

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of permanent His-bundle pacemaker implantation for treating heart failure

Heart failure is when your heart is not able to pump blood around your body well enough. In this procedure, a wire is inserted through a vein into the heart and attached to its specialised electrical conduction pathway (His bundle). This differs from traditional pacemaker placement, when the wire is attached to heart muscle. The wire is then connected to a pacemaker placed under the skin of the chest, which delivers electrical pulses. The aim is to help the heart pump blood more efficiently.

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Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2020.

Procedure name

- Permanent His-bundle pacemaker implantation for treating heart failure

Professional societies

- The British Cardiovascular Intervention Society
- The British Cardiovascular Society
- The Royal College of Surgeons (London)
- The Royal College of Surgeons (Edinburgh)
- Royal College of Physicians (London)
- Royal College of Physicians of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow

Description of the procedure

Indications and current treatment

Heart failure is a complex clinical syndrome of symptoms and signs that happen when the heart is not working well enough. It leads to reduced blood flow to body tissues and can cause oedema in the lungs (causing breathlessness) and swelling of the legs. Other symptoms include reduced ability to exercise, fatigue and malaise. Heart failure can be caused by structural or functional abnormalities of the heart.

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Treatments for heart failure are described in [NICE's guideline on diagnosing and managing chronic heart failure in adults](#). Initial treatments include drugs to improve heart function. However, as heart failure becomes more severe, it can become unresponsive to drugs alone. Implantation of specific devices to sense and stimulate the heart chambers might then be recommended as an adjunctive treatment. This is known as cardiac resynchronisation therapy (CRT) which may also include inserting a defibrillator (CRT-D) or pacing (CRT-P).

Other treatments include cardiac rehabilitation, coronary revascularisation (when there is coronary artery narrowing), a heart transplant and palliative care. Permanent His-bundle pacemaker implantation may be another option for people with advanced heart failure.

What the procedure involves

The aim of implanting a permanent pacemaker at the His bundle is to produce normal physiological ventricular activation via the His-Purkinje system.

The procedure is usually done under local anaesthesia, with or without sedation, in a cardiac catheterisation laboratory. A pacemaker generator is implanted under the skin near the collarbone, usually on the left side of the chest (although the right side is possible). A standard or dedicated pacing lead is inserted through the subclavian, cephalic or axillary vein into the heart. This is done under fluoroscopic guidance and continuous electrocardiogram monitoring or mapping, and using a standard or specially designed His-delivery sheath. It is then positioned and secured to the His bundle, where it can directly stimulate the His-bundle fibres. An electrogram from the tip of the lead is used to ensure a His signal and that the pacing lead is correctly placed. The pacemaker generator is securely connected to the His-bundle lead. The generator can be adjusted transcutaneously to ensure optimum His-bundle pacing.

Efficacy summary

Implantation success rate

A systematic review and meta-analysis of 11 observational studies (including 494 patients) assessing permanent His-bundle pacing (HBP) for heart failure (either cardiac resynchronisation therapy [CRT] or atrioventricular node [AVN] ablation for cardiomyopathy with atrial fibrillation [AF]) reported that the overall HBP implant success rate was 82% (407/494).¹

In a case series of 39 patients with cardiomyopathy, reduced left ventricular ejection fraction (LVEF), right bundle branch block (RBBB) and heart failure who had permanent HBP as a primary or rescue strategy for CRT, HBP was

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successful in 95% (37/39). Narrowing of RBBB was seen in 78% (29/37) of patients, and fusion between HBP and right ventricle (RV) pacing was seen in 22% (8/37) of patients.³

In a case-control study of 86 patients with persistent AF, heart failure and an implantable cardioverter defibrillator (ICD) indication, the success rate of HBP plus AVN ablation was 95% (52/55). AVN ablation failed in 1 patient, who had an ICD and medication. The other 2 patients had biventricular (BiV) pacing because of high HBP thresholds.⁴

Electrocardiographic parameters

QRS duration

In the systematic review and meta-analysis of 11 studies, a pooled analysis of 4 studies showed that, for patients with AF and AVN ablation (n=159), there was no statistically significant difference between baseline and follow-up QRS duration (102 ms compared with 115 ms; mean difference [MD] -13.38, 95% confidence interval [CI] -29.86 to 3.10, p=0.11, I²=93%). For patients with CRT, meta-analysis of 7 of the studies (n=221) showed that the paced QRS duration statistically significantly decreased after HBP (from 165 ms at baseline to 116 ms; MD 48.96, 95% CI 38.43 to 59.49, p<0.00001; I²=87%).¹

In a randomised pilot trial of 40 patients with CRT indications, intention-to-treat analysis showed that patients who had HBP-CRT (n=16) had statistically significantly shorter QRS duration (electrical resynchronisation) compared with those who had BiV-CRT (n=24; 125 ms compared with 164 ms, p<0.001). QRS width narrowed statistically significantly from baseline with HBP-CRT (from 174 ms to 125 ms, p<0.001), whereas the change was not statistically significant with BiV-CRT (from 165 ms to 164 ms, p=0.82).²

In the case series of 39 patients, overall, QRS duration decreased statistically significantly from 158 ms at baseline to 127 ms (p=0.0001) during a mean follow up of 15 months. Patients with underlying ventricular pacing at baseline also had a statistically significant narrowing of paced QRS duration (from 198 ms to 141 ms, p=0.0002).³

In a case series of 14 patients with permanent AF, heart failure, BBB, QRS complex width greater than 130 ms, and reduced LVEF who had ICD or CRT-D systems with HBP, the mean duration of QRS statistically significantly shortened from 159 ms to 128 ms (p=0.016) in 93% of patients.⁵

Pacing threshold

In the systematic review and meta-analysis of 11 studies, pooled analysis of 9 of the studies (n=328) showed that, compared with baseline threshold, capture threshold increased at follow up (1.35 V compared with 1.67 V; MD -0.24, 95% CI -0.42 to -0.06, $p=0.001$, $I^2=39\%$). Pooled analysis of 3 of the studies (n=134) showed that bundle branch block correction thresholds also increased at follow up (2.41 V compared with 2.73 V; MD -0.33, 95% CI -0.61 to -0.05, $p=0.02$, $I^2=9\%$).¹

In the case series of 39 patients, His capture threshold increased from a baseline of 1.1 V to 1.3 V at a mean follow up of 15 months ($p=0.6$). Threshold for narrowing of BBB, increased from 1.4 V at implant to 1.6 V at 1 ms during follow up ($p=0.6$).³

Echocardiographic parameters

Left ventricular ejection fraction

In the systematic review and meta-analysis of 11 studies, pooled analysis of 10 of the studies (n=329) showed that LVEF statistically significantly improved from 37% at baseline to 48% at follow up (MD -11.17, 95% CI -15.89 to -6.45, $p<0.0001$, $I^2=88\%$).¹

In the randomised pilot trial of 40 patients, intention-to-treat analysis showed that, at a median follow up of 6.2 months, LVEF improved statistically significantly in both arms relative to baseline. Patients who had His-CRT had a median increase in LVEF from 28% to 35% ($p<0.001$). Patients who had BiV-CRT had a median increase in LVEF from 28% to 32% ($p<0.001$). Patients who had HBP-CRT had a higher echocardiographic response than BiV-CRT (80% compared with 57%, $p=0.14$) but this did not reach statistical significance.²

In the case series of 39 patients, overall LVEF increased statistically significantly from 31% at baseline to 39% at a mean follow up of 15 months ($p=0.0001$). Among patients with an LVEF of less than 35%, LVEF increased statistically significantly from 26% to 34% ($p=0.0001$).³

In the case-control study of 86 patients, compared with ICD implantation plus drug therapy, HBP plus AVN ablation statistically significantly improved LVEF (15% compared with 3%, $p<0.001$) and decreased left ventricle end-systolic volume (LVESV; 39 millilitre compared with 2 millilitre, $p<0.01$) at a median follow up of 24 months. In patients with a baseline LVEF of less than 40%, similar improvement in LVEF and LVESV was seen in both groups.⁴

In the case series of 14 patients, mean LVEF statistically significantly improved from 24% to 38% ($p=0.0015$) in 93% of patients.⁵

Left ventricular end-diastolic dimensions

In the systematic review of 11 studies, pooled analysis of 7 of the studies ($n=185$) showed that left ventricular end-diastolic dimensions (LVEDD) statistically significantly decreased from 58.2 mm at baseline to 52.8 mm at follow up (MD 5.06, 95% CI 2.72 to 7.40, $p<0.0001$, $I^2=69\%$).¹

In the case series of 39 patients, there was no statistically significant change in LVEDD from baseline during a mean follow up of 15 months (from 57 mm to 56 mm, $p=0.4$). In addition, no statistically significant differences were noted in RV internal dimensions ($p=0.4$) or pulmonary artery systolic pressures ($p=0.5$) with permanent HBP.³

In the case series of 14 patients, the mean LVEDD statistically significantly decreased from 71 mm to 59 mm ($p<0.001$) in 93% of patients.⁵

Left ventricular end-systolic dimension

In the case series of 14 patients, mean LVESD decreased from 59 mm to 47 mm ($p=0.0026$) in 93% of patients.⁵

Brain natriuretic peptide level

In the systematic review of 11 studies, pooled analysis of 3 of the studies ($n=94$) showed that brain natriuretic peptide levels decreased from 609.3 pg/ml at baseline to 216.6 pg/ml after HBP (MD 375.03, 95% CI 158.82 to 591.25, $p=0.0007$, $I^2=60\%$).¹

New York Heart Association class

In the systematic review and meta-analysis of 11 studies, pooled analysis of 8 of the studies ($n=312$) showed that New York Heart Association (NYHA) functional class statistically significantly improved from 2.8 at baseline to 1.6 at follow up (MD 1.15, 95% CI 0.82 to 1.49, $p<0.0001$, $I^2=92\%$).¹

In the randomised pilot trial of 40 patients, median NYHA class at baseline was comparable between the 2 groups (functional class 3 compared 2.75, $p=0.66$). Improvement by more than 1 functional class was similar between the 2 groups at 6 months (53% HBP-CRT compared with 39% BiV-CRT, $p=0.41$) and at 12 months (25% HBP-CRT compared with 31% BiV-CRT, $p=0.89$).²

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In the case series of 39 patients, there was a statistically significant improvement in overall NYHA functional class from 2.8 at baseline to 2.0 ($p<0.0001$) during a mean follow up of 15 months.³

In the case-control study of 86 patients, NYHA functional class improved in both groups (from a baseline 2.73 to 1.42 with HBP and AVN, and from 2.57 to 1.73 with ICD and drug therapy, $p<0.01$).⁴

In the case series of 14 patients, the mean NYHA class statistically significantly improved from 3.07 to 1.65 ($p<0.001$) in 93% of patients.⁵

Medication use

In the case-control study of 86 patients, the number of patients taking medications statistically significantly decreased after permanent HBP plus AVN ablation (group 1) compared with ICD plus medical therapy (group 2). This was true for both amiodarone (25% compared with 0% respectively, $p<0.001$) and digoxin (46% compared with 25% respectively, $p=0.024$).⁴

Quality of life

In the randomised pilot trial of 40 patients, quality of life was assessed using Kansas City cardiomyopathy questionnaire (KCCQ). The median total KCCQ score at baseline was 101 points (78 to 112 points). Rise in KCCQ was noted both for patients who had His-CRT (median 116 points) and those who had BiV-CRT (median 110 points), and was not statistically significantly different between the 2 groups ($p=0.22$) at a median follow up of 6 months.²

Safety summary

Mortality

In the systematic review of 11 studies, mortality rate was 9% (31/342) at a mean follow up of 23.7 months. Further details were not reported in the study.¹

In the case series of 39 patients, 2 patients died as a result of non-cardiovascular causes (malignancy in 1 patient, and stroke, infection and sepsis in another patient).³

In the case-control study of 86 patients, 10% (6/52) of patients who had HBP plus AVN (in group 1) died. In 1 patient, it was a sudden cardiac death, 2 died from multiple organ failure, 2 died from cerebral haemorrhage and 1 died from respiratory failure. In all, 26% (8/31) of patients who had ICD plus drug therapy

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(in group 2) died. Two deaths were because of uraemia and multiple organ failure; and 6 were from unknown causes.⁴

In the case series of 14 patients, 1 patient died because of heart failure aggravation after 3 months follow up.⁵

Heart failure-related hospitalisations

Heart failure-related hospitalisations were reported in 6% (12/205) of patients at a mean follow up of 23.7 months in the systematic review of 11 studies.¹

In the case series of 39 patients, 2 patients were admitted with heart failure-related hospitalisations.³

In the case-control study of 86 patients, 15 patients had 1 or more episodes of heart failure-related hospitalisation during follow up (9 patients in group 2 – ICD plus drug therapy, and 6 patients in group 1 – HBP plus AVN). The incidence of adverse events (heart failure hospitalisation or death) was statistically significantly higher in group 2 compared with group 1 ($p=0.01$) at a median follow up of 30.5 months.⁴

New-onset atrial fibrillation

In the case series of 39 patients, 2 patients developed new-onset AF.³

Increase in capture threshold

In the case series of 39 patients, increase in capture threshold (defined as a more than 1 V increase) was noted in 8% (3/39) of patients, 1 of which resulted in loss of bundle branch block recruitment at maximum programmable outputs.³

Infection

In the case series of 39 patients, 1 patient developed pocket infection at 2 months. The device was explanted and successfully re-implanted with HBP after 3 months.³

Repeated procedures

In the case series of 39 patients, repeat procedures (replacement of the His lead with an LV lead) were needed in 1 patient.³

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts listed the following anecdotal adverse events: acute injury to the His bundle resulting in AV block (usually transient) or persistent RBBB. They considered that the following were theoretical adverse events: challenges with extraction of His-bundle leads, clinically significant radiation exposure because of longer screening times and higher pacing thresholds resulting in premature battery longevity.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to permanent His-bundle pacemaker implantation for treating heart failure. The following databases were searched, covering the period from their start to 01.07.2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the [literature search strategy](#)). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Heart failure.
Intervention/test	Permanent His-bundle pacemaker implantation for treatment
Outcome	Articles were retrieved if the abstract contained information relevant to the safety or efficacy
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base

List of studies included in the IP overview

This IP overview is based on 673 patients from 1 systematic review¹, 1 randomised controlled trial², 1 case-control study⁴ and 2 case series^{3,5}.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the [appendix](#).

Table 2 Summary of key efficacy and safety findings on permanent His-bundle pacemaker implantation for treating heart failure

Study 1 Qian Z (2018)

Details

Study type	Systematic review and meta-analysis
Country	China
Study search period	Databases searched: PubMed, Embase until August 2018.
Study population and number	n=11 observational studies (494 patients) on permanent His-bundle pacing [HBP] in patients with heart failure. Indications: 1. cardiomyopathy with atrial fibrillation [AF] having atrioventricular [AV] node ablation [4 studies with 73 patients]. 2. cardiac resynchronisation therapy [CRT] indications (7 studies- de novo implantation [in 4 studies], CRT non-response [in 1 study], patients with pacing induced cardiomyopathy [in 1 study] and failed left ventricle lead placement or CRT failure [in 1 study])
Age and sex	Average age 72 years; 63% were male
Study selection criteria	Inclusion criteria: studies with selective or non-selective His-bundle pacing in patients with heart failure and LV dyssynchrony were included. Exclusion criteria: studies with non-heart failure patients, with duplicate data and non-original articles were excluded.
Technique	Permanent HBP with 69 cm Select Secure™ 3830 (Medtronic) pacing lead.
Follow up	Range from 12 to 37 months
Conflict of interest/source of funding	None; study supported by science and technical department of Jiangsu province.

Analysis

Follow-up issues: follow-up period varied across studies.

Study design issues: search was limited to English language studies. Study selection and data extraction were done by 2 reviewers. Review manager was used to do meta-analysis using random effects model. Sensitivity analyses was done to identify heterogeneity. Publication bias was also evaluated. A p value <0.05 was considered statistically significant in the analyses.

Study population issues: 33% of patients had ischemic aetiology. Several clinical situations were assessed.

Other issues: authors state that there was no uniformity in pacing pulse width and measuring QRS durations with selective and non-selective HBP.

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Key efficacy and safety findings

Efficacy and Safety							
Number of patients analysed: 494 Implantation success The overall HBP implant success rate was 82.4% (407/494). QRS duration Pooled analysis of 4 studies shows that for patients with AF and AVN ablation (n=159), there was no statistically significant difference between baseline and follow-up QRS duration (102.3±11.4 ms versus 115.3±12.0 ms; MD -13.38 [95% CI -29.86 to 3.10], p=0.11, I²=93%). For patients with CRT, pooled analysis of 7 studies (with 221 patients) shows that the paced QRS duration markedly decreased after HBP (from 165.4±8.7 ms at baseline to 116.9±15.8 ms; MD 48.96 [95% CI 38.43 to 59.49], p< 0.00001; I²=87%). Pacing threshold Pooled analysis of 9 studies (with 328 patients) shows that compared to baseline threshold, capture threshold (1.35±0.55 V versus 1.67±0.87 V, MD -0.24 [95% CI -0.42 to -0.06], p=0.001, I²=39%) increased at follow up. Pooled analysis of 3 studies (with 134 patients) shows that bundle branch block correction thresholds (2.41±0.60V versus 2.73±0.84 V, MD -0.33 [95% CI -0.61 to -0.05], p=0.02, I²=9%) increased at follow up. Clinical outcomes NYHA functional class Pooled analysis of 8 studies with 312 patients shows that NYHA functional class statistically significantly improved from 2.8±0.4 at baseline to 1.6±0.4 at follow up (MD 1.15, 95% CI 0.82 to 1.49, p<0.0001, I²=92%). LV function Pooled analysis of 10 studies with 329 patients for CRT and heart failure with AF having AVN ablation shows that LVEF improved from 36.9±3.3% at baseline to 48.1±3.0% at follow up (MD -11.17, 95% CI -15.89 to -6.45, p<0.0001, I²=88%). Left ventricular end-diastolic dimension (LVEDD) Pooled analysis of 7 studies with 185 patients shows that LVEDD decreased from baseline 58.2 ± 1.7mm to 52.8±1.7mm at follow up (MD 5.06, 95% CI 2.72 to 7.40, p<0.0001, I²=69%). Brain Natriuretic Peptide (BNP) level Pooled analysis of 3 studies with 94 patients shows that BNP level decreased from 609.3±67.1 pg/ml at baseline to 216.6±99.2 pg/ml after HBP (MD 375.03, 95% CI 158.82 to 591.25, p=0.0007, I²=60%). Safety <table border="1"> <thead> <tr> <th>Adverse events at mean follow up 23.7 months</th><th>% (n)</th></tr> </thead> <tbody> <tr> <td>Heart failure-related hospitalisations</td><td>5.9 (12/205)</td></tr> <tr> <td>Death</td><td>9.1 (31/342)</td></tr> </tbody> </table> Abbreviations used: AF, atrial fibrillation; AVN, atrioventricular node; CI, confidence interval; CRT, cardiac resynchronisation therapy; HBP, His bundle pacing; LVEF, left ventricular ejection fraction; MD, mean difference; NYHA, New York Heart Association.		Adverse events at mean follow up 23.7 months	% (n)	Heart failure-related hospitalisations	5.9 (12/205)	Death	9.1 (31/342)
Adverse events at mean follow up 23.7 months	% (n)						
Heart failure-related hospitalisations	5.9 (12/205)						
Death	9.1 (31/342)						

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Study 2 Upadhyay GA (2019)

Details

Study type	Randomised controlled trial (His Sync pilot trial-NCT0270045)
Country	USA (7 centres)
Recruitment period	2016 to 2018
Study population and number	n=40 patients meeting standard indications for cardiac resynchronisation therapy [CRT] (e.g., NYHA I2 to 4 patients with QRS .120 ms) 16 His bundle pacing (HBP)-CRT versus 24 biventricular (BiV) -CRT
Age and sex	mean age was 64.6± 12.6 years; 62% female.
Patient selection criteria	<u>Inclusion criteria:</u> patients older than 18 years with heart failure meeting ACCF /AHA /HRS class 1 or class 2 guideline indications for CRT. <u>Exclusion criteria:</u> existing CRT device, pregnancy, or inability to provide consent owing to either medical or psychiatric comorbidity.
Technique	HBP-CRT done using 69 cm Medtronic Select Secure Model 3830 lead as described above in 16 patients. 11 done as per protocol; 5 patients crossed over from BiV-CRT to HBP-CRT (inability to cannulate the coronary sinus [CS] in 2, suboptimal cannulation of the CS in 2 and vascular occlusion in 1). BiV-CRT or traditional CS lead had CS cannulation and left ventricular lead placement as per routine implant procedure. (n=24) 14 were inserted as per protocol, 10 crossed over from HBP-CRT to BiV-CRT (failure to achieve QRS narrowing <130ms in 3, no correction due to IVCD in 5, inability to map His bundle in 2). Crossovers were based on prespecified criteria.
Follow up	Average 12.2 months
Conflict of interest/source of funding	No funding for study but authors have been consultants/speakers/ received research grants from companies (Abbott, Biotronik, Boston Scientific, and Medtronic). 2 universities received institutional support from companies.

Analysis

Follow-up issues: 1 BiV-CRT patient withdrew after randomisation; patients were followed up at regular intervals and 1 patient was lost to follow up.

Study design issues: prospective small study, underpowered to detect differences between groups; patients were blinded to treatment allocation; Intention to treat analysis was done. High rates of crossover were noted in both arms of the study (48% [10/21] to HBP-CRT and 26% [5/19] to BiV-CRT) and were not statistically significantly different (p=0.20). Inclusion of intraventricular conduction delay accounted for most crossovers in patients allocated to HBP-CRT.

Study population issues: study included a broad population based on current guidelines for traditional BiV-CRT. 65% had a history of coronary artery disease, 33% had a history of paroxysmal or persistent atrial fibrillation, and 48% had a history of chronic kidney disease. All patients were on medical therapy. No statistically significant differences were noted in baseline demographic characteristics in both arms of the study.

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Key efficacy and safety findings

Efficacy and safety

Number of patients analysed: 40

Procedure time

The mean procedural time was 2.9±1.3 hours for HBP-CRT and 2.4 ± 1.2 hours for BiV-CRT (P =0 .25). Crossover patients had statistically significantly longer procedural times than those that were implanted per protocol (3.3 ± 1.6 hours vs 2.3 ± 0.9 hours, p=0 .04).

Electrocardiographic and echocardiographic outcomes (intention to analysis)

	HBP-CRT (n=16)			BiV-CRT (n=24)			P value between groups
	Baseline	Follow up	P value	Baseline	Follow up	P value	
QRS duration, msec	174±18	125±22	<0.001	165±17	164±25	0.82	<0.001
LVEF % median 6 months	28	34.6	<0.001	27.7	32	<0.001	
Median change in LVEF %		+7.2			+5.9		0.17
Rate of echocardiographic response %		80			57		0.14
LVESV %		-22±24			-19±14		0.62

NYHA functional class

	HBP-CRT	BiV-CRT	P value
NYHA class, baseline, median	3	2.75	0.66
Improvement >1 functional class at 6 months, % of patients	53%	39%	0.41
12 months, % of patients	25%	31%	0.89

Quality of life (assessed using KCCQ score)

The median total KCCQ score at baseline was 101 points (78 to 112 points). Rise in KCCQ was noted both for patients who had His-CRT (median 116 points [18 to 25 points]) and those who had BiV-CRT (median 110 points [12 to 16 points]) and was not statistically significantly different between the 2 groups (p=0.22) at median 6 months follow up.

Adverse events

	HBP-CRT	BiV-CRT	Total
Periprocedural complications			
Transient ischemic attack with aphasia (resolved in follow up)	1 (with severe PVD after crossover and prolonged procedure)		
Atrial lead micro-dislodgement associated with pericardial effusion	2 (1 had cross over)		
Hematoma (needed evacuation, no sequelae)		1	

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12 months			
All-cause mortality	2*		
Cardiovascular hospitalisations [^]			6
Ventricular tachycardia/fibrillation needing device therapy	2*	0	
* Two patients needed device therapy, 1 resulted in pulseless electrical activity and death (BiV-CRT crossed over to HBP-CRT). One other death occurred outside the hospital; device interrogation data were unavailable (HBP-CRT). [^]3 due to heart failure hospitalisation, 2 periprocedural, and 1 for atrial fibrillation needing cardioversion. Abbreviations used: BiV-CRT, biventricular cardiac resynchronisation therapy; HBP-CRT, His bundle pacing cardiac resynchronisation therapy; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; NYHA, New York heart association; NS, not significant.			

Study 3 Sharma PS (2018)

Details

Study type	Case series
Country	USA, UK, Hong Kong (5 centres)
Recruitment period	Not reported
Study population and number	n=39 patients with right bundle branch block (RBBB), and heart failure <u>Indications for HBP:</u> atrioventricular [AV] block with RBBB (n=7), right ventricle paced rhythm with RBBB (n=8), RBBB alone (n=24) <u>HBP strategy:</u> primary rescue [instead of left ventricle- LV lead] (n=34), rescue strategy [after a failed LV lead] (n=5)
Age and sex	Mean age 72±10 years, male 85% (33/39).
Patient selection criteria	Patients with reduced LV ejection fraction <50%, RBBB, QRS duration ≥120 ms, and New York Heart Association class 2 to 4 heart failure were included.
Technique	Permanent HBP was done using the 69 cm Select Secure™ 3830 (Medtronic) pacing lead. The HB region was mapped until pacing resulted in HB capture with or without correction of RBBB. The lead was then fixed at the optimal position. The HB capture thresholds and bundle branch correction thresholds were assessed and recorded at a pulse width of 1.0 ms. If an acceptable HB capture could not be achieved after 5 attempts of lead positioning or a fluoroscopy duration of 20 minutes, it was considered a failure. When an HB electrogram was not recordable during mapping, pace-mapping was done in a unipolar fashion. If primary HBP was unsuccessful in patients with indication for CRT, an LV lead was implanted in the coronary venous branches. 73% (26/39) patients had CRT device [ICD/pacemaker]; 27% (10/39) without indication for CRT (LVEF>35%) had a dual chamber or single pacemaker/ICD.
Follow up	average 15±23 months (median, 9 months; range, 0 to 53 months).
Conflict of interest/source of funding	4 authors served as speakers and consultants for Medtronic and other companies and received research support.

Analysis

Follow-up issues: Patients were followed in clinic at 2 weeks, 3 months, and 1 year and by remote monitoring every 3 months. Three patients were lost to follow up.

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Study design issues: small retrospective cohort study with several indications for permanent HBP and study not adequately powered to assess the impact of HBP. Surgeons had previous experience in HBP implantation. Echocardiograms were analysed by cardiologists blinded to the type of device implanted. P value less than 0.05 was considered statistically significant.

Study population issues: 72% patients had NYHA class 3 or 4. 46% patients had ischemic cardiomyopathy.

Key efficacy and safety findings

Efficacy				Safety	
Number of patients analysed: 39				Complications and adverse events	
Procedure outcomes					
	% (n)				% (n)
HBP implantation success rate	95 (37/39)			Increase in capture threshold* (1 of which resulted in loss of BBB recruitment at maximum programmable outputs)	9 (3)
Primary strategy success	94 (32/34)			Device pocket infection (at 2 months, device explanted and reimplanted after 3 months)	3 (1)
Rescue strategy success	100 (5/5)			Replacement of His lead with LV lead	3 (1)
Narrowing of RBBB	78 (29/37)			New-onset atrial fibrillation^^	6 (2)
Without narrowing of RBBB but fusion between HBP and RV pacing	22 (8/37)			Heart failure hospitalisation^	6 (2)
His capture and bundle branch correction thresholds				Repeat procedure (replacement of His lead with LV lead)	3 (1)
	Baseline mean±SD	Post HBP mean±SD	P value	Death (malignancy-1, stroke/infection/sepsis-1)	6 (2)
His capture threshold, V at 1 ms,	1.1±0.6	1.3±0.9	0.6	*defined as a ≥1 V increase in capture threshold from implant.	
RBBB recruitment threshold	1.4±0.7	1.6±2.4	0.6		
Echocardiographic outcomes				^defined as a hospital admission or an urgent care visit for intensive treatment for heart failure with intravenous diuretics or inotropic medications.	
	Baseline mean±SD	Post HBP mean±SD	P value		
Overall QRS duration, ms, (n=37)	158±24	127±17	0.0001	^^ defined as at least 6 minutes of continuous AF as documented by the device log.	
RV paced QRS duration, (n=8)	198±28	141±16	0.0002		
Clinical outcomes					
	Baseline mean±SD	Post HBP mean±SD	P value		
LVEF, %,	31±10	39±13	0.0001		
Baseline LVEF ≤35%, n=25	26±7	34±12	0.0001		
Baseline LVEF 35% to 50%, n=12	41±3	49±7	0.009		
LVEDD, mm,	57±7	56±10	0.4		
PASP, mmHg,	42±12	39±12	0.5		
RVID, mm,	43±4	42±6	0.4		
NYHA class,	2.8±0.6	2.0±0.7	0.0001		
Abbreviations used: AF, atrial fibrillation; AVN, atrioventricular node; CRT, cardiac resynchronisation therapy; HBP, His bundle pacing; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RBBB, right bundle branch block; RVID, right ventricular internal diameter; SD, standard deviation.					

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Study 4 Wang (2019)

Details

Study type	Case control study
Country	China
Recruitment period	2010 to 2018
Study population and number	n=86 patients with persistent atrial fibrillation [AF] and heart failure [HF] who had ICD implantation and atrioventricular node [AVN] node ablation
Age and sex	Mean age 67.75±9.98 years, 74% were male.
Patient selection criteria	<u>Inclusion criteria:</u> 18 years old, with ICD implantation indications as per the 2008 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines; narrow QRS duration (≤ 130 ms, except right bundle-branch block); symptomatic HF and long-lasting persistent or permanent AF even though their heart rate was controlled (ventricular rate ≤ 100 beats/min [bpm] over the 24-hour recording period) with pharmacologic treatment. <u>Exclusion criteria:</u> pregnant women, severe mitral or aortic valve regurgitation, congenital heart disease needing cardiac surgery, or severe chronic obstructive pulmonary disease.
Technique	Group 1: 55 patients had His-Purkinje conduction system pacing (HPSP) with ICD combined with AVN ablation. 69 cm Select Secure™ 3830 (Medtronic) pacing lead was used. AVN ablation was done at the time of HBP lead implantation (in 44). An ablation catheter was inserted through femoral vein to AV junction and ablation done at least 8 mm proximal to the His pacing lead tip until complete heart block was achieved. LBBP was done in 8 patients with inadequate HBP parameters (His capture threshold was high >2 V at 0.5 ms or if there was a rise in His capture threshold of >1 V following AVN ablation) and was achieved by screwing the lead deeply into the interventricular septum (positioned <1 cm distal to the HBP) site. Back-up LV lead was implanted in 31 patients for biventricular pacing if there was a threshold rise on His lead. In 8 patients atrial lead was inserted to establish sinus rhythm. Group 2: 31 patients had ICD with optimal drug therapy
Follow up	Median 30.5 months
Conflict of interest/source of funding	None; study was funded by the Key Research and Development Program of Zhejiang and the Major Project of the Science and Technology of Wenzhou.

Analysis

Follow-up issues: medium term follow up; follow up was done at standard time points (1,3, 6 and 12 months).

Study design issues: single-centre, retrospective, case-control study; treatments were allocated according to patient choice. Study protocol was slightly changed and back up lead was not inserted in half of the study patients. Some study patients chose right ventricular pacing as back up pacing instead of biventricular pacing. ICD was used as primary or secondary prevention and settings varied according to patient's characteristics. A p value less than 0.005 was considered statistically significant.

Study population issues: most baseline characteristics were similar in the 2 groups. However, group 1 had a higher percentage of patients with a secondary prevention indication for ICD

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implantation (51.6% versus 19.2%, respectively); and higher baseline LV ejection fraction (LVEF) ($42.77 \pm 15.97\%$ versus $35.09 \pm 11.65\%$, $p < 0.001$) compared with group 2. Incidence of ischemic cardiomyopathy was higher in group 2.

Other issues:

Key efficacy and safety findings

Efficacy and safety

Number of patients analysed: 86

Procedure outcomes

	HPSP +AVN ablation (group 1) % (n=55)	ICD (group 2) % (n=31)
Successful implantation	94.5 (52/55) ^^	100*
Failure	5.5 (3/55) ^	

*4 had AVN ablation +HBP due to inappropriate shock or refractory heart failure.

^ 2 with high HBP pacing threshold had BiV pacing and 1 had ICD and medication.

^^ 39 had HBP with CRT defibrillator and 13 had dual chamber ICD. HBP was achieved in 44 and LBP in 8.

Medication use

The number of patients taking medications decreased after permanent HPSP with AVN ablation in group 1 compared to group 2 (amiodarone 25.0% versus 0%, p<0.001; and digoxin 46.2% versus 25.0%, p=0.024). There was a statistically significantly greater reduction in medication use in group 1 compared with group 2 (p<0.001).

Echocardiographic parameters

	Group 2 (ICD implant) (n=31)				Group 1 (HBP+AVN ablation) (n=52)			
	n	Baseline	Follow up	P valu e	n	Baseline	Follow up	P value
LVEF %	26/31	39.64±14.57	43.01±14.30	0.097	49/52	34.8±11.23	49.44±14.90	<0.001
LVEF < 40%	19/9	31.68±5.40	36.62±10.39	0.063	38/40	29.78±5.87	46.22±14.68	<0.001
Mean LVESV , ml	26/31	134.23±66.71	132.23±86.24	0.869	49/52	122.69±65.18	83.68±62.53	<0.001
LVESV <40%	19/9	164.08±50.57	161.22±83.59	0.863	38/40	137.68±61.29	95.79±65.95	<0.001

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NYHA functional class

NYHA functional class improved in both groups from a baseline 2.57 ± 0.68 to 1.73 ± 0.74 in HBP and AVN ablation group and 2.73 ± 0.59 to 1.42 ± 0.53 in ICD implant group ($p < 0.01$).

Adverse events

	Group 2 (ICD implant) % (n=31)	Group 1 (HBP+AVN ablation) % (n=52)
Mortality	26 (8/31) ^	10 (6/52) ^^ ($p=0.01$)
Heart failure-related hospitalisation (>1 episode)	29 (9/31)	11 (6/52) ($p=0.01$)
Inappropriate shocks (episodes)*	15.6% (4/31) 11 episodes	0 ($p < 0.01$)

^2 died due to uraemia and multiple organ failure; and unknown in other 6 cases.

^^sudden cardiac death in 1, multiple organ failure in 2, cerebral haemorrhage in 2, and respiratory failure in 5.

* AF with a rapid ventricular rate is the most common cause; 3 of 4 patients had 10 inappropriate shock episodes caused by AF, and abnormal sensing led to 1 inappropriate shock episode in the remaining patient.

Abbreviations used: AVN, atrioventricular node; HPSP, His Purkinje conduction system pacing; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association.

Study 5 Boczar K (2019)

Details

Study type	Case series
Country	Poland (one centre)
Recruitment period	Not reported
Study population and number	n=14 patients with permanent with atrial fibrillation, heart failure, bundle branch block, with QRS complex with >130ms, and reduced LVEF.
Age and sex	Mean age 67 years; 78% (11/14) male
Patient selection criteria	Inclusion criteria: permanent atrial fibrillation with optimal medical treatment, no atrioventricular node ablation, heart failure NYHA class 3 to 4, bundle branch block and QRS complex width >130 ms or QRS <130 ms with high percentage of pacing, LVEF < 35% or 40% referred for ICD or secondary prevention of sudden cardiac death, implantation of ICD/ CRT-D +HBP and consent for ICD/CRT-D + HBP implantation.
Technique	Primary implantation of CRT-D systems with His bundle pacing (HBP) done in 10 patients. ICD + HBP in one patient Upgrade from ICD to ICD+ HBP done in 2 patients Upgrade from CRT-D to CRT-D+ HBP in one patient. Selective HBP and optimised medical therapy given for all.
Follow up	Mean follow up 14.4 months
Conflict of interest/source of funding	none

Analysis

Follow-up issues: complete follow up.

Study design issues: small sample, patients were followed up through telemonitoring every 3 months.

Study population issues: 64% (9/14) of patients had non-ischaemic cardiomyopathy. NYHA functional class 3 was present in 13 patients, and one had class 4. LBBB was present in 10 patients, and RBBB was present in 4 patients.

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Key efficacy and safety findings

Efficacy				Safety									
Number of patients analysed: 14 All procedures were successful. Clinical and echocardiogram results (n=13)				<table><tr><th>Adverse event</th><th>n</th></tr><tr><td>Death due to heart failure aggravation after 3 months</td><td>1</td></tr><tr><td>Lead dislodgement</td><td>0</td></tr><tr><td>Loss of HBP</td><td>0</td></tr></table>		Adverse event	n	Death due to heart failure aggravation after 3 months	1	Lead dislodgement	0	Loss of HBP	0
Adverse event	n												
Death due to heart failure aggravation after 3 months	1												
Lead dislodgement	0												
Loss of HBP	0												
	Baseline	Follow up	P value										
Mean QRS, ms	159.2±28.6	128±12	0.016										
Mean LVEF, %	24.36±10.7	38±10	0.0015										
LVEDD, mm	71±8	59±4	<0.001										
LVESD, mm	59±11	47±9	0.0026										
MR	2.4±0.8	2.0±0.4	0.134										
NYHA class	3.07±0.33	1.65±0.69	<0.001										
Mean% of HBP		97											
There were no ventricular tachycardia/fibrillation or high voltage therapies.													
Abbreviations used: LEVF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NYHA class, New York Heart Association classification.													

Validity and generalisability of the studies

- Evidence on use of permanent HBP in patients with existing heart failure in a range of settings, such as after AV nodal ablation for atrial fibrillation, narrow QRS complex and associated with prolonged PR interval, narrowing or reversing a bundle branch block for cardiac resynchronisation was assessed in this report.
- Evidence on permanent HBP for treating heart failure is mainly from few small observational studies with limited long-term follow-up data.
- There is only 1 pilot randomised controlled trial comparing permanent His-bundle pacing CRT with biventricular CRT. In some observational studies included in the systematic review, HBP was assessed as a primary strategy for CRT or as a rescue strategy when biventricular pacing failed.

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- Evidence on use of permanent HBP for patients with uncomplicated bradycardia was excluded from this report.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Cardiac contractility modulation device implantation for heart failure (2019). NICE Interventional Procedures Guidance IPG 655 (2019). Available from <https://www.nice.org.uk/guidance/IPG655>
- Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery. NICE Interventional Procedures Guidance IPG 177 (2006). Available from <https://www.nice.org.uk/guidance/IPG177>

Technology appraisals

- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. NICE technology appraisal guidance 314 (2014). Available from <http://www.nice.org.uk/guidance/TA314>
Cardiac resynchronisation therapy for treating heart failure. NICE technology appraisal guidance 120 (2007). Available from <http://www.nice.org.uk/guidance/TA120>

NICE guidelines

- Chronic heart failure in adults: diagnosis and management. NICE guideline NG106 (2018). Available from <https://www.nice.org.uk/guidance/NG106>

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- Acute heart failure: diagnosis and management. NICE clinical guideline CG187 (2014). Available from <https://www.nice.org.uk/guidance/cg187>
- Atrial fibrillation: the management of atrial fibrillation. NICE guidelines CG180 (2014). Available from <https://www.nice.org.uk/guidance/CG180>

Medical technologies guidance

- ENDURALIFE powered CRT-D devices for treating heart failure. NICE Medical Technologies Guidance 33 (2017). Available from <https://www.nice.org.uk/guidance/mtg33>

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One professional expert questionnaire for permanent His-bundle pacemaker implantation for treating heart failure was submitted and can be found on the [NICE website](#).

Patient commentators' opinions

NICE's Public Involvement Programme sent questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). One commentary from a patient who has had this procedure was discussed by the committee.

Company engagement

A structured information request was sent to one company who manufacture a potentially relevant device for use in this procedure. NICE received one completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

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Issues for consideration by IPAC

- Ongoing studies:
 - NCT02671903: The His optimised pacing evaluated for heart failure trial (HOPE-HF). AV optimisation delivered with direct His bundle pacing, in patients with heart failure, long PR without left bundle branch block: randomised multicentre clinical outcome study. This is a double-blind, crossover study. N=160. Patients will be allocated in random order to either 6 months treatment periods of (1) No pacing; (2) or AV optimised direct His-bundle pacing before crossing over to alternative arm. The primary endpoint is exercise capacity. Study completion date August 2020, location: London.
 - NCT03614169: Direct HIS-pacing as an alternative to Biventricular pacing in symptomatic heart failure patients with severely reduced LVEF and a true left bundle branch block, randomised controlled trial, n=50, primary outcome: success rate of obtaining capture of HIS-bundle with narrowing of the QRS-duration study completion date 6 months; location: Denmark, completion date November 2020.
 - NCT03719040: The physiologic pacing registry is an observational multicentre registry with 1000 patients undergoing implantation of a physiologic pacing device (Abbott pacemaker), defibrillator, or a cardiac resynchronization therapy (CRT) pacemaker (CRT-P) or CRT defibrillator (CRT-D) according to the clinical site's routine care. Primary outcomes assessed during the procedure and at 6 months are workflow, electrical performance and programming, and adverse events associated with HBP implants. Study is conducted in 20 locations (based in USA, Europe and India) and sponsored by

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Abbott medical devices. Study completion date May 2022. Status-recruiting.

References

1. Qian Z, Zou F, Wang Y et al. (2018) Permanent His bundle pacing in heart failure patients. A systematic review and meta-analysis. *PACE: pacing and clinical electrophysiology* 42(2): 139-45
2. Upadhyay GA, Vijayaraman P, Nayak HM et al. (2019) On-treatment comparison between corrective His bundle pacing and biventricular pacing for cardiac resynchronization: A secondary analysis of the His-SYNC Pilot Trial. *Heart Rhythm Society* 16(12): 1797-807
3. Sharma PS, Naperkowski A, Bauch TD et al. (2018) Permanent His bundle pacing for cardiac resynchronization therapy in patients with heart failure and right bundle branch block. *Circ Arrhythm Electrophysiol* 11: e006613.
4. Wang S, Wu S, Xu L et al. (2019) Feasibility and efficacy of His bundle pacing or left bundle pacing combined with atrioventricular node ablation in patients with persistent atrial fibrillation and implantable cardioverter-defibrillator therapy. *Journal of the American Heart Association* 8: e014253
5. Boczar K, Slawuta A, Zabek A et al. (2019) Cardiac resynchronisation therapy with His bundle pacing. *Pacing Clinical Electrophysiology* 42 (3): 374-80

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	16/12/2020	Issue 12 of 12, December 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	16/12/2020	Issue 12 of 12, December 2020
MEDLINE (Ovid)	16/12/2020	1946 to December 15, 2020
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	16/12/2020	1946 to December 15, 2020
EMBASE (Ovid)	16/12/2020	1974 to 2020 December 15
International HTA database (INAHTA)	16/12/2020	-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

- 1 heart failure/ (117919)
- 2 cardiomyopathy, dilated/ (15630)
- 3 shock, cardiogenic/ (8482)
- 4 ventricular dysfunction/ (1747)
- 5 cardiac output, low/ (5502)
- 6 ((heart* or cardiac* or myocardial or cardio* or ventric*) adj4 (failure or decompensation or insufficient* or dysfunct* or "stand still")).tw. (203015)
- 7 ((congestive or chronic) adj4 "heart failure").tw. (51099)
- 8 ((dilated or congestive) adj4 cardiomyopath\$).tw. (17274)
- 9 "cardiogenic shock".tw. (9593)
- 10 (("left ventricular" or "left ventricle") adj4 (failure or insufficien* or dysfunction*)).tw. (23726)
- 11 (lvsd or hf or chf).tw. (45679)
- 12 Bundle-Branch Block/ (8957)
- 13 ((bundle-branch* or "bundle branch*" or fascicul*) adj4 block*).tw. (8607)
- 14 (LBBB or RBBB).tw. (2040)
- 15 ((prolong* or delay*) adj4 PR adj4 interval*).tw. (637)
- 16 or/1-15 (286387)
- 17 ((His-bundle* or (bundle* adj4 His) or Hisbundle*) adj4 pacing).tw. (317)

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- 18 ("His pacing*" or his-pacing*).tw. (17)
- 19 HBP.tw. (1875)
- 20 or/17-19 (2147)
- 21 16 and 20 (204)
- 22 SureScan.tw. (12)
- 23 SelectSecure.tw. (17)
- 24 or/21-23 (233)
- 25 Animals/ not Humans/ (4679062)
- 26 24 not 25 (225)
- 27 limit 26 to english language (207)
- 28 limit 27 to ed=20191023-20200731 (26)
- 29 limit 28 to ed=20200701-20201231 (42)

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients and follow up	Direction of conclusions	Reasons for non-inclusion in table 2
Ajjola OA, Upadhyay GA, Macias C et al. (2017) Permanent His bundle pacing for cardiac resynchronization therapy: initial feasibility study in lieu of left ventricular lead. Heart Rhythm; 14:1353–61	Case series N=21 patients with an indication for CRT had HBP in the LV lead port. Follow-up 12 months	Implant success 76% (16/21), 4 patients died. Narrowing QRS duration was achieved in 76% patients with bundle branch block and improvements in clinical and echocardiographic outcomes were seen.	Study added in Qian 2018 systematic review added to table 2.
Ali N, Keene D, Arnold A et al (2018). His bundle pacing: a new frontier in the treatment of heart failure. Arrhythmia & Electrophysiology Review 7(2): 103-2.	Review	Article explores the physiology, technology and potential roles of His bundle pacing in preventing and treating heart failure such as targeting patients with PR prolongation, but a narrow QRS duration.	Review
Ali N, Shin MS, Whinnett Z et al (2020). The Emerging Role of Cardiac Conduction System Pacing as a Treatment for Heart Failure. Current Heart Failure Reports; vol. 17 (no. 5); 288-298	Review	Conduction system pacing can deliver more effective ventricular resynchronization than BVP, which has the potential to deliver greater improvements in cardiac function. It may also provide the opportunity to extend pacing therapy for heart failure to patients who do not have LBBB.	Review
Anderson RD, Prabhu M, Kalman JM et al (2019). Intra-Hisian Wenckebach Phenomenon During His Bundle Pacing: A Hazard Associated With "Precision" Medicine. JACC: Clinical Electrophysiology 5, 4, pages 530-531.	Case report of a 46-year-old woman who had implantation of an elective His-bundle (HB) pacemaker.	Wenckebach pattern, intra-Hisian position and lead tip-induced injury was noted during HIS pacing. Device check the following day showed no further atrioventricular block and the His lead threshold had reduced to 0.5 V at 1 ms.	Larger studies included in table 2.
Arnold AD, Shun-Shin MJ, Keene D et al (2018). His resynchronization versus biventricular pacing in	Case series (prospective) N=23 patients with heart failure and left bundle branch block referred for conventional CRT	left ventricular activation time was shortened by HBP in 18 patients. HBP was more effective at delivering ventricular	This an acute hemodynamic study of temporary HBP, without active

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patients with heart failure and left bundle branch block. Journal of the American College of Cardiology 72, 24: 3112-22	head-to-head, acute crossover comparison between His bundle pacing and conventional biventricular CRT.	resynchronisation than biventricular pacing: greater reduction in QRS duration ($p=0.007$), left ventricular activation time ($p=0.002$), and left ventricular dyssynchrony index ($p<0.001$). HBP also produced a greater acute hemodynamic response ($p=0.04$).	fixation, which is used in permanent HBP.
Barba-Pichardo R, Manovel Sanchez A, Fernandez-Gomez JM et al (2013). Ventricular resynchronization therapy by direct His-bundle pacing using an internal cardioverter defibrillator. Europace 15, 83–8	Case series N=16 patients with refractory heart failure with LBBB derived for CRT and internal cardioverter defibrillator insertion had permanent DHBP. Follow-up 31.3 months	Implant success 56% Basal conduction disturbances were corrected in 81% (13/16). the electrode was not successfully fixed in 4 patients. A definitive resynchronisation was achieved, with improvement in functional class and parameters of LV function in 9 patients.	Study added in Qian 2018 systematic review added to table 2.
Bhatt AG, Musat DL, Milstein N et al (2018) The efficacy of His bundle pacing: lessons learned from implementation for the first time at an experienced electrophysiology center. JACC: Clinical Electrophysiology 4, 11: 1397-406	Case series (retrospective analysis) N=427 (Permanent HBP 101 versus Non-HBP 326) Follow-up 12 months	Acute implant success rate was 75%. HBP in the presence of bundle branch block-BBB (64% vs. 85%; $p=0.05$) or complete heart block (56% vs. 83%; $p=0.03$) was statistically significantly less successful. Atrioventricular block in combination with BBB further affects outcomes. In the presence of BBB, Mobitz II AV block and complete heart block statistically significantly attenuated HBP success compared with Mobitz I atrioventricular block (62% vs. 100%; $p=0.02$).	Most patients had Mobitz I or Mobitz II block. Only 28% (24/101) had congestive heart failure.
Boczar K, Slawuta A, Zabek A et al (2018) Cardiac resynchronization therapy with His bundle pacing as a method of treatment of chronic heart failure in patients with permanent atrial fibrillation and left bundle branch block. Journal of electrocardiology. 51, 3: 405-8	Case report 71-year-old woman with dilated cardiomyopathy , NYHA functional class III and AF was implanted CRT combined with direct His-bundle pacing. The indication was a left bundle branch block with a QRS complex of 178 ms and a left ventricular EF of 15%, left ventricular end-diastolic diameter (LVEDD) of 75 mm.	After 8 months of follow-up the LVEDD was 60 mm with EF 35–40%. At 12 months, statistically significant improvement in reduction of congestive heart failure parameters noted.	Larger studies included in table 2.

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Deshmukh P, Casavant DA, Romanyshyn M et al (2000). Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. <i>Circulation</i> ; 101: 869–77	Case series N=14 patients with chronic AF and dilated myopathy and normal activation had permanent direct His bundle pacing (DHBP). Follow-up mean 23.4 months	Implant success was 85.7% (12/14). Lead complications included exit block needing reoperative adjustment and gross lead dislodgment. DHBP results in a reduction of left ventricular dimensions and improved cardiac function	Heart failure status not reported. Included in Zanon 2018 systematic review.
Deshmukh PM, Romanyshyn M. (2004). Direct His-bundle pacing: present and future. <i>Pacing Clinical Electrophysiology</i> ; 27: 862–70	Case series N=54 patients with LVEF <40%, dilated cardiomyopathy, narrow QRS complex of <120 ms, AF needing AV nodal ablation, NYHA functional class III/IV, congestive HF had DHBP (n=39) or PHP/RVOT pacing (n=15). Mean follow-up 42 months.	Implant success 72% (39/54). At 42 months, 29 patients were alive, with improved ejection fraction, functional class. DHBP is associated with a superior Treppe effect and increased cardiopulmonary reserve when compared with right ventricular pacing.	Study added in Qian 2018 systematic review added to table 2.
Grosse Meininghaus D, Lengiewicz M, Blembel K et al (2020). A case report of simultaneous His pacemaker implantation and atrioventricular junction ablation following unsuccessful treatment of atrial fibrillation. <i>European Heart Journal - Case Reports</i> ; vol. 4 (4).	Case report	Atrioventricular junction ablation simultaneously with the pacemaker implantation procedure is safe and feasible. His pacing is at least an alternative for cardiac resynchronization therapy.	Larger studies included in table 2.
Huang W, Su L, Wu S, et al. (2017) Benefits of permanent His bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. <i>J Am Heart Assoc</i> ; 6: e005309	Case series N=52 AF patients with heart failure had AVN ablation and DHBP and para hisian pacing (PHP) for symptomatic AF. Follow-up median 21.1 months.	Implant success 81 (42/52) %, death n=2. Permanent HBP post-atrioventricular node ablation statistically significantly improved echocardiographic measurements and New York Heart Association classification and reduced diuretics use for heart failure management in atrial fibrillation patients with narrow QRS who suffered from heart failure with preserved or reduced ejection fraction.	Study added in Qian 2018 systematic review added to table 2.
Huang W, Su L, Wu S, et al. (2019) Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block.	Case series N=74 patients with HF and LBBB had permanent HBP leads implanted if the LBBB correction threshold was	LBBB correction was achieved in 97.3% (72/74) and 75.7% (56/74) patients had pHBP while 18 patients did not have because of no LBBB	Study added in Qian 2018 systematic review added to table 2.

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Heart; 105 : 137-43	<3.5V/0.5 ms or 3.0 V/1.0 ms. Median follow-up 37.1 months.	correction (n=2), high LBBB correction thresholds (n=10) and fixation failure (n=6). At 3-year follow-up, LVEF increased, LVESV decreased, and NYHA Class improved. LBBB correction threshold remained stable. 3 patients died.	
Keene D, Arnold A, Shun-Shin MJ et al (2018) Rationale and design of the randomized multicentre His optimized pacing evaluated for heart failure (HOPE-HF) trial. ESC Heart Fail. 5(5): 965-76	NCT02671903 Double-blind randomised, crossover study. n=160 patients with PR prolongation (≥ 200 ms), LV impairment ($EF \leq 40\%$), and narrow QRS (≤ 140 ms) or RBBB have a cardiac device with leads in right atrium and His bundle. Some also have a defibrillator lead. Those not eligible for ICD have a backup pacing lead in an LV branch of the coronary sinus.	Patients are allocated in random order to 6 months of (i) haemodynamically optimised dual chamber His-bundle pacing and (ii) backup pacing only, using the non-His ventricular lead. The primary endpoint is change in exercise capacity assessed by peak oxygen uptake.	Study details, due to report findings 2020.
Kamenik M, Osmancik P, Stros P et al (2020). Pacing-induced right ventricular cardiomyopathy resynchronized using His bundle pacing. Cor et Vasa; vol. 62 (no. 1); 80-84	Case report	A 79-year-old male developed left ventricular dysfunction with heart failure within 6 months of right ventricular septal pacing upgraded to CRT-D, and one of the pacing leads was implanted in the His bundle area. Selective His bundle pacing led to normalization of QRS duration and a significant improvement of heart failure symptoms.	Larger studies included in table 2.
Khaira KB, Singh R, Devabhaktuni S et al (2020). Left Bundle Branch Block-Induced Cardiomyopathy in a Transplanted Heart Treated With His Bundle Pacing. JACC: Case Reports; vol. 2 (no. 12); 1932-1936	Case report	A 70-year-old male with heart transplant developed left bundle branch block followed by new-onset left ventricular systolic dysfunction underwent His bundle pacing for cardiac resynchronization therapy with complete normalization of his ejection fraction.	Larger studies included in table 2.
Lustgarten DL, Crespo EM, Arkhipova-Jenkins I et al (2015). His-bundle pacing versus biventricular pacing in cardiac resynchronization	Cross over comparative study N=29 patients with indication for CRT were implanted with right atrial	Implant success 57%. HBP was found to have an equivalent CRT response. Clinical outcomes significantly improved for	Study added in Qian 2018 systematic review added to table 2.

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therapy patients: a crossover design comparison. Heart rhythm; 12, 7: 1548-57	pacing lead, LV pacing lead, defibrillator lead and permanent HBP lead. Randomised to HBP or biventricular pacing and crossed over to other pacing modality after 6 months. Follow-up 12 months	both pacing modes from baseline. QRS narrowing was seen in 21 patients.	
Muthumala A, Vijayaraman P (2020). Clinical outcomes of His-Purkinje conduction system pacing. PACE - Pacing and Clinical Electrophysiology.	Review	This review focused on the clinical outcomes of His-Purkinje conduction system pacing (HPCSP) including mortality and morbidity of heart failure hospitalization and symptoms.	Review
Mrak M, Pavsic N, Stublar J et al (2020). Resynchronization therapy with His bundle pacing in a patient after coronary sinus reducer implantation. Journal of Cardiology Cases; vol. 22 (no. 5); 226-229.	70-year-old patient with ischemic cardiomyopathy and wide QRS complex after CSR implantation.	HBP led to acute improvement in hemodynamic parameters and exercise capacity that persisted at follow-up. Successful cardiac resynchronization with His bundle pacing (HBP) achieved after coronary sinus reducer implantation.	Larger studies included in table 2.
Moskal P, Jastrzebski M, Krakowiak A et al (2020). Rate-related block during permanent His bundle pacing. Journal of cardiovascular electrophysiology; vol. 31 (no. 1); 240-242.	Review		Review
Morina-Vazquez P, Moraleda-Salas MT, Arce-Leon A et al (2020). Electrocardiographic patterns predictive of left bundle branch block correction with His bundle pacing. PACE - Pacing and Clinical Electrophysiology; vol. 43 (no. 11); 1318-1324	Prospective study N=70 patients with LBBB and CRT had permanent HBP.	In patients with LBBB and CRT indication, the QS pattern in lead V1 predicts the correction of the QRS with HBP. In the case of rS pattern in lead V1, the ratio descending/ascending S wave component duration has a strong correlation with the LBBB correction.	Correlation between the different electrocardiographic patterns assessed.
Prakash VS, Hegde AV, Nagamalesh U.M et al (2020). His bundle pacing-is it the final frontier of physiological pacing ?-A single centre experience from the Indian sub-Continent. Indian Heart Journal;	Case series N=61 patients, with a guideline based indication for permanent pacing underwent a HBP pacemaker implantation. 6 months follow-up.	HBP is a feasible procedure in the hands of an experienced operator, with stable lead performance. It does not appear to be associated with pacing mediated left ventricular dysfunction at intermediate term follow up.	Indications not clearly specified.

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2020; vol. 72 (no. 3); 160-165.			
Sarkar R, Kaur D, Subramanian M et al. (2019) Permanent HIS bundle pacing feasibility in routine clinical practice: experience from an Indian center. Indian Heart Journal 71 360e363	Case series N=22 patients permanent with pacing for conduction disease and resynchronisation therapy had permanent HBP. Follow-up of 15 ± 6.5 months	Successful implantation in 86% (19/22) patients, achieving selective HBP in 14 patients. There was a statistically significant improvement in LVEF (49.3 ± 9.3 vs. 36.7 ± 9.2) in the LV dysfunction subgroup (n = 6). In one patient, lead revision was needed.	Heterogenous study cohort. (sick sinus syndrome in 1 patient, and AV Junction ablation needing pacing therapy for 11 patients and 7 patients in need of cardiac resynchronisation therapy (CRT).
Sharma PS et al. (2018) Permanent His bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multi-center experience, Heart Rhythm 15, 413-420	Case series N=106 patients with an indication for CRT HBP as a rescue strategy for failed BVP (group 1) or as a primary strategy for patients with AV block, or high ventricular pacing burden (group 2). Mean follow-up 14 months	Implant success 90% (95/106). Both groups showed significant narrowing of QRS, increase in LVEF and improvement in NYHA class. Lead complications occurred in 7 patients.	Study added in Qian 2018 systematic review added to table 2.
Shan P, Su L, Zhou X et al (2018). Beneficial effects of upgrading His bundle pacing in chronically paced patients with left ventricular ejection fraction < 50%. Heart Rhythm 15: 405-12	Case series N=18 patients with pacing dependent heart failure and LVEF <50% (CRT 'non-responders' and pacing included cardiomyopathy) had HBP. Follow-up 36.2 months	Implant success 89%, 1 patient died. QRS duration was shortened, LVEF increased, LV end diastolic dimensions decreased. Other improvements included mitral valve regurgitation, NYHA functional class and cardiothoracic ratios.	Study added in Qian 2018 systematic review added to table 2.
Shan P, Su L, Chen X et al. (2016) Direct His-bundle pacing improved left ventricular function and remodelling in a biventricular pacing nonresponder. The Canadian Journal of Cardiology. 32:1577 e1571-1577 e1574.	Case report A heart failure patient who had AVJ ablation for chronic atrial fibrillation and had a cardiac resynchronisation therapy defibrillator device. Because of the lack of clinical response to biventricular pacing, the device was revised with the addition of direct His bundle pacing.	Significant improvement in functional status and left ventricular indices was reported after His bundle pacing.	Larger studies added to table 2.
Singh R, Devabhaktuni S, Ezzeddine F et al (2020). His-bundle pacing: A novel treatment for left bundle branch block-mediated	Retrospective case series N=7 patients with LBBB-mediated cardiomyopathy had HBP for cardiac	Left ventricular ejection fraction improved on average from 25% to 50% (p = .0001). The left ventricular end-systolic dimension decreased from	Larger studies included in table 2.

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cardiomyopathy. Journal of Cardiovascular Electrophysiology; vol. 31 (no. 10); 2730-2736	resynchronization therapy (CRT). Follow-up 14.5 months.	47 to 37 mm ($p = .003$) and the left ventricular end-diastolic dimension decreased from 55 to 48 mm ($p = .03$). QRS duration with HBP-CRT decreased from 152 to 115 ms.	
Sohaib SMA, Wright I, Lim E et al (2015). Atrioventricular optimized direct His bundle pacing improves acute hemodynamic function in patients with heart failure and PR interval prolongation without left bundle branch block. Journal of American Clinical Cardiology: clinical electrophysiology 1, 6: 582-91	Case series N=16 patients with systolic heart failure, PR interval prolongation and narrow QRS duration, or right bundle branch block were included. Temporary direct His bundle pacing (n=14) versus temporary biventricular pacing (n=14).	Pacing improves acute hemodynamic function; it can be achieved by single site His pacing shows that its mechanism is AV shortening. The improvement is 60% of the effect size previously reported for biventricular pacing in left bundle branch block.	Permanent direct His bundle pacing has not specifically been tested in the population of patients included in this study.
Su L, Xu L, Wu SJ, Huang WJ. (2016) Pacing and sensing optimization of permanent His-bundle pacing in cardiac resynchronization therapy/implantable cardioverter defibrillators patients: value of integrated bipolar configuration. Europace; 18:1399–405	Case series N=38 patients (25 with CRT-D, cardiac resynchronisation therapy defibrillator; 13 with ICD, implantable cardioverter defibrillator) had PHBP.	Incorporation of HBP into a CRT-D/ICD system is feasible and pacing thresholds/ sensing can be optimised using a novel integrated bipolar configuration with the RV lead. This study showed that HBP lead with HB tip-RV coil configuration has better electrical performance with respect to CT, RWA, and pulse-energy consumption than those with HB unipolar configuration and HB bipolar tip-ring configuration, during implant, and at 1 and 3 months in selected CRT-D and ICD patients.	Pacing thresholds reported. Bipolar configuration HB tip RV coil tested. Heart failure status was not reported.
Teng AE, Lustgarten DL, Vijayaraman P et al. (2016) Usefulness of His bundle pacing to achieve electrical resynchronization in patients with complete left bundle branch block and the relation between native QRS axis, duration, and normalization. American Journal of Cardiology; 118:527–34	Case series N=29 patients with LBBB with pacing or CRT indication had selective or non-selective PHBP.	HBP induces significant QRS narrowing in most patients, and normalisation in patients with shorter baseline QRS duration. The lack of correlation between native QRS axis and narrowing suggests that proximal His-Purkinje block causes most cases of LBBB, or that additional mechanisms underlie HBP efficacy.	Heart failure status was not reported.

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Upadhyay GA, Vijayaraman P, Nayak HM, et al. (2019) His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure: a randomized pilot trial (HIS-SYNC). J Am Coll Cardiol; 74:157–9	RCT (NCT02700425). 21 His pacing versus 19 biventricular pacing (BiV) for cardiac resynchronisation therapy (CRT) in patients with heart failure. Crossovers were permitted	His corrective pacing was effective as an initial strategy for CRT with a significant reduction in QRS duration. Improvement in EF with His-CRT was greater than with BiV, but the difference was not statistically significant with high crossover rates.	Multiple publication of a study added to table 2.
Tung, R.; Nayak, H.M.; Vijayaraman, P. (2019) His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure: a randomized pilot trial (HIS-SYNC). Heart Rhythm; 2019; vol. 16 (no. 6); 965	RCT (NCT02700425). 21 His pacing versus 19 biventricular pacing (BiV) for cardiac resynchronisation therapy (CRT) in patients with heart failure. Crossovers were permitted.	His corrective pacing was effective as an initial strategy for CRT with a significant reduction in QRS duration. Improvement in EF with His-CRT was greater than with BiV, but the difference was not statistically significant with high crossover rates.	Multiple publication of a study added to table 2.
Upadhyay, G.A.; Tung, R (2020) Keeping pace with the competition: His bundle versus biventricular pacing in heart failure. Current opinion in cardiology; 35 (3); 295-307	Review	HBP is emerging as an alternative strategy for CRT and may have a role in patients in whom traditional BiV is not achievable or ineffective.	Review
Vijayaraman P, Dandamudi G, Ellenbogen KA. (2016) Electrophysiological observations of acute His bundle injury during permanent His bundle pacing. J Electrocardiol; 49:664–9	Case series N=358 patients with AV conduction disease and sinus node dysfunction had selective and non-selective PHBP. Median follow up 21 months	28 patients developed acute trauma- AV block, LBBB, RBBB during HBP implant. Conduction recovered in 7 AVB and LBBB patients. Lead induced RBBB resolved in 21 patients. Complete resolution occurred in 19/28 patients.	Heart failure status was not reported in study.
Vijayaraman P, Herweg B, Ellenbogen KA et al (2019). His-optimized cardiac resynchronization therapy to maximize electrical resynchronization a feasibility study. Circulation Arrhythmia Electrophysiology. 12	Case series N=27 patients with advanced heart failure (left bundle branch block 17, intraventricular conduction defect 5, and right ventricular pacing 5) referred for CRT in addition to LV lead. HBP followed by LV pacing (His-optimised CRT [HOT-CRT]). Follow-up: median 14 months	HOT-CRT was successful in 25 of 27 patients. QRS duration statistically significantly narrowed from 183 to 162±17 ms with biventricular pacing ($P=0.003$), to 151±24 ms during HBP ($P<0.0001$), and further to 120±16 ms during HOT-CRT ($P<0.0001$). During a mean follow-up of 14±10 months, LVEF improved from 24±7% to 38±10%, ($p<0.0001$), and NYHA functional class changed from 3.3 to 2.04.	His bundle pacing optimised with sequential left ventricular pacing.

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Vijayaraman P, Subzposh FA, Naperkowski A (2019). Extraction of the permanent His bundle pacing lead: Safety outcomes and feasibility of reimplantation. Heart rhythm; vol. 16 (no. 8); 1196-1203.	Case series N=30 patients undergoing extraction of leads from the His bundle location after 6 months duration for standard indications.	The indications for removal of the HBP leads were infection (n = 3), lead failure (n = 22), nonfunctional lead (n = 3), and upgrade to implantable cardioverter-defibrillator (n = 2). The mean duration of the implanted leads was 25 +/- 18 months (range 6-72 months). Removal of HBP leads was successful in 8 of 8 patients (100%) with <=12-month duration and 21 of 22 patients (95%) with >12-month duration. Extraction tools were used in 4 patients, while manual traction was successful in the remaining patients. Reimplantation in the His-Purkinje conduction system was successful in 86% (19/22) patients. The overall success rate of extraction of chronically implanted HBP leads was high with a low complication rate. The need for mechanical extraction tools was low, and reimplantation in the His-Purkinje conduction system was feasible.	Various indications
Yang QJQ, Raja DC, Stolcman S et al (2020). Cardiac Resynchronization with His-CRT-D in a patient with severe heart failure and Scimitar syndrome. Pacing and clinical electrophysiology : PACE	Case report	His-CRT-D pacing for a patient with heart failure with severely reduced ejection fraction, left bundle branch block and congenital heart disease characterized by Scimitar syndrome with cardiac dextroposition was successful and facilitated by imaging.	Larger studies included in table 2.
Ye Y, Zhang Z, Sheng X et al (2018). Upgrade to his bundle pacing in pacing dependant patients referred for pulse generator change.: feasibility and intermediate term follow up. International Journal of Cardiology. 260, 88-92.	Case series N=12 long term RV pacing dependant patients referred for pulse generator exchange had HBP (3 patients with<40% EF also had BVP). Median 6 months follow-up.	Implantation 100% successful. A statistically significant reduction in mean QRS duration from 157 to 109 (p<0.001) was noted. After 6 months follow-up, NYHA functional class improved (p=0.007), and LVID diameter reduced (p=0.03). HBP improves heart failure symptoms with preserved LVEF by long term RVP.	Larger studies included in table 2.

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Zanon F, Ellenbogen KA, Dandamudi G et al. (2018) Permanent His-bundle pacing: a systematic literature review and meta-analysis. <i>Europace</i> 20, 1819-926	Systematic review and meta-analysis N=26 studies (1438 patients). 62.1% were implanted due to atrioventricular block.	Average implant success rate was 84.8% and was higher with use of catheter-delivered systems (92.1%; $p < 0.001$). Average pacing thresholds were 1.71 V at implant and 1.79 V at >3months follow-up; although, pulse widths varied. Average LVEFs were 42.8% at baseline and 49.5% at follow-up. There were 43 complications in 907 patients (in 17 studies).	Heart failure status was not reported in most studies (16/25). Commonly reported indication was AV block in 62% and AF was present in 41% patients.
Zhuang L, Mao Y, Wu L et al. (2018) Effects of right ventricular septum or His-bundle pacing versus right ventricular apical pacing on cardiac function: A systematic review and meta-analysis of randomized controlled trials. <i>Journal of International Medical Research</i> 46(9) 3848-60	Systematic review and meta-analysis N=17 studies (1290 patients) 14 RCTs [parallel design] comparing RVA and RVS pacing and 3 studies (cross over design) comparing HBP with pacing at other sites.	Compared with RVA pacing, RVS or HBP exhibited a higher left ventricular ejection fraction (LVEF) (weighted mean difference 3.28; 95% CI 1.45, 5.12) at the end of follow-up.	Different pacing sites and varied populations assessed.