (SD ± 8) - (N = 72) SF-36, vitality - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 63 units (SD ± 23) - (N = 72) SF-36, vitality - 1 y - 66 units (SD ± 25) - (N = 74) SF-36, vitality - 2 y - 70 units (SD ± 19) - (N = 72) 6-min walk test - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 356 m (SD ± 97) - (N = 72) 6-min walk test - 1 y - 385 m (SD ± 107) - (N = 72) 6-min walk test - 2 y - 374 m (SD ± 100) - (N = 72)	

				BIV pacing, age, < 70 y – (N = NR) LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 28.9 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 63.5% **BIV pacing, age, ≥ 70 y – (N = NR)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 23 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 64.3% **BIV pacing, DM, No – (N = NR)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 25.6 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 63.7% **BIV pacing, DM, Yes – (N = NR)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 27.5 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 64.3% **BIV pacing, diastolic dysfunction, No – (N = NR)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 25.9 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 64.8% **BIV pacing, diastolic dysfunction, Yes – (N = NR)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 26.3 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 63.3% **BIV pacing, sex, female – (N = NR)**	

				LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 23.3 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 64.3% **BIV pacing, sex, male – (N = NR)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 28 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 63.5% **BIV pacing, heart block – (N = NR)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 26.1 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 62.2% **BIV pacing, HTN, No – (N = NR)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 26.4 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 64.2% **BIV pacing, HTN, Yes – (N = NR)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 26 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 63.7% **BIV pacing, SND - (N = 32)** LV volume, end-systolic - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 26.1 mL LVEF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 65.2% **<u>Safety endpoint</u>:** **RV pacing - (N = 88)** Hospitalization, congestive HF - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 21 (23.9%)	

				Mortality, all-cause - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 11 (14.67%) - (N = 75) Mortality, cardiovascular-related - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 6 (8%) - (N = 75) Mortality, device-related - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 0 (0%) - (N = 75) Mortality, procedure-related - 4.3 y (SD ± 1.2) [total: 2.7–6.7 y] - 0 (0%) - (N = 75) **BIV pacing - (N = 89)** Hospitalization, congestive HF - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 13 (14.6%) Mortality, all-cause - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 12 (16.22%) - (N = 74) Mortality, cardiovascular-related - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 4 (5.41%) - (N = 74) Mortality, device-related - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 0 (0%) - (N = 74) Mortality, procedure-related - 5.3 y (SD ± 1.5) [total: 2.5–7.8 y] - 0 (0%) - (N = 74)	

Data Supplement 6. Nonrandomized Trials, Observational Studies, and/or Registries

Study Acronym; Author; Year Published' PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Sharma PS, et al. 2015 (10) 25446158	**Study type:** Retrospective observational **Size:** 173	**Inclusion criteria:** Patients who received an implantable pacemaker for the prevention or treatment of bradycardia between January 2011 and October 2011 **Exclusion criteria:** Patients undergoing device implantation for CRT, AV node ablation, pulse generator changes, and lead revision	**1° endpoint:** **RV pacing - (N = 98):** AF - baseline – 2 y - 3 (3%) Hospitalization, congestive HF - baseline – 2 y - 9 (9.2%) Infection, device - baseline – 2 y - 1 (1.02%) Mortality, all-cause - baseline – 2 y - 14 (14%) Pericardial effusion - baseline – 2 y - 0 (0%) Pneumothorax - baseline – 2 y - 1 (1.02%) Ventricular lead revision - baseline – 2 y - 2 (2.04%) Ventricular lead revision, High pacing Threshold - baseline – 2 y - 0 (0%) Ventricular lead revision, lead dislodgement - baseline – 2 y - 2 (2.04%) Ventricular lead revision, loss of capture - baseline – 2 y - 0 (0%) **RV pacing, ventricular pacing, > 40% - (N = 60):** AF - baseline – 2 y - 2 (3.3%) Hospitalization, congestive HF - baseline – 2 y - 9 (15%) Mortality, all-cause - baseline – 2 y - 11 (18%) **His-bundle pacing - (N = 75):** AF - baseline – 2 y - 2 (3%) Hospitalization, congestive HF - baseline – 2 y - 2 (3%) Infection, Device - baseline – 2 y - 0 (0%)	• Permanent his-bundle pacing without a mapping catheter or a backup RV lead was successfully achieved in 80% of patients. • Clinical outcomes were better in the his-bundle pacing group than in the RV pacing group.

			Mortality, all-cause - baseline – 2 y - 9 (12%) Pericardial effusion - baseline – 2 y - 0 (0%) Pneumothorax - baseline – 2 y - 0 (0%) Ventricular lead revision - baseline – 2 y - 3 (4%) Ventricular lead revision, High pacing Threshold - baseline – 2 y - 1 (1.33%) Ventricular lead revision, lead dislodgement - baseline – 2 y - 0 (0%) Ventricular lead revision, loss of capture - baseline – 2 y - 2 (2.67%) **His-bundle pacing, ventricular pacing, >40% - (N = 47):** AF - baseline – 2 y - 1 (2%) Hospitalization, congestive HF - baseline – 2 y - 1 (2%) Mortality, all-cause - baseline – 2 y - 6 (13%) **Results:** N/A	
Zanon F, et al. 2008 (11) 18407969	**Study type:** Non-randomized controlled trial **Size:** 12	**Inclusion criteria:** - Patients with standard indication for permanent pacemaker - Patients with preserved His bundle conduction **Exclusion criteria:** - History of coronary artery disease, including angina pectoris, myocardial infarction, or previous revascularization procedure	**1° endpoint:** **RV apical pacing - (N = 12)** Adverse events, complications or adverse events, complaints - 3 mo duration - 0 (0%) Dyssynchrony index, mechanical - 3 mo duration - 22.02 ms (SD ± 8.44) LV volume, end-diastolic, per body surface Area - 3 mo duration - 67.3 mL/m² (SD ± 23.2) LV volume, end-systolic, per body surface Area - 3 mo duration - 27.3 mL/m² (SD ± 18.9) LVEF - 3 mo duration - 61 % (SD ± 10) NYHA class - 3 mo duration - 2 (SD ± 0.6)	• Compared to RV apical pacing, direct His bundle pacing provided superior distribution of myocardial blood flow and reduction of mitral regurgitation and LV dyssynchrony.

		- History of vascular arterial disease including stroke - Diabetes - Previous episodes of HF - Uncontrolled HTN - Valve disease - Coronary or vascular event occurrence during the study	**Direct His Bundle pacing - (N = 12)** Adverse events, complications or adverse events, complaints - 3 mo duration - 0 (0%) Dyssynchrony index, mechanical - 3 mo duration - 13.75 ms (SD ± 4.28) LV volume, end-diastolic, per body surface Area - 3 mo duration - 68.2 mL/m² (SD ± 15.6) LV volume, end-systolic, per body surface Area - 3 mo duration - 25.5 mL/m² (SD ± 12.9) LVEF - 3 mo duration - 63 % (SD ± 12) NYHA class - 3 mo duration - 2 (SD ± 0.7) **Results:** N/A	
Doshi RN, et al. 2005 (12) 16302897	**Study type:** Prospective, patient-blinded, randomized, multicenter clinical trial. **Size:** 184	**Inclusion criteria:** - Chronic AF for >30 d - Requirement for AV node ablation and pacing therapy to manage medically refractory rapid ventricular rates - Symptoms limiting ambulation to <450 m with a 6-min hallway walk test - Stable medical therapy. **Exclusion criteria:** - NYHA class IV - Requirement for defibrillator therapy or cardiac surgery - Presence of a prosthetic valve because of the	**1° endpoint:** **RV apical pacing - (N = 35)** LVEF>45% Preimplant: 242.7±87.8 6 wk: 309.6±110.3 3 mo: 337.2±112.6 6 mo: 304.4±105 Improvement between preimplant and 6 mo 61.7 ± 86.0 **BIV pacing - (N = 54)** LVEF>45% Preimplant: 287.3±108.9 0.45 6 wk: 353.8±106.7 0.23 3 mo: 353.8±106.7 0.49 6 mo: 354.8±127.7 0.05 Improvement between preimplant and 6 mo 67.5±81.9 **Results:** N/A	• N/A

		potential for confounding echocardiographic measurements.		

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