HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

His-bundle-pacing for patients requiring a permanent pacemaker or cardiac resynchronisation

Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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List of abbreviations

AE.....Adverse events
AF.....Atrial fibrillation
AVB.....atrioventricular block
BiV-CRT.....Biventricular cardiac resynchronisation therapy
BMI.....Body Mass Index
BNP.....B-type natriuretic peptide
BVP.....Biventricular pacing
CABG.....Coronary artery bypass graft surgery
CE.....Conformité Européenne
CHOP-code.....Coding systems for procedures in Switzerland ("Schweizerische Operationsklassifikation")
CI.....Confidence interval
COMET.....Core Outcome Measure in Effectiveness Trials
COPD.....Chronic obstructive pulmonary disease

CRT.....Cardiac resynchronisation therapy
ECG.....Electrocardiogram
eGFR.....estimated glomerular filtration rate
EUnetHTA .....European Network for Health Technology Assessment
ESC .....European Society of Cardiology
GRADE.....Grading of Recommendations, Assessment, Development and Evaluation
HBP.....His-bundle pacing
HFmEF.....Heart failure with a mildly reduced ejection fraction
HFpEF.....Heart failure with a preserved ejection fraction
HFrEF.....Heart failure with a reduced ejection fraction
HTA .....Health Technology Assessment
ICD-10 .....International Classification of Diseases, 10th revision
ICTRP.....International Clinical Trial Registry Platform
INAHTA.....International Network of Agencies for Health Technology Assessment
LBBAP.....Left bundle branch area pacing
LBBP.....Left bundle branch pacing
LKF-catalogie.....Catalogue for medical procedures in Austria ("Leistungsorientierte Krankenanstaltenfinanzierung")
LV.....Left ventricle
LVEF.....Left ventricular ejection fraction
MACE .....Major adverse cardiovascular events
MeSH .....Medical Subject Headings
ms .....milliseconds
NA .....not applicable
NICE.....National Institute for Health and Care Excellence
NR.....not reported
NYHA .....New York Heart Association
OPS-code .....Coding system for procedures in Germany ("Operationen- und Prozedurenschlüssel")
p.....p-value
PCI .....Percutaneous coronary intervention
PICO .....Framework for research questions on Population, Intervention, Comparators and Outcomes
PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analyses
pts.....patients
QoL .....Quality-of-life
RBBB .....Right bundle branch block
RCT.....Randomised controlled trial
RiV-CRT.....Right ventricular cardiac resynchronisation therapy
RoB.....Risk of Bias
ROBIS-I .....Risk of Bias in non-randomised Studies of Interventions
RVAP .....Right ventricular area pacing
RVP .....Right ventricular pacing
SAE.....Serious adverse events
V .....Volt
yrs.....years

Executive Summary

Introduction

Some patients require a permanent pacemaker or cardiac resynchronisation to help control their heartbeat. Possible indications, among others, are heart failure, cardiac conduction system disease (e.g., atrioventricular block) or atrial fibrillation. Established pacing systems can be classified as right ventricular pacing (RVP) or biventricular pacing (BVP). BVP is also called cardiac resynchronisation therapy, as it helps to synchronise the contraction of both ventricles.

cardiac pacing/ resynchronisation: heart failure, conduction system disease, atrial fibrillation

A newer type of pacing system is the so-called physiological pacing (as opposed to ventricular pacing). His-bundle pacing (HBP) belongs to this new group of pacing systems. HBP directly stimulates the cardiac conduction system intending to improve cardiac function and synchronisation by pacing only a single site. The pacing lead is attached to the His-bundle, with the lead connected to the pacemaker generator. The procedure is usually performed in a cardiac catheterization laboratory.

His-bundle pacing (HBP): newer type of pacing system, directly stimulating the cardiac conduction system

Methods

This report aimed to assess whether HBP in patients with heart failure, cardiac conduction system disease or atrial fibrillation is more effective and safer regarding patient-relevant outcomes and adverse events in comparison with standard care (e.g., RVP or BVP).

HBP more effective and safer than standard care (e.g. RVP, BVP)?

To evaluate the effectiveness and safety of HBP, a systematic search from 2017 to 2021 was conducted in the following databases: Medline, Embase, The Cochrane Library, and HTA-INAHTA. To identify possibly relevant primary studies published before 2017, a systematic review (published in 2018) was assessed using the AMSTAR-II checklist. The included studies from this systematic review were then screened in addition. In total, 833 potentially relevant hits were identified.

systematic search: 2017-2021

SR 2018 (to identify studies before 2017): AMSTAR-II assessment

The study selection, data extraction and assessment of the methodological quality of the studies were performed independently by two researchers. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was further used for the qualitative evidence synthesis.

selection, extraction and quality appraisal: conducted by 2 researchers

Domain effectiveness

For clinical effectiveness, the crucial outcomes quality-of-life, and the New York Heart Association (NYHA) functional class, were used as evidence to derive a recommendation. Additional outcomes, such as implant success, electrocardiographic, echocardiographic, or laboratory parameters, were further defined as important.

crucial outcomes effectiveness: QoL and NYHA functional class

Domain safety

For safety, all (serious) adverse events, such as mortality, complications, hospitalisations or increase in capture threshold, were defined as crucial outcomes to derive a recommendation.

crucial outcomes safety: all (serious) adverse events

Results

Available evidence

3 RCTs (indication: heart failure), 1 observational study (indication: cardiac conduction system disorders)

Three randomised controlled trials (RCTs) and one retrospective cohort study were eligible for inclusion in this report. In the RCTs, a total of 163 patients were analysed, whereas the retrospective cohort study analysed 765 patients. All RCTs investigated HBP use in patients with heart failure, and the retrospective cohort study included patients with cardiac conduction system disorders. The lengths of follow-up ranged from six months to two years.

Clinical effectiveness

NYHA class: stat. sign. improvement (1 RCT), no stat.sign. difference (2 RCTs) Quality-of-life: stat.sign. improvement (1 RCT)

One RCT detected a statistically significant improvement in the NYHA functional class favouring HBP compared to RVP. Two RCTs, comparing HBP with BVP, could not detect a statistically significant difference between groups. The health-related quality-of-life was assessed in one RCT, with a statistically significant difference favouring HBP compared to RVP. The quality of evidence was assessed as very low for both effectiveness outcomes.

Safety

mortality: no stat. sign. difference stat.sign. difference for composite adverse events, but not for individual adverse events

There was no statistically significant difference between groups in two RCTs and the observational study for mortality. For adverse events or complications, one RCT found a statistically significant lower rate for total adverse events (compared to RVP). For the composite of mortality, hospitalisation or upgrade to BVP, the observational study found a statistically significant lower rate (compared to RVP). None of the three RCTs or the observational study detected a statistically significant difference for individual adverse events.

hospitalisations: no stat.sign. difference (RCTs), fewer hospitalisations (observational study), capture threshold stat.sign. increased in all 4 studies

Regarding hospitalisations, one RCT did not detect a statistically significant difference, while another RCT only reported the total number of hospitalisations across both groups. In the observational study, statistically significant fewer hospitalisations occurred in the HBP group. The increase in capture threshold was assessed in all three RCTs and the observational study, with statistically significant higher values in the HBP group (compared to RVP or BVP), both at baseline and at follow-up.

Upcoming evidence

12 ongoing RCTs

In the search for upcoming evidence, twelve ongoing RCTs were identified. The estimated completion dates range from 2022 to 2026.

Reimbursement

HBP currently not reimbursed in Austria

At this point, HBP is not refunded by the Austrian healthcare system. The comparator pacing techniques (RVP or BVP) are reimbursed in the hospital benefit catalogue.

Discussion

The overall quality of evidence for the clinical effectiveness and safety of HBP compared to RVP or BVP is very low (GRADE rating). Limitations of the RCTs were an imprecision of data, as all three included RCTs had small sample sizes and limited lengths of follow-up. Additionally, there were unbalanced deviations from intended interventions in two of the three RCTs. The observational study was limited by its retrospective data collection, with statistically significant differences at baseline between groups. The overall RoB was high for the RCTs and moderate for the observational study.

limitations: deviations from intended interventions, small sample sizes, short follow-up, moderate to high RoB in studies

At present, the evidence is insufficient to show that HBP is more effective and safer than the comparators. Randomised evidence was only available for one of the indications (heart failure). Some evidence suggests that HBP may achieve better results in certain conditions when compared to RVP. However, the results were insufficient to prove a benefit compared to BVP. At this point, it is unclear if and to what extent the increased pacing thresholds could potentially lead to shorter battery life. For both comparators, the quality of evidence was very low regarding the crucial outcomes.

insufficient evidence to prove a benefit, quality of evidence very low

safety concerns due to increased pacing thresholds

Conclusion

Based on the available evidence, inclusion in the hospital benefit catalogue is currently not recommended. Reevaluation is recommended in 2026 if the larger ongoing randomised controlled trials are published.

inclusion currently not recommended

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Indikationen für permanente Schrittmachersysteme oder kardiale Resynchronisation

Bei manchen Herzerkrankungen benötigen Patient*innen einen permanenten Herzschrittmacher oder eine kardiale Resynchronisationstherapie. Zu diesen Indikationen zählen, unter anderem, Herzinsuffizienz, Erkrankungen des Erregungsleitungssystems (wie z. B. atrioventrikulärer Block), oder Vorhofflimmern. Etablierte Schrittmachersysteme können eingeteilt werden in rechtsventrikuläre (eng. rightventricular pacing = RVP) oder biventrikuläre (eng. biventricular pacing = BVP). Mit dem BVP lässt sich außerdem eine kardiale Resynchronisation erzielen, da die Kontraktion beider Ventrikel synchron stimuliert wird.

Beschreibung der Technologie

„physiologische" Schrittmacher-Systeme: His-BündelStimulation (HBP)

Mit den sogenannten physiologischen Schrittmachern gibt es eine neue Gruppe von Schrittmachern. Die Stimulation des His-Bündels (eng. His-bundle pacing = HBP) gehört zu dieser neueren Gruppe von Schrittmachern. Mittels HBP wird direkt das Erregungsleitungssystem des Herzens stimuliert (im Gegensatz zu den ventrikulären Schrittmachern). Damit soll, obwohl die Stimulation nur an einer Stelle erfolgt, die kardiale Funktion und Synchronisation verbessert werden. Dazu wird die Elektrode am His-Bündel fixiert und mit dem Impulsgeber verbunden. Die Implantation des Schrittmachersystems erfolgt in der Regel in Herzkatheterlaboren.

Methoden

Ziel: Wirksamkeit und Sicherheit des HBP in Bezug auf patient*innenrelevante klinische Endpunkte

Ziel der vorliegenden systematischen Übersichtsarbeit war es, den Einsatz von HBP in Patient*innen mit Herzinsuffizienz, Erkrankungen des Erregungsleitungssystems oder Vorhofflimmern, im Vergleich zur Standardversorgung mit ventrikulären Schrittmachersystemen (RVP oder BVP) zu erheben. Die Forschungsfrage war, ob HBP wirksamer und sicherer hinsichtlich patient*innen-relevanter klinischer Endpunkte, wie Lebensqualität, Funktionsklasse oder unerwünschter Nebenwirkungen ist.

Vorabsuche: systematische Übersichtsarbeit aus 2018

AMSTAR-II-Bewertung

Zunächst wurde eine systematische Vorabsuche nach systematischen Übersichtsarbeiten zu HBP in der Datenbank Embase durchgeführt (32 Referenzen). Aus diesen wurde die rezenteste systematische Übersichtsarbeit (2018 publiziert), welche alle Indikationen des HBP umfasste, ausgewählt. Die methodische Qualität dieser systematischen Übersichtsarbeit wurde anhand der AMSTAR-II Checkliste überprüft und mit hoher Qualität bewertet. Zweck dieses Vorgehens war die Identifikation potentiell relevanter Primärstudien, die vor 2017 publiziert wurden.

systematische Suche: 2017-2021

Für den Zeitraum, welcher durch die systematische Übersichtsarbeit von 2018 nicht abgedeckt war, wurde eine systematische Literatursuche in den folgenden vier Datenbanken durchgeführt: Medline, Embase, The Cochrane Library und HTA-INAHTA. Dieser Suchzeitraum umfasste Mai 2017 bis Dezember 2021. Nach Deduplizierung konnten insgesamt 833 potentielle Treffer identifiziert werden. Zusätzlich wurden 104 Publikationen, welche von den zwei Herstellern der Technologie (Medtronic Inc., Abbott Laboratories)

übermittelt wurden, berücksichtigt. Eine Suche nach aktuell laufenden Studien in drei klinischen Registern (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) ergab 87 potentielle Treffer.

Die Studienauswahl, Datenextraktion und Bewertung der methodischen Qualität der Studien wurden von zwei Personen unabhängig voneinander durchgeführt. Die Daten zu den ausgewählten Endpunkten wurden studienübergreifend mit Hilfe von GRADE (Grading of Recommendations, Assessment, Development and Evaluation) eingestuft.

Datenextraktion und GRADE-Bewertung von 2 Personen durchgeführt

Endpunkte klinische Wirksamkeit

Zur Bewertung der klinischen Wirksamkeit wurden die Lebensqualität (eng. quality-of-life = QoL) und die Funktionsklasse nach der New York Heart Association (NYHA) als entscheidende Endpunkte für eine Empfehlung herangezogen. Zusätzlich wurden Implantationsrate, elektrokardiographische Parameter, echokardiographische Parameter und Laborparameter als wichtige Endpunkte definiert.

Endpunkte für Empfehlung hinsichtlich der klinischen Wirksamkeit

Endpunkte Sicherheit

Für die Bewertung der Sicherheit wurden alle (schwerwiegenden) unerwünschten Ereignisse, wie etwa die Mortalität, die Komplikationen, die Hospitalisierungen oder die Zunahme der Schrittmacherschwelle, als entscheidende Endpunkte für die Ableitung einer Empfehlung definiert.

Endpunkte für Empfehlung hinsichtlich der Sicherheit

Ergebnisse

Verfügbare Evidenz

Für die vorliegende systematische Übersichtsarbeit wurden drei randomisiert-kontrollierte Studien (eng. randomised controlled trials = RCTs) und eine retrospektive Kohortenstudie inkludiert. In den RCTs wurden insgesamt 163 Patient*innen untersucht, während die Kohortenstudie 765 Patient*innen umfasste. In allen drei RCTs wurde der Einsatz von HBP bei Patient*innen mit Herzinsuffizienz überprüft. Die retrospektive Kohortenstudie inkludierte Patient*innen mit Erkrankungen des Erregungsleitungssystems. Der Beobachtungszeitraum der Studien reichte von sechs Monaten bis zwei Jahre.

Evidenzsynthese aus 4 Studien: 3 RCTs (163 Patient*innen), 1 Kohortenstudie (765 Patient*innen) Beobachtungszeitraum: 6 bis 24 Monate

Klinische Wirksamkeit

In Bezug auf die NYHA Funktionsklasse zeigte ein RCT eine statistisch signifikante Verbesserung bei Verwendung von HBP im Vergleich zu RVP. Zwei weitere RCTs konnten im Vergleich mit BVP keinen statistisch signifikanten Unterschied zwischen den Gruppen nachweisen. Die Lebensqualität wurde in einem RCT erhoben, mit einem statistisch signifikanten Unterschied zugunsten von HBP im Vergleich zu RVP. Die Qualität der Evidenz für beide als entscheidend eingestuften Endpunkte war sehr niedrig.

Funktionsklasse (NYHA): stat.sign. Verbesserung (1 RCT), kein stat.sign. Unterschied (2 RCTs) QoL: stat.sign. Verbesserung (1 RCT)

In zwei RCTs waren die Implantationsraten für HBP im Vergleich zu BVP niedriger, wobei keine p-Werte berichtet wurden. Die Länge der QRS-Dauer (elektrokardiographischer Parameter) wurde in allen drei RCTs erhoben. Dabei fand ein RCT einen statistisch signifikanten Unterschied zugunsten von HBP (im Vergleich zu RVP), während zwei RCTs keinen statistisch signifikanten Unterschied fanden (im Vergleich zu BVP). Die linksventrikuläre Ejektionsfraktion (echokardiographischer Parameter) zeigte in einem RCT einen statistisch signifikanten Unterschied zugunsten der HBP im Vergleich zur RVP. In zwei weiteren RCTs wurde mit BVP verglichen, dabei fand sich

Implantationsrate, QRS-Dauer, linksventrikuläre Ejektionsfraktion, Laborparameter NT-proBNP

kein statistisch signifikanter Unterschied zwischen den Gruppen. Für den Laborparameter NT-proBNP konnte in einem RCT kein statistisch signifikanter Unterschied zwischen den Gruppen gezeigt werden.

Qualität der Evidenz: sehr niedrig bis niedrig

Die Qualität der Evidenz für diese als wichtig eingestuften Endpunkte wurde als sehr niedrig (Implantationsrate, QRS-Dauer, linksventrikuläre Ejektionsfraktion) bis niedrig (NT-proBNP) eingestuft.

Sicherheit

Mortalität ohne stat. sign. Unterschied (2 RCTs)

stat.sign. Unterschiede für zusammengesetzte Nebenwirkungen, jedoch nicht für einzeln betrachtete Nebenwirkungen

Die Mortalität wurde in zwei RCTs und in der Beobachtungsstudie erhoben. Dabei wurde kein statistisch signifikanter Unterschied zwischen den Gruppen berichtet. Bezüglich unerwünschter Nebenwirkungen und Komplikationen wurde von einem RCT eine statistisch signifikant niedrigere Häufigkeit für die Gesamtrate an Nebenwirkungen berichtet (verglichen mit RVP). Für den kombinierten Endpunkt aus Mortalität, Hospitalisierung oder Notwendigkeit eines Upgrades zu BVP, fand die Beobachtungsstudie eine statistisch signifikante niedrigere Rate bei Einsatz von HBP (verglichen mit RVP). Für keine der einzeln betrachteten unerwünschte Ereignisse wurden statistisch signifikante Unterschiede zwischen den Gruppen identifiziert (in drei RCTs und der Beobachtungsstudie).

Hospitalisierungen: stat.sign. Unterschied in Beobachtungs-studie, nicht stat.sign. in 2 RCTs; Schrittmacher-schwelle: in allen Studien stat.sign. Unterschied zuungunsten HBP

Die Rate an Hospitalisierungen wurde in zwei RCTs erhoben. Ein RCT fand dabei keinen statistisch signifikanten Unterschied, das andere RCT berichtete lediglich die Gesamtrate an Hospitalisierungen über beide Gruppen, wodurch kein Vergleich möglich war. In der Beobachtungsstudie wurden für die Interventionsgruppe mit HBP statistisch signifikant weniger Hospitalisierungen berichtet. Die Zunahme der Schrittmacherschwellen wurde in allen drei RCTs und der Beobachtungsstudie erhoben. Dabei wurde ein statistisch signifikanter Unterschied zuungunsten der HBP im Vergleich zu RVP oder BVP gezeigt, sowohl zu Studienbeginn als auch am Ende des Beobachtungszeitraumes.

Qualität der Evidenz: sehr niedrig bis niedrig

Die Qualität der Evidenz für diese als entscheidend eingestuften Endpunkte der Sicherheit wurde als sehr niedrig (Mortalität, unerwünschte Nebenwirkungen, Komplikationen und Hospitalisierungen) bis niedrig (Zunahme der Schrittmacherschwelle) bewertet.

Laufende Studien

12 laufende RCTs, 2022 bis 2026 abgeschlossen

Es wurden zwölf derzeit laufende RCTs identifiziert, welche voraussichtlich zwischen 2022 und 2026 abgeschlossen sein werden. Darüber hinaus wurden zwei weitere RCTs identifiziert, die kürzlich abgeschlossen wurden, mit noch ausstehender Publikation der Ergebnisse. Die untersuchten Indikationen für den Einsatz von HBP in diesen Studien sind Erkrankungen des Erregungsleitungssystems, Herzinsuffizienz, Vorhofflimmern und Schrittmacherindikation nach perkutanem Aortenklappenersatz. Die Studiengrößen der RCTs reichen von 16 bis 334 Studienteilnehmer*innen.

Kostenerstattung

derzeit keine Kostenerstattung für HBP, jedoch für RVP oder BVP

Derzeit gibt es im österreichischen stationären LKF-Katalog keinen Erstattungscode für einen permanenten Schrittmacher oder kardiale Resynchronisation durch HBP. Die im Vergleich betrachteten ventrikulären Schrittmachersysteme (RVP oder BVP) haben Erstattungscodes im LKF-Katalog.

Diskussion

sehr niedrige Gesamtqualität der Evidenz, Verzerrungspotenzial in den Studien

Insgesamt ist die Gesamtqualität der Evidenz für die klinische Wirksamkeit und Sicherheit des HBP im Vergleich zu RVP oder BVP sehr niedrig (GRADE-Einstufung). Limitierende Faktoren aller inkludierten RCTs waren unzureichende Präzision aufgrund der kleinen Stichprobengrößen und den kurzen Beobachtungszeiträumen. Darüber hinaus gab es in zwei RCTs nennenswerte Abweichungen von den geplanten Interventionen. Die Beobachtungsstudie erfolgte retrospektiv und zeigte zu Studienbeginn statistisch signifikante Unterschiede zwischen den Gruppen. Das Verzerrungspotenzial (eng. risk of bias = RoB) war in drei Studien hoch und in einer Studie moderat.

unzureichende Evidenz für klinische Wirksamkeit und Sicherheit, randomisierte Studien bisher nur für 1 Indikation, laufende Studien abzuwarten

Derzeit ist die Evidenz für einen wirksameren und sicheren Einsatz von HBP im Vergleich zur Standardtherapie unzureichend. Randomisierte Studien lagen nur für eine der Indikationen (Herzinsuffizienz) vor. Im Vergleich zu RVP gibt es Anhaltspunkte, dass HBP in gewissen Bedingungen bessere Ergebnisse erzielen könnte. Im Vergleich zu BVP waren die Ergebnisse hingegen unzureichend um einen Vorteil zu belegen. Nach jetzigem Stand ist außerdem unklar ob, und inwiefern, die erhöhten Schrittmacherschwellen zu einer kürzeren Batterielebensdauer führen könnten. Die Qualität der Evidenz für die als entscheidend klassifizierten Endpunkte war, für beide Komparatoren, sehr niedrig. In Anbetracht der verfügbaren Evidenz sollten Ergebnisse aus aktuell laufenden Studien zu HBP abgewartet werden.

Empfehlung

Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen

Aufgrund der vorliegenden Evidenz wird die Aufnahme in den Leistungskatalog derzeit nicht empfohlen. Eine Re-Evaluierung wird 2026 empfohlen, wenn die aktuell laufenden, größeren randomisiert-kontrollierten Studien veröffentlicht sind.

1 Background

1.1 Overview of the disease, health condition and target population[1]

His-Bündel-Stimulation: als Schrittmacher oder zur kardialen Resynchronisationstherapie

His-bundle pacing (HBP) is a type of cardiac pacing with the aim of producing a normal physiological ventricular activation via the His-Purkinje conduction system [1]. HBP is used as an alternative to other types of pacing, such as biventricular pacing (BVP) or right ventricular pacing (RVP) [2, 3]. HBP can be used for cardiac resynchronisation therapy in patients with heart failure, or as a permanent pacemaker in cardiac conduction system disease (e.g. atrioventricular block) or in patients with bradycardic atrial fibrillation [4][2, 3].

Heart failure

Herzinsuffizienz: unzureichende Pumpfunktion, Blutzirkulation eingeschränkt

Heart failure describes a condition in which the heart's pumping capacity is insufficient for the demands, resulting in impaired relative blood circulation. Patients with heart failure have a backlog of blood in the venous system, leading to congestion. Among the symptoms of heart failure is oedema in the legs or shortness of breath due to pulmonary fluid retention [5]. However, clinical signs of heart failure may not be present in the early stages of heart failure or in optimally treated patients [6].

Einteilung: links/rechts/beidseitig, akut/chronisch

Heart failure can be classified according to the affected ventricle (left-sided failure, right-sided failure, and biventricular failure), condition (acute or chronic course of disease), pathophysiology (ischemic, in the context of myocarditis or valvular) and echocardiographic characteristics (systolic, diastolic, or combined heart failure) [5].

diagnostische Kriterien ESC, 2021

The diagnostic heart failure classification 2021 from the European Society of Cardiology is based on the measurement of the left ventricular ejection fraction (LVEF) [6][4]:

Pumpfunktion (LVEF):

- Reduced LVEF refers to measures ≤40% (a significant reduction in left ventricular systolic function). This is designated as heart failure with a reduced ejection fraction (HFrEF),

HFrEF: reduziert (≤40 %)

- LVEF between 41% and 49% (mildly reduced left ventricular systolic function). This is described as heart failure with a mildly reduced ejection fraction (HFmrEF),

HFmrEF: mäßig reduziert (41 %-49 %)

- LVEF ≥50%, but symptoms and signs of heart failure, with structural and/or functional cardiac abnormalities and/or raised natriuretic peptides. This is referred to as heart failure with a preserved ejection fraction (HFpEF).

HFpEF: erhalten (≥50 %)

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1 This section addresses the EUnetHTA Core Model® domain CUR.

2 **A0001** – For which health conditions, and for what purposes is His bundle pacing used?

3 **A0002** –What is the disease or health condition in the scope of this assessment?

4 **A0024** – How is heart failure, cardiac conduction system disease or atrial fibrillation currently diagnosed according to published guidelines and in practice?

Risikofaktoren für Herzinsuffizienz: Alter, Erbfaktoren, Lebensstil, kardiovaskuläre und weitere Erkrankungen, Ethnizität, Geschlecht

Risk factors for heart failure include, among others [7][5]:

- **Age**: people older than 65 years have a higher risk of heart failure, as well as other health conditions that can cause heart failure.
- **Family history**, genetics: the risk of heart failure is higher if another family member has been diagnosed with heart failure. Certain gene mutations can raise the risk.
- **Lifestyle habits**: an unhealthy diet, smoking, drug use, alcohol use, lack of physical activity can raise the risk of heart failure.
- **Other medical conditions**: any heart or blood vessel condition, serious lung disease or infections can increase the risk of heart failure. Long-term health conditions (obesity, high blood pressure, diabetes, sleep apnea, chronic kidney disease, anaemia, thyroid disease, iron overload), cancer treatments (radiation or chemotherapy), and atrial fibrillation can also cause heart failure.
- **Race or ethnicity**: African Americans are more likely to have heart failure compared to people of other races.
- **Sex**: while common in both genders, men often develop heart failure at a younger age than women.

in Ö, 2019: 46.853 stationär dokumentiert

Prävalenz mit Alter zunehmend DE: gesamt 1-2 %, über 60 Jahre: 10 %

The prevalence of heart failure is 1-2% of the German population, with an increase in age (the prevalence in the group of >60 years of age is around 10%) [5]. There is limited conclusive data for the prevalence of heart failure in Austria. The documentation of diagnoses and procedures of the inpatient setting can give approximate, albeit missing, data for the outpatient setting. In 2019, heart failure (ICD-10 code I50) was documented for 46,853 patients in the inpatient setting [8][6, 7].

Cardiac conduction system disease

Erkrankungen des kardialen Reizleitungssystems (Gruppe der Herzrhythmusstörungen)

The cardiac conduction system consists of the sinus node, the atrioventricular node, the His-bundle, the Tawara-bundle and the Purkinje-fibers. A disorder of any of these components is considered a cardiac conduction system disorder. The cardiac conduction system disorders are a subgroup of cardiac arrhythmias [9].

Risikofaktoren: Alter, Erbfaktoren, kardiovaskuläre und weitere Erkrankungen, div. Medikation

Risk factors for cardiac conduction system disease include, among others [10][5]:

- **Age**: while conduction disorders can happen at any age, certain disorders (such as sick sinus syndrome and bundle branch blocks) are more common in older adults.
- **Family history and genetics**: some disorders are more common among family members, including Brugada syndrome, complete heart block or third-degree atrioventricular block, and Wolff-Parkinson-White syndrome.
- **Other medical conditions**: autoimmune diseases, cardiomyopathy, complications of heart surgery or procedure, diseases in which there are deposits of abnormal substances in the heart, endocrine conditions, heart inflammation (myocarditis and pericarditis), high blood pressure, neuromuscular disorders or sleep apnea.

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[5] **A0003** – What are the known risk factors for heart failure, cardiac conduction system disease or atrial fibrillation?

[6] **A0007** – What is the target population in this assessment?

[7] **A0023** – How many people belong to the target population?

- **Medication**: antiarrhythmics, antidepressants and antipsychotic medicines, diuretics, beta-blockers, calcium channel blockers, digoxin, high blood pressure medicine, lithium, muscle relaxants and sedatives.

in Ö, 2019: Herzrhythmusstörungen stationär 120.821 dokumentiert

In Austria, cardiac arrhythmias in the inpatient setting were documented in 120,821 patients (ICD-10 codes I44-I49) in 2019. Of these, 67% account for atrial flutter and atrial fibrillation, with the remaining 33% accounting for cardiac conduction system disorders (atrioventricular blocks, bundle branch blocks, sick sinus syndrome) and other cardiac arrhythmias [8][6, 7].

Atrial fibrillation

Vorhofflimmern: häufig asymptomatische Rhythmusstörung; Risiko für Thromboembolien

Atrial fibrillation is a common cardiac rhythm disorder. Clinically, atrial fibrillation is often asymptomatic. When symptoms occur, there can be palpitations, brady- or tachyarrhythmias, syncopes, or exacerbated symptoms of heart failure. Due to a turbulent blood flow because of asynchronicity between the atrium and the ventricles, the risk of thromboembolism is significantly increased [11].

ESC 2020 Leitlinie: EKG-Kriterien für Diagnosestellung

According to the 2020 European Society of Cardiology guidelines for the diagnosis and management of atrial fibrillation, electrocardiogram (ECG) documentation is required to establish the diagnosis of atrial fibrillation: a standard 12-lead ECG recording or a single-lead ECG tracing of ≥30s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical atrial fibrillation [12][4].

Risikofaktoren für Vorhofflimmern:

Alter, Erbfaktoren, Lebensstil, kardiovaskuläre und weitere Erkrankungen, Ethnizität, vorausgegangene Thorax-OPs

Risk factors for atrial fibrillation include, among others [13][5]:

- **Age**: atrial fibrillation is rare in children and increases with age, especially after age 65.
- **Family history and genetics**: the risk of atrial fibrillation is higher when a family member is affected.
- **Lifestyle habits**: the risk of atrial fibrillation is increased by alcohol or drug use, reduced physical activity, smoking or stress.
- **Other medical conditions**: chronic kidney disease, conduction disorders, congenital heart defects, diabetes, heart attack, heart failure, heart inflammation, stiff heart tissue, heart valve diseases, high blood pressure, hyperthyroidism, ischemic heart disease, lung diseases (including chronic obstructive pulmonary disease), obesity, sarcoidosis, sleep apnea or venous thromboembolism.
- **Race or ethnicity**: in the United States, atrial fibrillation is more common among whites than African Americans, Hispanic Americans, or Asian Americans. Although people of European ancestry are more likely to develop the condition, African Americans with atrial fibrillation are more likely to have complications such as stroke, heart failure, or ischemic heart disease.
- **Surgery**: in the early days and weeks after surgery of the heart, lungs or oesophagus, there is an increased risk for atrial fibrillation.

in Ö, 2019: 80.950 stationär dokumentiert Prävalenz in DE: gesamt 1-2 %, Alter 35-74: 3 %

In the general German population, the prevalence for atrial fibrillation is 1-2% (about 3% in the age group 35-74), making it the most common persistent cardiac rhythm disorder [11]. In Austria, atrial flutter and atrial fibrillation were documented in 80,950 patients in the inpatient setting (ICD-10 code I48) [8][6, 7].

1.2 Current clinical practice[8]

Clinical guideline recommendations

Leitlinien USA, 2018: HBP als Alternative zu RVP:

Since 2018, HBP has been recommended as an alternative to RVP in clinical guidelines in the USA [14]:

IIa-Empfehlung: Pat. mit LVEF 36-50 % und AV-Block, mit >40 % ventrikulärer Schrittmacherzeit

- In patients with an LVEF between 36% to 50% and atrioventricular block, who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time, more physiological ventricular activation (e.g. cardiac resynchronisation therapy, His-bundle pacing) are preferred to right ventricular pacing to prevent heart failure (class of recommendation[9]: IIa (moderate strength of recommendation), level of evidence[10]: level of evidence B-R (moderate-quality evidence from one or more randomised-controlled-trials)).

IIb Empfehlung: Pat. mit AV-Block mit Indikation für perm. Schrittmacher

- In patients with an atrioventricular block at the level of the atrioventricular node who have an indication for permanent pacing, HBP may be considered to maintain physiologic ventricular activation (class of recommendation: IIb (weak strength of recommendation), level of evidence: B-R (moderate-quality evidence from one or more randomised-controlled-trials)).

ESC Leitlinie 2021:

HBP was first recommended in the Guidelines of the European Society for Cardiology in 2021 for the following indications [15]:

I-Empfehlung: HBP-Gerätprogrammierung

- In patients treated with HBP, device programming tailored to specific requirements of HBP is recommended (Class: I[11], Level: C[12]).

IIa-Empfehlung: als Alternative zur Koronarsinusleitung (kard. Resynchronisation)

- In cardiac resynchronisation therapy candidates in whom coronary sinus lead implantation is unsuccessful, HBP should be considered as a treatment option along with other techniques such as surgical epicardial lead (Class: IIa[13], Level: B[14]).

IIa-Empfehlung: zusätzlich rechtsventrikuläre Leitung als „Backup"

- In patients treated with HBP, implantation of a right ventricular lead used as "backup" for pacing should be considered in specific situations (e.g. pacemaker-dependency, high-grade atrioventricular block, infranodal block, high pacing threshold, planned atrioventricular node ablation), or for sensing in case of issues with detection, e.g. risk of ventricular undersensing or oversensing of atrial/His potentials (Class: IIa[13], Level: C[12]).

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8 This section addresses the EUnetHTA Core Model® domain CUR.

9 The class of recommendation indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk.

10 The level of evidence rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources.

11 Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective (is recommended or is indicated).

12 Level C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

13 Class IIa: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; weight of evidence/opinion is in favour of usefulness/efficacy (should be considered).

14 Level B: Data derived from a single randomised clinical trial or large non-randomised studies.

- HBP with a ventricular backup lead may be considered in patients in whom a "pace-and-ablate" strategy for rapidly conducted supraventricular arrhythmia is indicated, particularly when the intrinsic QRS is narrow (Class: IIb[15], Level: C[12]).

IIb-Empfehlung: Pat. mit Indikation zur „pace-and-ablate" Strategie

- HBP may be considered as an alternative to right-ventricular pacing in patients with atrioventricular block and LVEF >40%, who are anticipated to have >20% ventricular pacing (Class: IIb[15], Level: C[12]).

IIb-Empfehlung: mögliche Alternative zu RVP bei AV-Block mit LVEF >40 %

According to the submitting hospital, HBP has been used 25 times in the previous year with an estimated use of 40 times per year in the submitting hospital and an estimated use of 200 times per year in Austria[16].

HBP in Ö, Vorjahr: 25 Anwendungen

1.3 Features of the intervention[17]

Cardiac pacemakers can be classified according to [16]:

Einteilung kardialer Schrittmacher: „NBG-Klassifikation"

- **duration**: temporary (with an external pacemaker) or permanent (with an implantable pacemaker),
- **paced chambers**: none, atrium, ventricle or dual (atrium and ventricle),
- **sensed chambers**: none, atrium, ventricle or dual (atrium and ventricle),
- **response to sensing**: none, triggered, inhibited or dual (triggered and inhibited),
- **rate modulation**,
- **multisite pacing**: none, atrium, ventricle or dual (atrium and ventricle)

This classification is reflected in the NBG-coding system for pacing types implemented in 1988. However, as a newer modality of cardiac pacing, the His bundle pacing is not accurately reflected in this NBG classification system; the closest approximation is ventricular pacing [17].

NBG-Klassifikation nicht adäquat für HBP; am ehesten ventrikulärer Schrittmacher

Intervention: His bundle pacing

Temporary HBP in patients was reported as early as 1970 [18]. The first permanent pacing of the His-bundle was reported in 2000 [4], with a rapidly growing number of HBP implantations by the mid-2010s [19][18].

HBP temporär seit 1970; erste permanente Anwendung 2000

A permanent pacemaker at the His-bundle aims to produce normal physiological ventricular activation. HBP belongs to the conduction system pacing therapies, which follow the approach of directly pacing the cardiac conduction system. These conduction system pacing therapies are also referred to as physiological pacing therapies and are a relatively new type of pacemaker therapy. [1].

Ziel: physiologische Erregungsbildung

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[15] Class IIb: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; usefulness/efficacy is less well established by evidence/opinion (may be considered).

[16] **A0011** – How much is His bundle pacing utilised?

[17] This section addresses the EUnetHTA Core Model® domain TEC.

[18] **B0001** – What is His bundle pacing and what are the comparator(s)?

Schrittmacherdraht am His-Bündel fixiert; Durchführung in Lokalanästhesie in Herzkatheterlaboren

For this, the His-Purkinje system (see Figure 1-1 [20]) is paced, as opposed to ventricular pacing. First, a pacing lead is inserted through a vein into the heart (under fluoroscopic guidance and continuous electrocardiogram monitoring). Then, the pacing lead is positioned and attached to the His-bundle, with the lead connected to the pacemaker generator. The procedure is usually done under local anaesthesia in a cardiac catheterisation laboratory. The claimed benefit of HBP is to improve cardiac function without the requirement of an additional left ventricular lead, pacing only a single site [1][19].

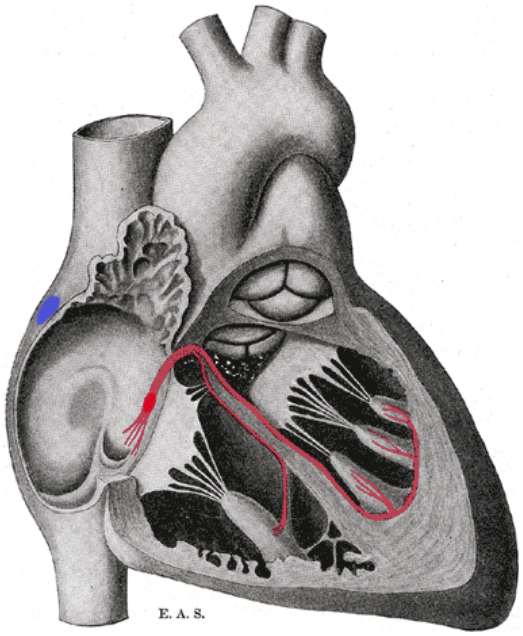

Figure 1-1: Schematic representation of the His-bundle (represented in red) (Source: [20]).

2 Hersteller: Medtronic Inc, Abbott Laboratories

Currently, there are two His-bundle pacing systems on the market: The Select-Secure model 3830® by Medtronic Inc. [21] and the Agilis HisPro® by Abbott Laboratories [22][20].

Comparators: Right-ventricular or bi-ventricular pacing

Komparatoren: rechtsventrikuläre oder biventrikuläre Schrittmachersysteme

Other pacing therapies are right ventricular pacing (RVP) or biventricular pacing (BVP) [23]. Opposed to His-bundle pacing, the electrode is located in either the right atrium or ventricle (for RVP) or additionally in the sinus coronarius (for BVP) [24]. Some of the possible negative consequences of these "conventional" ventricular pacing techniques include tricuspid regurgitation, endocarditis and pacemaker induced heart failure [25]. For an overview of RVP (single lead or double lead), see Figure 1-2 [26].

[19] **B0002** – What is the claimed benefit of His bundle pacing in relation to the comparator(s)?

[20] **B0003** – What is the phase of development and implementation of His bundle pacing and the comparator(s)?

weitere physiologische Schrittmacher: Linksschenkel-Stimulation (nicht Teil des Assessments)

Among the newer conduction system pacing therapies, another subgroup of pacing has been emerging recently: left bundle branch pacing/left bundle branch area pacing (LBBP/LBBAP). LBBP is defined as the capture of the left bundle branch via transventricular septal approach to maintain synchrony of the left ventricle with lower pacing thresholds [27]. However, the evaluation of LBBP is beyond the scope of this assessment.

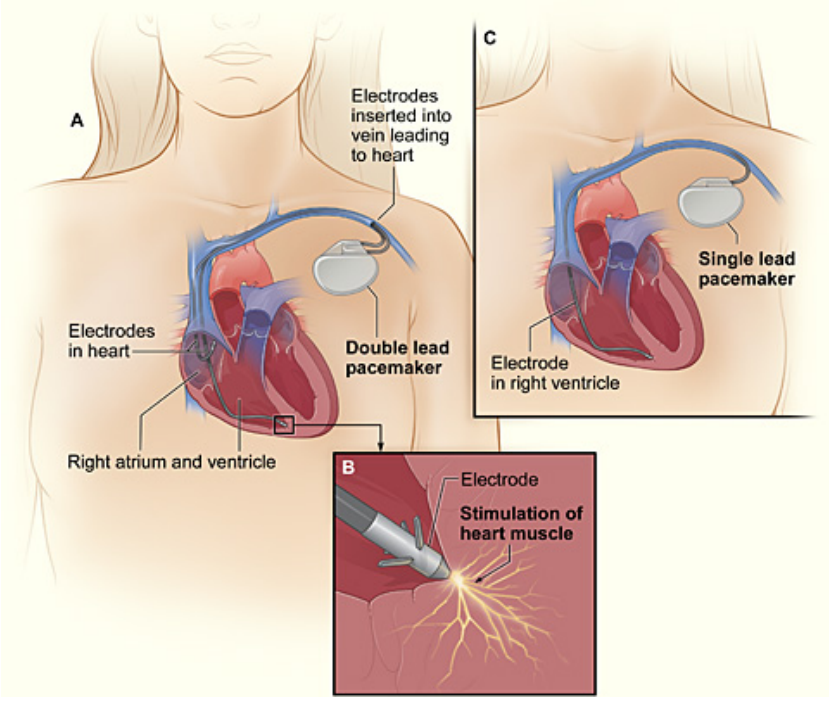

Figure 1-2: Single lead and double lead pacemaker with electrode location (Source: [26])

An overview of the characteristics of the intervention and comparison technologies is given in Table 1-1.

Table 1-1: Features of the intervention and comparators [28, 29]

	Intervention/Technology	Comparator	Comparator
Name	His bundle pacing (HBP)	Right ventricular pacing (RVP)	Biventricular pacing (BVP)
Proprietary name	SelectSecure, model 3830® [21] Agilis HisPro® [22]	-	-
Manufacturer	Medtronic Inc. Abbott Laboratories	-	-
Indications	■ Heart failure, ■ cardiac conduction system disease, ■ atrial fibrillation	■ Sinus node dysfunction, ■ acquired atrioventricular block, ■ chronic bifascicular block, ■ after acute phase of myocardial infarction, ■ neurocardiogenic syncope and hypersensitive carotid sinus syndrome, ■ post-cardiac transplantation, ■ hypertrophic cardiomyopathy, ■ pacing to detect and terminate tachycardia, ■ cardiac resynchronisation therapy in patients with severe systolic heart failure	
Contraindications	■ Local infection at the implantation site ■ Active systemic infection with bacteremia ■ Severe bleeding tendencies (relative contraindication) ■ Active anticoagulation therapy (relative contraindication ■ Severe lung disease and positive end-expiratory pressure ventilation (relative contraindication for the internal jugular and subclavian access)		

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

personelle Anforderungen

According to the submitting hospital, the personnel requirements to administer HBP are an experienced surgeon, a surgical technologist, a radiologic technologist, a cardiologic technologist, and nursing staff with sedation expertise[21].

technische Anforderungen

An operating room equipped with fluoroscopy screening and an electroanatomical mapping system in an internal medicine department are needed to use HBP[22].

Setting, benötigte Materialien

According to the submitting hospital, HBP is to be used in the inpatient setting with an occupancy period of two to four days (in usual cases three days) and a frequency of use of one to two times (in usual cases one time). The procedure unit is defined as per application. In addition to the standard material of a pacemaker, the following materials are required as supplies: special His-sheath, special pacemaker lead for His stimulation, patches for 3D-system, diagnostic 4-pole JSN-catheter, medical clips[23].

[21] **B0004** – Who administers His bundle pacing and the comparator(s) and in what context and level of care are they provided?

[22] **B0008** – What kind of special premises are needed to use His bundle pacing and the comparator(s)?

[23] **B0009** – What supplies are needed to use His bundle pacing and the comparator(s)?

Regulatory & reimbursement status

CE-Zertifizierung: erstmals 2003

The CE mark for the SelectSecure model 3830® lead by Medtronic Inc. was first issued on January 31st in 2003. The last reissue was on February 1st 2018, and the CE certificate is valid until February 1st 2023. The CE mark for the Agilis HisPro® by Abbott Laboratories was issued on March 31st 2021, and the CE certificate is valid until May 26th 2024. The formal indications for HBP are (1) high-grade atrioventricular block with an expected >20% ventricular stimulation, (2) first-degree atrioventricular block with a long PQ-interval, (3) atrioventricular node ablation due to atrial fibrillation and (4) upgrade for cardiomyopathy requiring a pacemaker. Further, HBP can be used in the context of cardiac resynchronisation therapy (CRT) [30][24].

LKF-Katalog in Ö, 2022: HBP kein Eintrag; Komparatoren (RVP, BVP, CRT) gelistet

in DE: Code 5-377.n
in CH: Code 39.A1.21

In the Austrian catalogue for medical procedures (LKF-catalogue), HBP is not included. Comparator procedures (RVP, BVP, CRT) are included in the 2022 edition and, as such, are reimbursed [31][25]. In other European countries, HBP is listed in some catalogues: In Germany, the procedure code "OPS code 5-377.n – System for stimulation of the conduction system" covers conduction system pacing, stimulation of the His bundle (His bundle pacing) or stimulation of the Tawara branch [32]. In Switzerland, the procedure code "CHOP code 39.A1.21 – Placement of an electrode for the direct stimulation of the intracardiac conduction system (His bundle pacing)" was added to the medical procedure catalogue in 2022 [33][25].

[24] **A0020** – For which indications has His bundle pacing received marketing authorisation or CE marking?

[25] **A0021** – What is the reimbursement status of His bundle pacing?

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Compared with other types of permanent pacing in patients with cardiac conduction system disease, bradycardic atrial fibrillation, or cardiac resynchronisation in patients with heart failure, is His bundle pacing more effective and safer in terms of patient-relevant outcomes and adverse events?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 2-1.

Table 2-1: Inclusion criteria

Population	Patients requiring a permanent pacemaker or cardiac resynchronisation, as an alternative to other types of pacemaker or cardiac resynchronisation therapy devices, in the following indications: ■ in patients with heart failure ■ in patients with cardiac conduction system disease (e.g., atrioventricular block), with left ventricular ejection fraction above 40% and anticipated pacing >20%[26]. ■ in patients with atrial fibrillation and "ablate and pace" strategy **Rationale:** Appropriate patient populations were selected according to the European Society of Cardiology (ESC) Guidelines on cardiac pacing and cardiac resynchronisation therapy [15] **ICD-10-GM:** I50.12, I50.13, I48.0, I48.1, I48.2, I44.1, I44.2 **MeSH Terms:** Heart failure [C14.280.434], Atrial Fibrillation [C14.280.067.198, C23.550.073.198], Atrioventricular block [C14.280.067.558.230, C14.280.123.500.230, C23.550.073.425.062], Cardiac Conduction System Disease [C14.280.123]
Intervention	Permanent His bundle pacemaker (HBP) implantation **Procedure description:** a permanent pacemaker at the His bundle is implanted with the aim of producing normal physiological ventricular activation via the His-Purkinje system. The procedure is usually done under local anaesthesia in a cardiac catheterization laboratory. **Product Names:** ■ 69 cm Select Secure 3830 pacing lead® (Medtronic Inc.) ■ Agilis HisPro® (Abbot Laboratories) **MeSH Terms:** Pacemaker, Artificial [E07.305.250.750], Cardiac Pacing, Artificial [E02.331.200], Cardiac Resynchronization Therapy Devices [E07.305.250.750.500]
Control	Standard care (e.g. right-ventricular or biventricular cardiac resynchronisation therapy (RiV-CRT or BiV-CRT), right-ventricular pacing) **Exclusion:** His-bundle pacing as both intervention and comparator (e.g., studies comparing selective to non-selective his-bundle pacing or atrial-side to ventricular-side his-bundle pacing), left bundle branch pacing **Rationale:** Appropriate comparators were selected according to the European Society of Cardiology (ESC) Guidelines on cardiac pacing and cardiac resynchronisation therapy [15] **MeSH Terms:** Pacemaker, Artificial [E07.305.250.750], Cardiac Pacing, Artificial [E02.331.200], Cardiac Resynchronization Therapy Devices [E07.305.250.750.500]

[26] The American Heart Association guidelines recommend HBP in patients with an LVEF between 36% to 50% and atrioventricular block, who have an indication for permanent pacing and are expected to require ventricular pacing >40% of the time. Study populations fulfilling these criteria were also eligible for inclusion.

Outcomes	
Efficacy	■ Quality-of-life (measured using a validated instrument) ■ New York Heart Association (NYHA) Class ■ Implantation success rate ■ Electrocardiographic parameters (QRS duration, pacing threshold) ■ Echocardiographic parameters (left ventricular ejection fraction (LVEF)) ■ B-type natriuretic peptide (BNP) ■ Medication use **Rationale:** Appropriate clinical efficacy outcomes were selected according to a systematic review by the National Institute for Health and Care Excellence (NICE) on permanent HBP implantation for treating heart failure [1], as well as the Cardiology Audit and Registration Data Standards (CARDS) [34], identified by screening the COMET Initiative database [35]
Safety	■ Mortality ■ Major adverse cardiovascular events (MACE) ■ Serious adverse events (SAE) ■ Adverse events (AE) ■ Heart failure-related hospitalisations ■ New-onset atrial fibrillation ■ Increase in capture threshold ■ Infection ■ Repeated procedures **Rationale:** Appropriate clinical safety outcomes were selected according to a systematic review by the National Institute for Health and Care Excellence (NICE) on permanent HBP implantation for treating heart failure [1], as well as the Cardiology Audit and Registration Data Standards (CARDS) [34], identified by screening the COMET Initiative database [35]
Study design	
Efficacy	■ Randomised controlled trials ■ Prospective non-randomised controlled trials/prospective comparative studies, with low or moderate risk of bias (according to ROBINS-I assessment tool [36]) **Exclusion:** Retrospective studies, single-arm studies (e.g. case series)
Safety	■ Randomised controlled trials ■ Prospective non-randomised controlled trials/prospective comparative studies/retrospective comparative studies, with low or moderate risk of bias (according to ROBINS-I assessment tool [36]). **Exclusion:** Retrospective comparative studies <500 patients, single-arm studies (e.g. case series)
Language	English, German
Publication period	No restriction

3 Methods

3.1 Research questions

Forschungsfragen nach EUnetHTA

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customized to the specific objectives of this assessment [37]. These research questions are listed as the **Fehler! Verweisquelle konnte nicht gefunden werden.** in the Appendix, Table A-9, Table A-10, Table A-11, and Table A-12.

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische vorab-Suche nach systematischen Reviews (SRs) zur Identifikation von Primärstudien

A systematic literature search for relevant systematic reviews was conducted in December 2021 in the bibliographic database Embase. The search terms "His bundle" or "His bundle pacing" were used, and the filters for systematic reviews, meta-analyses or Cochrane reviews were applied. This search resulted in 32 hits. The specific search strategy can be found in the Appendix.

Auswahl eines SRs mit hoher Qualität

The systematic reviews were then screened regarding their match to the current PICO question by two independent researchers (RJ, BW). The aim was to select the most recent high-quality systematic review for the purpose of identification of potentially relevant primary studies.

SR 2018: Qualitätsbewertung durch AMSTAR-II

One systematic review, published in 2018 [4], was identified as the most recent systematic review that covered all potential patient populations for His-bundle pacing. Next, the quality of this systematic review was assessed by two independent researchers (RJ, BW) using the AMSTAR-II critical appraisal tool [38], with a particular focus on the quality of the search methodology.

systematische Literatursuche in 4 Datenbanken

For the time period not covered by the chosen systematic review, a further systematic literature search was conducted in December 2021 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- HTA-INAHTA

Zeitraum: 2017-2021, deutsche und englische Literatur

The systematic search was limited to the years May 2017 to December 2021 and to articles published in English or German, resulting in 1,211 records identified through database searching. After deduplication, overall, 807 citations were included. The specific search strategy employed can be found in the Appendix.

insgesamt 833 Publikationen identifiziert

The 26 included studies from the systematic review [4] were added to the records identified through database searching, resulting in overall 833 hits after deduplication. The aim of this approach was to include all potentially relevant articles that were published before May 2017.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 17.01.2021 resulting in 87 potential relevant hits.

Hersteller: 104 Publikationen

Manufacturers from the most common products (SelectSecure, model 3830®, Medtronic Inc. [21], Agilis HisPro®, Abbott Laboratories [22]) submitted a total of 104 publications of which no new citations were identified.

3.2.2 Flow chart of study selection

Literaturauswahl

Overall 833 hits were identified. The references were screened by two independent researchers, and in case of disagreement, a third researcher was involved in solving the differences. The selection process is displayed in Figure 3-1.

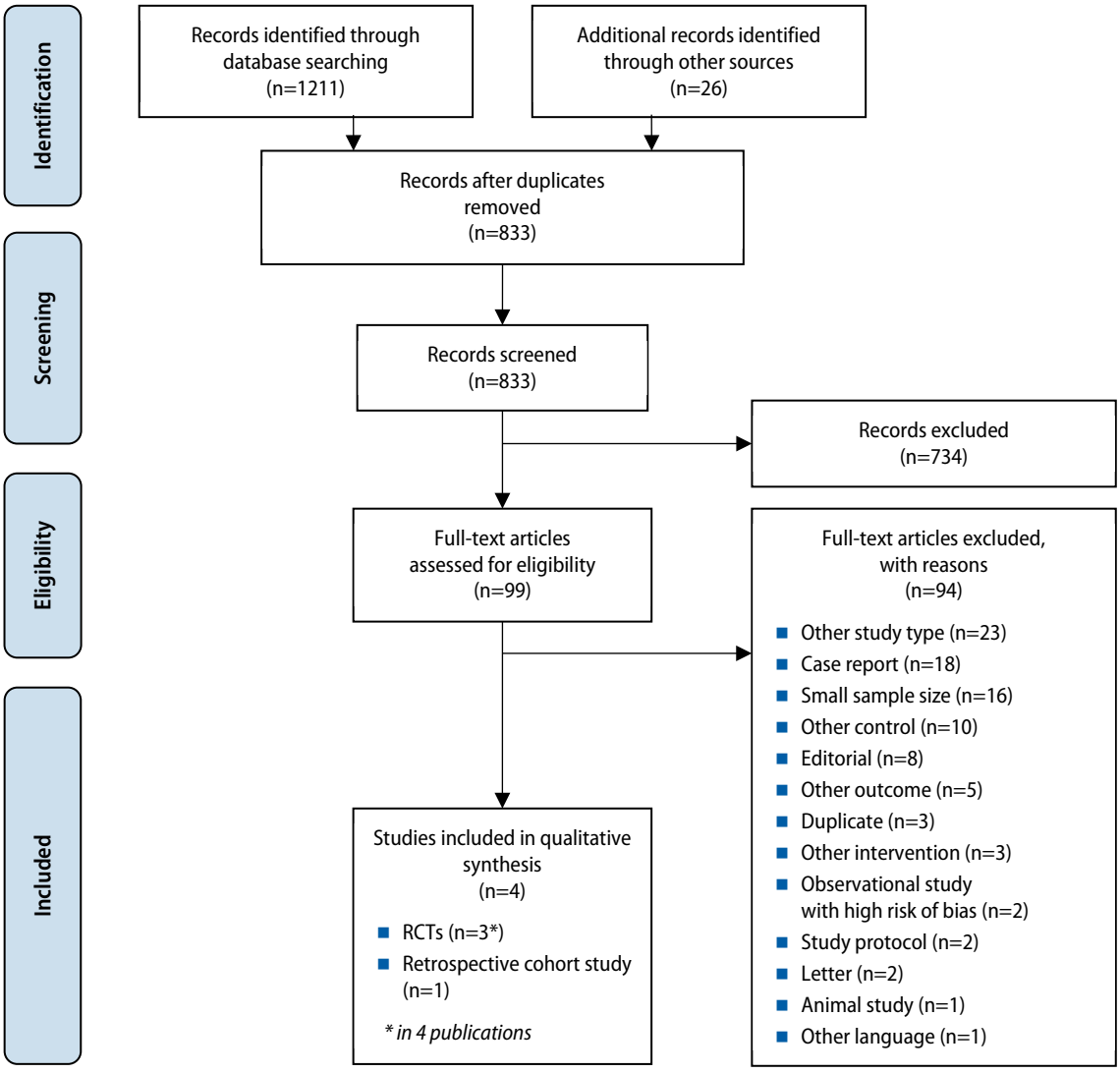

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Datenextraktion aus Studien

Relevant data from eligible primary studies were systematically extracted into data-extraction tables. One researcher (RJ) extracted the data, and another researcher (BW) checked and verified the extracted data.

Qualitätsbeurteilung der Studien mit Cochrane RoB Tool (v.2) und ROBINS-I

Two independent researchers (RJ, BW) systematically assessed the risk of bias (RoB) of the included studies using the Cochrane RoB v.2 tool (for RCTs) [39] and the ROBINS-I tool (for non-randomised controlled studies) [36], Table A-3, Table A-4.

3.2.4 Synthesis

qualitative Synthese der Evidenz

A qualitative synthesis of the evidence was performed. The research questions were answered in plain text format.

Zusammenfassung der Ergebnisse mit GRADE

We further used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) scheme to synthesise the identified evidence [40]. GRADE evidence tables and a GRADE summary of findings table were compiled.

All discrepancies were resolved by consensus. In case of disagreement, a third researcher (GG) was involved.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

The following outcomes were defined as *crucial* to derive a recommendation:

- Quality-of-life
- New York Heart Association (NYHA) Functional Classification

entscheidungsrelevante Endpunkte für klin. Wirksamkeit: Lebensqualität (QoL), Funktionsklasse nach NYHA

The outcomes defined as crucial to derive a recommendation are considered the most relevant to heart failure, cardiac conduction system disease or atrial fibrillation patients. They reflect the claims that HBP can potentially improve quality-of-life and symptoms of heart failure according to the NYHA functional class [41].

The **quality-of-life** is usually assessed using the Short Form Health Survey questionnaire "SF-36" and covers eight scales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health [42]. One of the included RCTs designed a quality-of-life questionnaire referring to the SF-36 scale, covering four domains: physiological function, psychological function, social relations and physical pain [43].

QoL: SF-36 Fragebogen bestehend aus 8 Domänen

The **NYHA functional classification** is a 4-level category to describe the severity of heart failure according to physical activity and symptoms in regard to breathing and/or angina symptoms (see Table 4-1). The NYHA functional class was assessed in all three included RCTs for effectiveness [43-46].

4 Funktionsklassen für Schweregrad der Herzinsuffizienz

Table 4-1: Overview of symptoms per New York Heart Association Functional Class [5]

NYHA Class	Symptoms
Class I	Known heart disease, but no limitation of physical activity.
Class II	No complaints at rest, but limitation of moderate physical activity (e.g. fatigue, palpitation or dyspnea when climbing two flights of stairs).
Class III	No complaints at rest, but marked limitation of light physical activity (e.g. fatigue, palpitation or dyspnea when climbing one flight of stairs).
Class IV	Symptoms of heart failure at rest, increasing discomfort in any physical activity.

Further outcomes were defined as *important*, but *not crucial* to derive a recommendation:

weitere wichtige Endpunkte für klin. Wirksamkeit:

- Implant success
- Electrocardiographic parameters
- Echocardiographic parameters
- Laboratory parameters

The outcome **implant success** describes the rate at which the intervention was successfully implanted and was reported in two of the included RCTs [44-46]. The given definition of implant success differed among the included studies: In one RCT, implant success was defined as implantation with the capture of the left bundle sustained through 6 months of follow-up [46]; in the other RCT, it was defined as successful implantation with correction of QRS [44, 45].

Implantationsrate (unterschiedlich definiert)

EKG-Parameter: Dauer des QRS-Komplexes

The **electrocardiographic parameters** describe the measurements of the electrocardiogram (ECG), such as the QRS duration in milliseconds. The QRS duration (before and after pacing) was reported in all three included RCTs [43-46].

Echokardiografie: linksventrikuläre Ejektionsfraktion

The **echocardiographic parameters** describe the measurements during the echocardiographic examination of a patient. The left ventricular ejection fraction (LVEF) was chosen as the parameter of interest because it is of importance in classifying the severity of heart failure according to the 2021 ESC guidelines [6]. The LVEF (before and after pacing) was reported in all three included RCTs [43-46].

Laborwert: NT-proBNP

For **laboratory parameters**, B-type natriuretic peptide (BNP) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) were chosen as the parameters of interest, as they provide diagnostic and prognostic value in regard to heart failure [5]. NT-proBNP is a natriuretic hormone released primarily from the heart ventricles. In patients with heart failure and left ventricular dysfunction, plasma NT-proBNP rises more than BNP. NT-proBNP was reported in one of the included RCTs [46].

4.1.2 Outcomes safety

entscheidungsrelevante Endpunkte für Sicherheit

The following outcomes were defined as *crucial* to derive a recommendation:

- Mortality
- Major adverse cardiac events (MACE)
- Serious adverse events (SAE)
- Adverse events/Complications
- Hospitalisations
- Increase in capture threshold

All outcomes regarding safety were defined as *crucial* to derive a recommendation in patients with heart failure, cardiac conduction system disease or atrial fibrillation.

Mortalität: 2 RCTs, und Kohortenstudie

Mortality describes the rate of patients that died during the study period and is considered a highly patient-relevant outcome measure when assessing the safety of cardiac pacemakers. Mortality was reported in two of the included RCTs [44-46] as well as in the observational cohort study [3].

schwerwiegende kardiovaskuläre Nebenwirkungen (MACE): nicht berichtet

MACE is a composite outcome frequently used in cardiovascular research. However, there is no unified definition of this outcome. Multiple adverse events included are heart failure, nonfatal myocardial infarction, recurrent angina pain, non-fatal stroke, rehospitalisation for cardiovascular-related illness, repeat percutaneous coronary intervention, coronary artery bypass grafting and all-cause mortality [47]. None of the included studies for safety reported on MACE. However, the observational cohort study described a composite outcome of all-cause mortality, heart failure hospitalisations or upgrade to biventricular pacing [3].

Definitionen (schwerer) unerwünschter Wirkungen der MDCG

The Medical Device Coordination Group guideline on reporting SAE or AE for medical devices defines SAE and AE as following [48]:

SAE is any adverse event that led to a) death, b) serious deterioration in the health of the subjected that resulted in any of the following: i) life-threatening illness or injury, ii) a permanent impairment of a body structure or a body

function, iii) in-patient hospitalisation or prolongation of existing hospitalisation, iv) medical or surgical intervention to prevent a life-threatening illness or injury, v) chronic disease; c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

None of the included studies for safety reported a composite outcome for SAE.

AE is any medical occurrence, unintended disease, injury, or clinical signs (including an abnormal laboratory finding), in users (whether or not related to the investigational medical device). Both anticipated as well as unanticipated events are included; events relating to the investigational device or in relation to the procedures involved are also included.

unerwünschte Ereignisse/Komplikationen: in 3 RCTs, und Kohortenstudie

AE and complications were reported in all three of the included RCTs [43-46] and in the observational cohort study [3]. Hemopneumothorax, pericardial effusion or catheter electrode displacement were reported in one RCT [43]. Ventricular tachycardia, ventricular fibrillation or infectious complications were reported in another RCT [44, 45]. Periprocedural complications were reported in two RCTs [44-46]. In the included cohort study, upgrade to biventricular pacing, the requirement of ventricular lead revision, pericardial effusion, infection necessitating device or lead removal or premature battery depletion were reported [3].

Hospitalisierungen: in 2 RCTs

Hospitalisations is the proportion of patients being admitted to the hospital for any condition requiring treatment. Hospitalisations were reported in two of the included RCTs [44-46], although one of these RCTs only reported the total number of hospitalisations across both the intervention and the control group [44, 45].

Zunahme der Schrittmacherschwelle: in 3 RCTs, und Kohortenstudie

The **increase in capture threshold** describes the difference in pacing threshold when using a permanent cardiac pacemaker. The pacing capture threshold can be measured in volts (V), and pulse width in milliseconds (ms) is defined as the minimum amount of energy needed to capture the myocardial tissue electrically. When the pacing threshold is high, the battery life of the pacemaker can be adversely shortened [49]. The pacing capture threshold was assessed in all three RCTs [43-46] and in the observational cohort study [3].

4.2 Included studies

4.2.1 Included studies effectiveness

inkludierte Studien für klin. Wirksamkeit: 3 RCTs

In order to assess the effectiveness of HBP in patients with heart failure, cardiac conduction system disease or atrial fibrillation, we identified three RCTs to be included [43, 44, 46]. For one of the RCTs [44], we identified a research letter (with an intention-to-treat analysis) in addition to the full-text publication (with a per-protocol analysis) [45]. The body of evidence of all three RCTs [43-46] will be described in this evidence synthesis.

in allen 3 RCTs: Indikation Herzinsuffizienz

In all three RCTs [43-46], patients with heart failure were enrolled to be treated with HBP. In one of the RCTs [43], patients with atrial fibrillation were additionally enrolled. For the indication of cardiac conduction system disease, no RCT was identified.

verwendetes Produkt: Medtronic His C304/C315, Medtronic 3830 SelectSecure

In all three RCTs, the product used for HBP was the Medtronic His-sheath® (C304 or C315) and the Medtronic 3830 SelectSecure lead® [43-46]. In one RCT, the comparator was RVP [43], whereas, in the other two RCTs, the comparison was BVP [44-46].

Ein- und Ausschlusskriterien der RCTs

Differences between the RCTs in the inclusion criteria were a higher age (between 40 and 80 years) in one RCT [43] compared to ≥18 years in two RCTs [44-46]. For two RCTs [43-45], all patients with heart failure were included, whereas one RCT only included heart failure patients with LVEF below 35% [46]. One RCT included patients with NYHA grade II-III [43], another RCT included patients with NYHA grade II-IV [46]. In all three RCTs, indication for a permanent pacemaker was a requirement [43-46]. While one RCT included both patients with heart failure or atrial fibrillation [43], another RCT had permanent atrial fibrillation as an exclusion reason [46]. Further exclusion criteria were severe heart valve disease [43], unstable angina pectoris [43], acute myocardial infarction [43], expected survival time less than 12 months [43], severe kidney disease [46], coronary artery bypass graft within three months before assessment [46], pregnancy [44, 45], or inability to participate due to unwillingness or medical/psychiatric co-morbidity [44-46]. In all three RCTs, an existing cardiac resynchronisation device was an exclusion criterion [43-46].

insgesamt 163 Pts eingeschlossen (Interventionsgruppe: 82; Kontrollgruppe: 81)

The three RCTs accounted for a total of 163 patients (Intervention group: 82 patients/Control group: 81 patients) [43-46]. In two RCTs, there was no statistically significant difference in age among groups [43-45]. In one RCT, the mean age in the intervention group was 63.8 ± 9.4 compared to 67.7 ± 9.0 in the control group, with no p-value reported. In two RCTs, there was no statistically significant gender difference between groups [43-45]. In one RCT, there was a statistically significant lower proportion of male participants in the study group (42% vs 77%, $p<0.05$) in the per-protocol analysis. In the intention-to-treat analysis, there were fewer male participants in the intervention group (56% vs 72%), with no p-value reported [46].

Follow-up: 6 Monate (1 RCT), bis 12 Monate (2 RCTs)

The follow-up of included was 12 months in one RCT [43] and six months in another RCT [46]. The follow-up of the third RCT was dependent on the assessed outcome: 6 months for QRS duration and LVEF change, and 12 months for cardiovascular hospitalisation or death [44, 45].

Study characteristics and results of included studies are displayed in detail in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

4.2.2 Additional included studies safety

für Sicherheitsendpunkte inkludiert: 1 Kohortenstudie (zstl. zu 3 RCTs)

To assess the safety of HBP, we identified one additional observational study that met our inclusion criteria [3]. This study was a registry-based retrospective cohort study and assessed the use of HBP in comparison to RVP. From the three RCTs [43-46]described in 4.2.1, safety outcomes were also included in the assessment.

Indikation: Bradykardie (Erregungsleitungsstörung)

765 Pts (IG: 332, KG: 433)

In the additionally included registry-based retrospective cohort study, patients with bradycardia (cardiac conduction system disease) were enrolled [3]. In this study, 765 patients were analysed, with 332 patients that received treatment with HBP and 433 patients that received treatment with RVP [3].

The inclusion criteria were patients ≥18 years of age that had a requirement for de novo permanent pacemaker implantation for bradycardia. Patients that had undergone cardiac resynchronisation therapy or had an existing cardiac implantable electronic device were excluded from the study.

durchschnittliches Alter: IG: 74,8 J; KG: 76,4 J

Vorhofflimmern: IG: 56,9 %; KG: 44,6 %

There was no statistically significant difference for age (74.8 ± 11.0 vs 76.4 ± 11.3, p>0.05), but for gender (60.2% male vs 52.4% male, p<0.05) between the HBP and the RVP group. There was a statistically significantly higher proportion of patients with atrial fibrillation in the study group (56.9% vs 44.6%, p<0.01) and a statistically significant shorter duration of QRS in the study group (104.5 ± 24.5 vs 110.5 ± 28.4, p<0.01). The other reported baseline characteristics and comorbidities had no statistically significant difference between groups (active smokers, hypertension, diabetes, hyperlipidemia, coronary artery disease, chronic kidney disease, ischemic stroke, heart failure, beta-blocker medication, baseline ejection fraction, ventricular pacing burden, sinus node dysfunction, atrioventricular conduction disease, dual-chamber permanent pacemaker.

Subgruppenanalyse: Pts mit LVEF <50 %

The cohort study also provided an analysis of a subgroup of patients with baseline LVEF <50%, with 37 patients in the study group and 62 patients in the control group. In this subgroup, a statistically significantly higher proportion of patients with atrial fibrillation (81% vs 58%, p<0.01) and a statistically significant higher percentage of baseline ejection fraction (38 ± 7 vs 36 ± 8, p<0.01) was present.

Follow-up: 23.9 ± 13.9 Monate

The mean follow-up of the entire cohort was 725 ± 423 days (23.9 ± 13.9 months), with no statistically significant difference between the study group (24.8 months) and control group (21.3 months), p<0.05.

Study characteristics and results of included studies are displayed in detail in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

4.3 Results

Mortality

Mortalität: 2 RCTs ohne p-Wert; Kohortenstudie ohne stat.sign. Unterschied

The *crucial* outcome **mortality** was reported in two RCTs [44-46] and in the retrospective cohort study [3]. The two RCTs did not report a p-value for the difference in mortality between HBP and BVP. The retrospective cohort study did not find a statistically significant difference in mortality between HBP and RVP[27].

2 RCTs: IG: 0 %-12,5 %; KG: 0 %

Kohortenstudie: IG: 17,2 %; KG: 21,4 %, Hazard Ratio: 0,728 (CI: 0,523-1.014)

Mortality at six months was reported in one RCT [46]. In this RCT, no deaths were reported in either the study group (n=25) or the control group (n=25), with no reported p-value. In the other RCT, mortality was reported at twelve months [44, 45]. In the intention-to-treat analysis, two deaths were reported across both groups, although without information on which study arm the deaths occurred [45]. In the per-protocol analysis, two patients in the study group (of 16 patients: 12.5%) died compared to no patients in the control group (of 24 patients: 0%), p-value not reported.

[27] **D0001** – What is the expected beneficial effect of His-bundle pacing on mortality?

Mortality at 24 months was reported in the retrospective cohort study [3], without statistical significance: 17.2% of patients in the intervention group died compared to 21.4% of patients in the control group. The hazard ratio was reported to be 0.728 (95% CI: 0.523-1.014), with a $p>0.05$.

For the effect of HBP on mortality due to causes other than heart failure, cardiac conduction system disease or atrial fibrillation, no evidence was found[28].

Morbidity

The *crucial* outcome **hospitalisations** and the *important* outcomes of **implant success**, **electrocardiographical parameters** (QRS duration), **echocardiographical parameters** (LVEF) and **laboratory parameters** (NT-proBNP) were considered when answering the research questions on morbidity[29].

Hospitalisierungen: 2 RCTs ohne p-Wert; Kohortenstudie mit stat.sign. Unterschied

Hospitalisations were reported in two RCTs [44-46] and in the retrospective cohort study [3]. In the RCTs, no p-value was reported. In the retrospective cohort study, hospitalisations were more common in the control group than in the intervention group with statistical significance.

2 RCTs: IG: 0 %; KG: 8 %

In one RCT, hospitalisations at six months were none in the study group (of 25 patients: 0%) compared with two cases in the control group (of 25 patients: 8%), p-value not reported. The reasons for the hospitalisations were dislodgement of the left ventricular lead in one case and device endocarditis in the other case [46]. In another RCT, hospitalisations at twelve months were reported for a total of six patients across both groups (of 41 patients: 15%). Hospitalisations for the individual study arms were not reported. The reasons for these six hospitalisations were heart failure in three cases (7%), periprocedural in two cases (5%) or atrial fibrillation requiring cardioversion in one case (2%) [44, 45].

Kohortenstudie: IG: 12,4 %; KG: 17,6 %; Hazard Ratio: 0,642 (CI: 0,439-0,939)

In the retrospective cohort study, hospitalisations due to heart failure were reported at 24 months. In the intervention group, 12.4% of patients compared to 17.6% of patients in the comparison group were hospitalized during the study period, with a hazard ratio of 0.642 (95% CI: 0.439-0.939); this finding was statistically significant ($p<0.05$).

Implantationsrate: 2 RCTs ohne p-Wert

Implant success was reported in two of the RCTs [44-46]. While the implant success rate was lower in the study group in comparison to the control group in both RCTs, the studies did not report p-values for these findings. The RCTs also used differing definitions for successful implantation.

Intention-to-treat: IG: 52 %-72 %; KG: 70 %-96 %

Per-protocol: IG: 73 %; KG: NR

In one RCT, implantation was considered successful when the left bundle capture was sustained through 6 months of follow up. In the intention-to-treat analysis, 18 patients (of 25 patients, 72%) compared to 24 patients (of 25 patients, 96%) had successful implantation, with no reported p-value. In the per-protocol analysis, implantations for 19 patients (of 26 patients, 73%) in the study group were successful, with values for the control group or p-values not reported [46]. In the other RCT, implantation was considered successful when there was a correction of QRS. In the intention-to-treat analysis, eleven pa-

[28] **D0003** – What is the effect of His-bundle pacing on the mortality due to causes other than heart failure, cardiac conduction system disease or atrial fibrillation?

[29] **D0005** – How does His-bundle pacing affect symptoms and findings (severity, frequency) of heart failure, cardiac conduction system disease or atrial fibrillation? & **D0006** – How does His-bundle pacing affect progression (or recurrence) of heart failure, cardiac conduction system disease or atrial fibrillation?

tients (of 21 patients, 52%) in the study group compared to 14 patients (of 20 patients, 70%) in the control group had successful implantation (without p-value) [44, 45].

Gründe für fehlgeschlagene Implantationen

In the first RCT, the reasons for failure in the study group were high pacing thresholds (His location found, but the threshold for capturing the left bundle required >5-10 V) in six patients (24%) or not capturing the left bundle in one patient (4%). In the control group, a dissection in the coronary sinus ostium occured in one patient (4%) [46]. In the second RCT, reasons for failure in the study group were intraventricular conduction delay in 5 patients (24%), failure to achieve QRS narrowing in three patients (14%) or inability to map His-bundle in two patients (9%). In contrast, the reasons for failure in the comparison group were unable to cannulate in two patients (10%), suboptimal coronary sinus target branch in two patients (10%) or vascular occlusion in one patient (5%) or withdrawal after randomization in one patient (5%) [44, 45].

Dauer QRS-Komplex: 3 RCTs

stat.sign. Unterschied in 1 RCT (KG: RVP)

kein stat.sign. Unterschied in 2 RCTs (KG: BVP)

QRS duration was reported in all three of the RCTs [43-46]. For this outcome, one RCT found a statistically significant difference favouring HBP to RVP [43]. Another RCT found no statistically significant difference when comparing HBP to BVP (intention-to-treat analysis) [46]. The third RCT found no statistically significant difference in the intention-to-treat analysis, but when analysing on-treatment or per-protocol, a statistically significant difference between groups was reported [44, 45].

IG: 115,05 ms – 144 ms
KG: 132,25 ms – 164 ms

In one RCT, QRS duration at 12 months follow-up was reported to be 115.05 ± 18.96 milliseconds in the study group compared to 132.25 ± 21.25 milliseconds in the control group, with statistical significance (p<0.01) [43]. In another RCT, in the intention-to-treat analysis, the QRS duration at six months follow-up was 131 ± 20 milliseconds in the study group compared to 134 ± 15 milliseconds in the control group with the p-value for the difference between groups reported being p>0.05. For the difference between groups in the per-protocol analysis, no p-value was reported (study group: 129 ± 20 milliseconds compared to 135 ± 15 milliseconds in the control group) [46]. In the third RCT, there was no statistically significant difference between groups in the intention-to-treat analysis, with values reported to be 144 ± 30 milliseconds in the study group compared to 152 ± 30ms in the control group (p>0.05). The difference between groups was statistically significant in the on-treatment analysis: 125 ± 22 milliseconds vs. 164 ± 25 milliseconds, with a p<0.01. In the per-protocol analysis, the difference was also reported to be statistically significant, with a QRS duration of 124 ± 19 milliseconds in the study group compared to 162 ± 24 milliseconds in the comparison group, p<0.01 [44, 45].

linksventrikuläre Ejektionsfraktion: in 3 RCTs; stat.sign. Unterschied in 1 RCT (KG: RVP), kein stat.sign. Unterschied in 2 RCTs (KG: BVP)

LVEF was reported in all three of the RCTs [43-46]. In one RCT, there was a statistically significant higher percentage of LVEF favouring HBP in comparison to RVP at twelve-month follow-up [43]. In another RCT, no statistically significant difference between groups was found in the intention-to-treat-analysis, but a statistically significant difference for LVEF favouring HBP in comparison to BVP in the per-protocol analysis was reported [46]. In the third RCT, there were no statistically significant differences for this outcome between groups in the intention-to-treat analysis, the on-treatment analysis or in the per-protocol analysis [44, 45].

IG: 45,37 %-48 %
KG: 39,57 %-43 %

In one RCT, LVEF was 45.37 ± 2.31% compared to 39.57 ± 2.27% in the control group, with this difference between groups being statistically significant (p<0.01) [43]. In another RCT, the difference between groups at six-

month follow-up was not statistically significant in the intention-to-treat analysis with 46 ± 9% compared to 43 ± 7% in the control group (p>0.05). However, when comparing between groups as per-protocol analysis, the difference was statistically significant with 48 ± 8% in the study group compared to 42 ± 8% in the control group (p<0.05) [46]. In the third RCT, the intention-to-treat analysis showed a median change in LVEF in the study group of +9.1% (IQR 5.0-14.4%), compared to +5.2% (IQR 1.5-11.3%) in the control group, without statistical significance (p>0.05). In the on-treatment analysis, the median change in LVEF was +7.2% in the study group compared to +5.9% in the comparison group (p>0.05). There was also no statistically significant difference in the median change in LVEF in the per-protocol analysis: +11.8% in the study group compared to +5.2% in the comparison group (p>0.05) [44, 45].

Laborparameter NT-proBNP: in 1 RCT, kein stat.sign. Unterschied zwischen den Gruppen

NT-proBNP was reported in one RCT [46]. While the decrease in this laboratory parameter was statistically significant within each group, the difference of the decrease between groups was not statistically significant in the intention-to-treat analysis. For the difference between groups in the per-protocol analysis, no p-value was reported [46].

ITT: IG: 59 ± 78; KG: 44 ± 32

In the intention-to-treat analysis of the RCT, NT-proBNP at six months follow-up was reported to be 59 ± 78pmol/l in the study group compared to 44 ± 32pmol/l in the comparison group without statistically significant difference between groups (p>0.05). In the per-protocol analysis, the study group had 45 ± 65pmol/l compared to 56 ± 55pmol/l in the comparison group (p-value not reported) [46].

Beobachtungsstudie: nur für Sicherheitsendpunkte eingeschlossen

Implant success, **QRS duration** and change in **LVEF** were also reported in the retrospective cohort study [3], but due to the observational study design, only safety outcomes were considered for the qualitative analysis (see Table 2-1 for an overview of outcome inclusion criteria according to study design).

Function

NYHA Funktionsklasse: in 3 RCTs stat.sign. Unterschied in 1 RCT, kein stat.sign. Unterschied in 2 RCTs

The *crucial* outcome **NYHA functional classification** was considered when answering the research questions on function[30]. The NYHA functional classification was reported in all three RCTs [43-46]. Comparisons within each study arm were reported in two RCTs, showing a statistically significant improvement when using either HBP or the comparison (RVP/BVP) [43, 46]. Comparisons between the intervention group and the control group were reported in all three RCTs, with a statistically significant improvement favouring the intervention compared to the comparator in one RCT [43], and no statistically significant difference between groups in two RCTs [44-46].

IG: 1,57 – 1,8 KG: 1,9-2,03

In one RCT, the difference in **NYHA functional** class at 12 months was statistically significant with 1.57 ± 0.26 in the study group compared to 2.03 ± 0.34 in the control group (p<0.05) [43].

In another RCT, the intention-to-treat-analysis at 6 months reported the NYHA functional class in the study group at 1.8 ± 0.4 compared to 1.9 ± 0.6 in the control group. This difference was not statistically significant (p>0.05). In the per-protocol analysis, the NYHA functional class in the study group was 1.8 ± 0.4 compared to 1.9 ± 0.5 in the comparison group, with no p-value

[30] **D0011** – What is the effect of His-bundle pacing on patients' body functions? & **D0016** – How does the use of His-bundle pacing affect activities of daily living?

reported for the comparison between groups. This RCT also reported the number of patients with a difference of NYHA functional class ≥1. In the intention-to-treat analysis, there were twelve patients in the study group (48%) compared to ten patients in the control group (40%), whereas in the per-protocol analysis, there were nine patients in the intervention group (47%) compared to 13 patients (42%), with no p-value reported for either analysis. [46].

The third RCT didn't report values for NYHA functional class at follow-up. Instead, the proportion of patients that had an improvement or decline in NYHA functional class ≥1 were reported at both six and twelve months, with no statistically significant difference between groups: The NYHA functional class improved ≥1 in 53% of patients in the study group compared to 39% of patients in the control group ($p>0.05$) at six months. At twelve months, the improvement was 25% in the study group compared to 31% in the control group ($p>0.05$). The decline of the NYHA functional class ≥1 was 0% in both groups at 6 months (p-value not reported). At twelve months, the decline was 6% in the study group compared to 0% in the control group ($p>0.05$) [44, 45].

Health-related quality-of-life

The *crucial* outcome **quality-of-life** was considered when answering the research questions on health-related quality-of-life[31].

QoL: in 1 RCT, mit stat.sign. Unterschied in 4 untersuchten Domänen zugunsten HBP (KG: RVP)

Quality-of-life was reported in one RCT [43]. For all four assessed domains of the quality-of-life questionnaire, a statistically significant improvement within each study arm, but also a statistically significant difference between groups (favouring HBP over RVP) was reported [43].

physiol. Funktion:
IG: 41.02 ± 2.58
KG: 37.50 ± 2.47;
psych. Funktion:
IG: 43.05 ± 2.92
KG: 39.42 ± 2.72;
soziale Bez.:
IG: 44.17 ± 2.84
KG: 39.06 ± 2.51;
phys. Schmerz:
IG: 44.56 ± 2.72
KG: 40.25 ± 3.06

In the RCT, at baseline there were no statistically significant differences between the intervention and the comparison group; at 12 months, the improvement for all four domains (physiological function, psychological function, social relations and physical pain) was greater in the study group compared to the control group. The physiological function at 12-month follow-up was 41.02 ± 2.58 in the study group compared to 37.50 ± 2.47 in the comparison group ($p<0.01$). For the psychological function, the study group showed 43.05 ± 2.92, whereas the control group value was 39.42 ± 2.72 ($p<0.01$). For social relations, the study group showed 44.17 ± 2.84 compared to 39.06 ± 2.51 in the comparison group ($p<0.01$). Regarding physical pain, the study group scored 44.56 ± 2.72 compared to 40.25 ± 3.06 in the comparison group ($p<0.01$) [43].

Patient safety

The *crucial* outcomes of **adverse events/complications** and **increase in capture threshold** were considered when answering the research question on patient safety[32].

[31] **D0012** – What is the effect of His-bundle pacing on generic health-related quality-of-life? &
D0013 – What is the effect of His-bundle pacing on disease-specific quality-of-life? &
D0017 – Was the use of His-bundle pacing worthwhile?

[32] **C0008** – How safe is His-bundle pacing in comparison to the comparator(s)?

unerwünschte Ereignisse/ Komplikationen: in 3 RCTs und Kohortenstudie; stat.sign. Unterschied in 1 RCT, keine p-Werte in 2 RCTs

Adverse events or complications were reported in all three RCTs [43-46] and in the observational cohort study [3]. In one RCT, a statistically significant difference between groups when comparing the total of adverse events in each group was found, favouring HBP in comparison to RVP [43]. In another RCT, the rate of periprocedural complications was the same for both groups [46]. In the third RCT, complications were reported only as per-protocol analysis, with no statistically significant difference for ventricular tachycardia or fibrillation, and no p-values reported for periprocedural or infectious complications [44, 45].

Kohortenstudie: stat.sign. Unterschied für kombinierten Endpunkt, kein stat.sign. Unterschied für Endpunkte einzeln betrachtet

In the retrospective cohort study, for the composite of all-cause mortality, heart failure hospitalisations or upgrade to biventricular pacing, a statistically significant difference favouring HBP over RVP was found. However, regarding necessary upgrade to biventricular pacing by itself, no statistically significant difference between groups was found. For required ventricular lead revision, pericardial effusion, infection necessitating device or lead removal or premature battery depletion, no p-values were reported [3].

RCTs: Hämopneumothorax, Perikarderguss, dislozierte Elektrode, periprozedurelle Komplikationen, ventrikuläre Tachykardie, Infektionen: keine stat.sign. Unterschiede

Gesamtkomplikationen (1 RCT): IG: 5,56 %; KG: 22,22 % stat.sign. Unterschied

In one RCT, hemopneumothorax occurred in no patients in the study group compared to 5.56% of patients in the control group ($p>0.05$). For pericardial effusion, there were 2.78% of patients in the study group compared to 8.33% affected in the comparison group ($p>0.05$). A catheter electrode displacement happened in 2.78% of patients in the study group compared to 8.33% ($p>0.05$). When taking the total of adverse events, there were 5.56% of patients affected in the study group compared to 22.22% of patients in the comparison group, with this difference being statistically significant ($p<0.05$) [43]. In another RCT, only periprocedural complications were reported. These were the same across both groups, with one patient in each group (4%) affected, with no reported p-value [46]. In the third RCT, adverse events were reported as per-protocol analysis. For ventricular tachycardia or ventricular fibrillation, there were two patients (12%) in the study group compared to no patients (0%) in the control group affected, without statistically significance ($p>0.05$). For periprocedural complications, there were one patient (6%) in the study group compared to three patients (12%) in the control group (p-value not reported). No infectious complications occurred in either group (p-value not reported).

Kohortenstudie: kombinierter Endpunkt (Mortalität, Hospitalisierung, Upgrade auf BVP): IG: 25 %; KG: 31,6 % stat.sign. Unterschied

In the retrospective cohort study, for the composite of all-cause mortality, heart failure hospitalisations, or upgrade to biventricular pacing, a statistically significant difference favouring HBP in comparison to RVP was found, with 25% in the study group affected compared to 31.6% in the control group (hazard ratio 0.71 and $p<0.05$). For a required upgrade to biventricular pacing, there were 0.3% of patients in the study group compared to 1.4% of patients in the control group (hazard ratio: 0.211, $p>0.05$). The ventricular lead revision was required in 4.2% of patients in the study group compared to 0.5% of patients in the control group (p-value not reported). Pericardial effusion occurred in no patients of the study group, with three patients in the control group (0.7%) affected (p-value not reported). An infection necessitating device or lead removal occurred in each group in one patient (0.3% vs 0.2%, p-value not reported). Premature battery depletion (pacemaker generator change 3.5 years after the initial implant) was slightly more common in the study group, with one patient affected in the study group (0.3%) compared to no patient in the control group (0%), with no reported p-value [3].

The **increase in capture threshold** was reported in all three RCTs [43-46] and in the observational cohort study [3]. In all three RCTs and in the retrospective cohort study, there was a statistically significant difference between groups at baseline and at follow-up, with higher pacing threshold values for HBP compared to RVP [3, 43], as well as higher pacing thresholds for HBP compared to BVP [44-46].

Zunahme der Schrittmacherschwelle: stat.sign. Unterschied zulasten HBP in 3 RCTs und Kohortenstudie

In one RCT, at 12-month follow-up the study group pacing threshold was 1.42 ± 0.61 Volt (V) compared to 0.78 ± 0.43V ($p<0.01$) [43]. In another RCT, at 6-month follow-up, the intention-to-treat analysis showed 2.3 ± 1.4V for the study group compared to 1.4 ± 0.5V in the comparison group ($p<0.05$). In the per-protocol analysis, the pacing thresholds were 2.4 ± 1.6 in the study group compared to 1.5 ± 0.6V in the comparison group ($p<0.05$) [46]. In the third RCT, at six-months follow-up, the intention-to-treat analysis showed 2.3 ± 1.4V for the study group compared to 1.5 ± 0.6V ($p<0.05$). In the per-protocol analysis, the pacing threshold was 2.4 ± 1.6 V compared to 1.5 ± 0.6V ($p<0.05$).

RCTs:
IG: 1,4-2,4 V
KG: 0,78-1,5 V

In the retrospective cohort study, at 24 months follow-up the pacing threshold in the study group was 1.56 ± 0.95V compared to 0.76 ± 0.29 in the comparison group ($p<0.01$). This study also reported the change in threshold within each group, with a change of 0.28 ± 1.1V in the study group compared to 0.16 ± 0.5V in the control group. This finding was not statistically significant ($p>0.05$) [3].

Kohortenstudie:
IG: 1,56 ± 0,95 V
KG: 0,76 ± 0,29 V

For harms related to dosage or frequency of applying HBP or the change of frequency or severity of harms over time or in different settings, no evidence was found. For the kind of data, records or registry to monitor the use of HBP, no evidence was found[33].

[33] **C0002** – Are the harms related to dosage or frequency of applying His-bundle pacing? &
C0004 – How does the frequency or severity of harms change over time or in different settings? &
C0007 – Is His-bundle pacing associated with user-dependent harms? &
B0010 – What kind of data/records and/or registry is needed to monitor the use of His-bundle pacing?

5 Quality of evidence

Risk of Bias (RoB) mit Cochrane RoB v.2 und ROBINS-I bewertet

The risk of bias (RoB) for individual studies was assessed with the Cochrane RoB v.2 tool (for RCTs) [39] and the ROBINS-I tool (for observational studies) [36]. RoB is presented in Table A-4 and Table A-5 in the Appendix. Across the three included RCTs, all three were ranked as having high RoB [43-46]. The included observational study for safety outcomes was ranked as having a moderate RoB [3].

RCTs: hohes RoB, Registerstudie: moderates RoB

The main reasons for the risk of bias were limited information on the used randomization tool and awareness of the carers delivering the intervention of participant's assignment to intervention in the RCTs, unbalanced deviations from intended intervention between groups, and some statistically significant differences at baseline. The observational study was limited in the retrospective data collection with statistically significant differences at baseline. In addition, the two-centre study design (with all interventions administered in the first centre and all comparisons administered in the second centre), with the start of follow up and start of intervention not coinciding for all participants, posed another risk of bias.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [40] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved in solving the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [40].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-6.

insgesamt sehr niedrige Qualität der Evidenz für die 3 Indikationen

Overall the strength of evidence for the effectiveness and safety of His-bundle pacing in comparison to standard care (with RVP or BVP) is very low for all indications (heart failure, cardiac conduction system disease, atrial fibrillation).

Table 5-1: Summary of findings table of His-bundle pacing

Outcome	Anticipated effects (HBP vs. SC with RVP/BVP)	Number of participants (studies)	Quality of the evidence (Importance)	Comments
Efficacy				
Quality-of-life	The study was able to detect a s.s.diff.: Physiological function: 41.02 ± 2.58 vs. 37.50 ± 2.47; p=0.000 Psychological function: 43.05 ± 2.92 vs. 39.42 ± 2.72; p=0.000 Social relations: 44.17 ± 2.84 vs. 39.06 ± 2.51; p=0.000 Physical pain: 44.56 ± 2.72 vs. 40.25 ± 3.06; p=0.000	72 (1 RCT)	⊕◯◯◯ Very low[a, b, c] (crucial)	-
NYHA Class	One study was able to detect a s.s.diff.: 1.57 ± 0.26 vs. 2.03 ± 0.34; p=0.000 Two studies were not able to detect a s.s.diff.: 1.8 ± 0.4 vs. 1.9 ± 0.6; p=0.56 Improvement NYHA ≥1: 25% vs. 31%; p=0.89	163 (3 RCTs)	⊕◯◯◯ Very low[a, c, d] (crucial)	6 month follow-up in one RCT, 12 month follow-up in two RCTs
Implant success	Two studies were not able to detect a s.s.diff.: 29/46 (63%) vs. 38/45 (84%); p=NR	91 (2 RCTs)	⊕◯◯◯ Very low[c, d, f] (important)	-
Electrocardiographic parameter: QRS duration	One study was able to detect a s.s.diff.: 115.05 ± 18.96 vs. 132.25 ± 21.25; p=0.000 Two studies were not able to detect a s.s.diff.: 131 ± 20 vs. 134 ± 15; p=0.51 144 ± 30 vs. 152 ± 30; p=0.42	163 (3 RCTs)	⊕◯◯◯ Very low[c, d, g] (imporant)	-
Echocardiographic parameter: LVEF	Two studies were able to detect a s.s.diff.: 45.37 ± 2.31 vs. 39.57 ± 2.27; p=0.000 48 ± 8 vs. 42 ± 8; p<0.05 One study was not able to detect a s.s.diff.: 31.9% vs. 34.0%; p=NR	163 (3 RCTs)	⊕◯◯◯ Very low[c, d, g] (important)	In one RCT, the s.s.diff. was only present in the per-protocol analysis, without a s.s.diff. in the intention-to-treat analysis
Laboratory parameter: NT-proBNP	The study was not able to detect a s.s.diff.: 59 ± 78 vs. 44 ± 32; p=0.46	50 (1 RCT)	⊕⊕◯◯ Low[c] (important)	-
Safety				
Mortality	Two studies were not able to detect a s.s.diff.: 0 (0%) vs. 0 (0%); p=NR 2 (12%) vs. 0 (0%); p=NR	91 (2 RCTs)	⊕◯◯◯ Very low[c, d, h] (crucial)	One RCT reported mortality as intention-to-treat, the other RCT as per-protocol
	The study was not able to detect a s.s.diff.: 17.2% vs. 21.4% Hazard ratio: 0.728 (95% CI: 0.523–1.014); p=0.06	765 (1 observational study)	⊕◯◯◯ Very low[i] (crucial)	-
Adverse events/Complications	For total AE, one study was able to detect a s.s.diff.: 5.56 vs. 22.22; p=0.041 For the other AE, the studies were not able to detect a s.s.diff.: Periprocedural complications: 2 (4.3%) vs. 4 (8.9%); p=NR Hemopneumothorax: 0.00 vs. 5.56; p=0.473 Pericardial effusion: 2.78 vs. 8.33; p=0.607 Catheter electrode displacement: 2.78 vs. 8.33; p=0.607 Ventricular tachycardia/ventricular fibrillation: 2 (12%) vs. 0 (0%); p=0.16 Infectious complications: 0 (0%) vs. 0 (0%); p=NR	163 (3 RCTs)	⊕◯◯◯ Very low[c, d, h] (crucial)	-

Outcome	Anticipated effects (HBP vs. SC with RVP/BVP)	Number of participants (studies)	Quality of the evidence (Importance)	Comments
	For the composite all-cause mortality, heart failure hospitalisations or upgrade to biventricular pacing, the study was able to detect a s.s.diff.: 25% vs. 31.6%; Hazard ratio: 0.71; p=0.02 For the other AE, the study was not able to detect a s.s.diff.: Upgrade to biventricular pacing: 0.3% vs. 1.4% Hazard ratio: 0.211 (95% CI: 0.025-1.752); p=0.15 Ventricular lead revision required: 4.2% vs. 0.5%; p=NR Pericardial effusion: 0% vs. 0.7%; p=NR Infection with device/lead removal: 0.3% vs. 0.2%; p=NR Premature battery depletion: 0.3% vs. 0%; p=NR	765 (1 observational study)	⨁◯◯◯ Very low[i] (crucial)	-
Hospitalisations	The studies were not able to detect a s.s.diff.: Hospitalisations per group: 0 (0%) vs. 2 (8%); p=NR Hospitalisations across groups: 6 (15%)	91 (2 RCTs)	⨁◯◯◯ Very low[a, c, e] (crucial)	In one RCT, only total values (across both groups) were reported for this outcome
	The study was able to detect a s.s.diff.: 12.4% vs. 17.6%; Hazard ratio: 0.642 (95%CI: 0.439-0.939); p=0.02	765 (1 observational study)	⨁◯◯◯ Very low[i] (crucial)	-
Capture threshold	The studies were able to detect a s.s.diff.: 1.42 ± 0.61 vs. 0.78 ± 0.43; p=0.000 2.3 ± 1.4 vs. 1.4 ± 0.5; p<0.05 2.00 (1.00-3.25) vs. 0.94 (0.75-1.25); p=0.004	163 (3 RCTs)	⨁⨁◯◯ Low[c] (crucial)	The s.s.diff. between groups was already present at baseline, indicating higher pacing thresholds when pacing the His-bundle
	The study was able to detect a s.s.diff.: 1.56 ± 0.95 vs. 0.76 ± 0.29; p<0.01 The study was not able to detect a s.s.diff.: Change in threshold: 0.28 ± 1.1 vs. 0.16 ± 0.5; p=0.09	765 (1 observational study)	⨁◯◯◯ Very low[i] (crucial)	The s.s.diff. between groups was already present at baseline. For the change in threshold between groups, no s.s.diff was found.

Abbreviations: BVP – biventricular pacing; CI – confidence interval; HBP – His-bundle pacing; LVEF – left ventricular ejection fraction; NR – not reported; n – number; NT-proBNP – N-terminal prohormone of brain natriuretic peptide; NYHA – New York Heart Association; p – p-value; QoL – quality-of-life; RCT – randomised controlled trial; RVP – rightventricular pacing; SC – standard care; s.s.diff – statistically significant difference; V – Volt

Explanations:

[a] *Participants and carers had knowledge of the assigned intervention, potentially influencing the measurement of this outcome.*

[b] *Not enough information on what kind of variation from the SF-36 questionnaire was used for the measurement.*

[c] *Small number of patients, studies were potentially statistically underpowered to detect a difference in this outcome.*

[d] *Variation in effect size present for this outcome.*

[e] *Unclear if inconsistency present, as one study only provided total values of this outcome across both groups.*

[f] *The definitions for implant success were differing across studies (e.g. capture of the left bundle branch vs. correction of QRS).*

[g] *Comparison of this outcome before and after pacing, but difference in timing of measurement across studies.*

[h] *Insufficient length of follow-up for measurement of this outcome.*

[i] *Retrospective data collection; statistically significant baseline differences in gender, atrial fibrillation, use of beta-blockers and QRS duration at baseline.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

6 Discussion

His-bundle pacing (HBP) is a type of cardiac pacing that belongs to the group of conduction system pacing therapies. HBP is often called physiological pacing, as the cardiac conduction system is paced directly, as opposed to ventricular pacing by right ventricular pacing (RVP) or bi-ventricular pacing (BVP). HBP can be used in patients with heart failure, cardiac conduction system disease or atrial fibrillation.

His-Bündel-Stimulation: bei Herzinsuffizienz, kard. Leitungsstörung, Vorhofflimmern

This report aimed to assess the clinical effectiveness and safety of HBP in patients with heart failure, cardiac conduction system disease or atrial fibrillation. Patient-relevant outcomes were assessed compared to standard care (e.g. rightventricular or biventricular cardiac resynchronisation therapy, or rightventricular pacing).

Ziel: Synthese der Evidenz für klin. Wirksamkeit und Sicherheit

Summary of evidence

This systematic review included four studies (three RCTs and one observational study). The three included RCTs assessed the use of HBP for patients with heart failure. In addition, one of these RCTs also included patients with atrial fibrillation. The included retrospective cohort study assessed the use of HBP for cardiac conduction system disorders (e.g., bradycardia). The comparators in the included studies were the use of BVP in two RCTs and RVP in one RCT and one cohort study.

Evidenzsynthese aus 4 Studien (3 RCTs, 1 Kohortenstudie)

Komparatoren: BVP, RVP

As such, randomised controlled evidence was only available for one of the indications (heart failure). For patients with cardiac conduction system disease (e.g., atrioventricular block), with left ventricular ejection fraction above 40% and anticipated pacing >20%, or patients with atrial fibrillation and "ablate and pace" strategy, no randomised controlled evidence was available.

bisher nur für 1 Indikation (Herzinsuffizienz) RCTs vorhanden

Overall, 928 patients were analysed in the four included studies assessing the use of HBP. Of these, 163 patients were included for clinical effectiveness outcomes.

insg. 928 Pat.; klin. Wirksamkeit: 163 Pat.

To assess the effect of HBP on the patient's body functions and activities of daily living, the New York Heart Association (NYHA) Class was reported in all three included RCTs. While one RCT detected a statistically significant improvement in the HBP group (compared to RVP), two RCTs were not able to detect a statistically significant difference (compared to BVP). The health-related quality-of-life was assessed in one RCT, with a statistically significant difference favouring HBP (compared to RVP). NYHA Class and quality-of-life were considered *crucial* effectiveness outcomes in this assessment. However, the quality of evidence was assessed as very low for both outcomes.

klinische Wirksamkeit: NYHA Funktion: stat. sign. in 1 RCT, keine stat. sign. in 2 RCTs

QoL: stat. sign. Verbesserung in 1 RCT (gegenüber RVP)

Two RCTs reported lower implant success rates for HBP compared to BVP, but no p-value was reported for this finding. The QRS duration (electrocardiographic parameter) was assessed in all three RCTs, with one study detecting a statistically significant difference (compared to RVP) and two studies showing no statistically significant difference (compared to BVP).

Implantationsrate für HBP geringer (ohne stat. sign.); QRS: 1 RCT mit/2 RCTs ohne stat. sign. Unterschied

The improvement in the left ventricular ejection fraction (LVEF) was statistically significant in favour of HBP in two RCTs (compared with RVP or BVP). However, in one of these RCTs (comparing to BVP), this statistical significance was not present in the intention-to-treat analysis. The third RCT (comparing to BVP) was also not able to detect a statistically significant difference

LVEF: Unterschied stat.sign. (vs. RVP), nicht stat.sign. (vs. BVP); NT-proBNP: kein stat.sign. Unterschied

regarding LVEF. The NT-proBNP (laboratory parameter) was assessed in one RCT, with a statistically significant decrease in each study arm (HBP or BVP), but no statistically significant difference between groups.

QoE klin. Wirksamkeit: sehr niedrig/niedrig

Implant success, QRS duration, LVEF and NT-proBNP were considered *important* effectiveness outcomes. For implant success, QRS duration and LVEF, the quality of evidence was assessed as very low; for NT-proBNP, the quality of evidence was assessed as low.

Sicherheit: Mortalität ohne stat. sign. Unterschiede (2 RCTs)

zusammengesetzte NW: stat.sign. niedriger bei HBP (1 RCT, Kohortenstudie)

For mortality, the evidence was inconclusive, with no statistically significant difference between groups in two RCTs and in the cohort study. For adverse events or complications, one RCT found a statistically significant lower rate for total adverse events (compared to RVP). For individual adverse events (such as periprocedural complications, hemopneumothorax, pericardial effusion, catheter electrode displacement, ventricular tachycardia/fibrillation or infectious complications), the three RCTs did not detect a statistically significant difference.

einzeln betrachtete NW: keine stat. sign. Unterschiede (3 RCTs, Kohortenstudie)

The cohort study found a statistically significant lower rate for the composite of mortality, hospitalisation or upgrade to BVP (compared to RVP). For individual adverse events (upgrade to BVP, ventricular lead revision, pericardial effusion, device infection or premature battery depletion), the cohort study could not detect a statistically significant difference.

Hospitalisierungen: Unterschied stat. sign. in Kohortenstudie, nicht stat.sign. in 2 RCTs; Schrittmacherschwelle: stat.sign. höher bei HBP

One RCT was not able to detect a statistically significant difference regarding hospitalisations. One RCT only reported the total number of hospitalisations across groups, making comparison difficult. The cohort study detected a statistically significant difference, with fewer hospitalisations occurring in the HBP group. For the increase in capture threshold, all three RCTs and the cohort study reported statistically significant higher values in the HBP group (compared to RVP or BVP), both at baseline and at follow-up.

QoE Sicherheit: sehr niedrig/niedrig

All of these safety outcome measures were considered *crucial* in this assessment. The quality of evidence for mortality, adverse events/complications and hospitalisations was assessed as very low. For the increase in capture threshold, the quality of evidence was considered low (in the RCTs) and very low (in the cohort study).

Interpretation of the findings

Ergebnisse decken sich mit anderen SRs:

The results of this systematic review complement the results from other recent systematic reviews:

Evidenz mit geringer Quantität/Qualität

höhere Schrittmacherschwelle als mögliches Batterieproblem

A systematic review by the National Institute for Health and Care Excellence, published in 2021, states that the evidence on the safety and efficacy of HBP for treating heart failure is inadequate in quality and quantity. The authors consulted professional experts that considered the higher pacing threshold could result in premature battery depletion as a theoretical adverse event. The recommendation of the systematic review is to perform the procedure only in the context of research, in specialist centres with experience in cardiac pacing [1]. Shorter battery life leads to more frequent pacemaker generator changes associated with significant periprocedural risk [50].

HBP möglicherweise der RVP vorzuziehen

Another systematic review, published in 2021, found that HBP was associated with decreased heart failure hospitalisations and preservation of LVEF, while also associated with increased procedure duration and increased lead revisions, in comparison to RVP [51].

This is in line with another systematic review published in 2021. This systematic review reports that physiological pacing with either HBP or left bundle branch pacing might be a better strategy than RVP in improving clinical outcomes, with larger RCTs needed for further verification [52].

größere RCTs gewünscht

A network meta-analysis of HBP, BVP or RVP as a primary strategy for atrioventricular conduction disease with normal or mildly reduced ejection fraction, published in 2020, found that both HBP and BVP were associated with significantly improved survival compared to RVP, with no significant difference between HBP and BVP [53].

keine stat. sign. Unterschiede im Vergleich zu BVP

One meta-analysis, published in 2018, concluded that HBP is practical and feasible in most patients with an acceptable pacing threshold and a low rate of complications. However, of 26 included studies in the meta-analysis, 17 studies were observational single-arm studies, limiting its comparative information [4].

Ergebnisse in Kontrast zu 1 SR (2018), Meta-Analyse mit vielen Beobachtungsstudien

Evidence gaps and ongoing studies

Twelve ongoing RCTs were identified with estimated completion dates within the next four years (see Table A-8). In these RCTs, the use of HBP is assessed for the treatment of cardiac conduction system disease, e.g. AV-block (n=4), heart failure (n=2), cardiac conduction system disease or heart failure (n=2), atrial fibrillation (n=1), atrial fibrillation or heart failure (n=1), pacing indication after transcatheter aortic valve implantation (n=1) or standard pacing indications (n=1). The number of enrolled patients in the ongoing RCTs ranges from 16 patients in the smallest to 334 patients in the largest RCT.

12 laufende RCTs, abgeschlossen bis 2026

The comparators in the ongoing RCTs are RVP (n=4), BVP (n=1), BiV-CRT (n=1), LV pacing (n=1), LBBP (n=1), atrial fibrillation ablation by pulmonary vein isolation (n=1), ventricular demand pacing (n=1), pharmacological treatment (n=1), or no pacing (n=1)

Komparatoren: RVP, BVP, BiV-CRT, LVP, LBBP und weitere

The assessed primary outcome measures of these ongoing RCTs are difference in LVEF (n=6), mortality (n=3), quality-of-life (n=3), exercise capacity (n=2), heart failure hospitalisation (n=2), capture threshold (n=1), laboratory parameter NT-proBNP (n=1), cardiac transplant (n=1), ventricular synchronisation (n=1), QRS duration (n=1), heart valve disease (n=1), left ventricular activation time (n=1) and implant success (n=1).

primäre Endpunkte: vielseitig

We also identified RCTs that recently reached their primary completion date, although not having published results yet. For example, the "HOPE-HF" trial (Clinical trials identifier: NCT02671903). This RCT compared HBP use for cardiac resynchronisation with conventional cardiac resynchronisation therapy, in a cross-over RCT design with 198 enrolled patients.

abgeschlossene RCTs, aber noch ohne Publikation

These ongoing trials could potentially influence the effect estimates considerably.

Internal and external validity

RCTs: wenig Studienteilnehmer, Abweichungen von geplanter Intervention

retrospektive Kohortenstudie: Vergleich zweier Zentren

This report is considerably limited by imprecision of data, as all included RCTs had small sample sizes. Another limiting factor was unbalanced deviations from intended intervention between groups in two RCTs, as well as some statistically significant differences at baseline in one RCT. The small number of cases also means that presumably, all patients included in these studies were treated by experienced implanters who were well acquainted with the method. This is relevant because HBP has a learning curve even for experienced implanters [54]. The cohort study is limited by its retrospective data collection, as well as the type of comparison between two study centres: all interventions were performed in one centre, compared to all comparators that were performed in a second centre, with statistically significant baseline differences between groups.

ext. Validität: Daten auf österreichischen Kontext übertragbar

The inclusion criteria of the studies reflected the intended patient population for HBP. The results are considered generalizable to the Austrian context. However, experience in administering the technology may influence the external validity of study results. A detailed description of the applicability of the body of evidence to the Austrian context is provided in the Appendix, Table A-7.

Limitations

Ausschluss kleinerer Studien durch strenge Einschlusskriterien

This report excluded retrospective comparative studies with a high risk of bias (according to ROBINS-I) or less than 500 patients enrolled. Also, all single-arm studies (e.g. case series) were excluded from the evidence synthesis. This could have led to not capturing the full available body of evidence.

Ausschluss von Studien mit experimentellen Verfahren im Vergleich

Also, studies comparing different HBP implantation techniques (such as selective HBP vs non-selective HBP) or studies comparing HBP with other experimental forms of cardiac conduction system pacing (e.g. left bundle branch pacing) were excluded. Given the narrow scope of this assessment, this was not relevant to answer our research questions.

kein Einfluss auf Resultate erwartet

While these results should be considered when planning future RCTs to compare HBP to conventional therapies, these studies would not have changed the current interpretation of the comparative clinical effectiveness and safety of HBP.

Conclusion

Schlussfolgerung: Evidenz unzureichend, Qualität der Evidenz sehr niedrig; Bedenken zu Implantationsraten und Batterielebenszeit

The available evidence is insufficient to prove that HBP is superior to standard care. Some evidence suggests that HBP may be superior to RVP in certain conditions, but in comparison to BVP, the evidence for additional benefit is insufficient. For all crucial outcomes assessed in this report, the quality of evidence was very low. The theoretical benefit of physiologic stimulation of the conduction system is counterbalanced by the problem of increased stimulation thresholds and, possibly, a shorter battery life.

laufende RCTs sind abzuwarten

Due to inconclusive evidence and limited lengths of follow-up in the available studies, larger high-quality randomised controlled trials with appropriate follow-up lengths are to be awaited.

7 Recommendation

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlungsschema

Table 7-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

The current evidence is not sufficient to prove that the assessed technology His-bundle pacing is more effective and safer than the comparators. Some study results indicated better results for His-bundle pacing when compared to right-ventricular pacing. When comparing with biventricular pacing, the results are insufficient to prove a benefit. Due to the very low quality of evidence for both comparators regarding the crucial outcomes, the inclusion in the catalogue of benefits is currently not recommended.

Aufnahme in den Leistungskatalog: derzeit nicht empfohlen

New study results could potentially influence the effect estimates. Therefore, the re-evaluation is recommended in 2026 if the larger ongoing randomised trials are published.

Re-Evaluierung für 2026 empfohlen

8 References

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Appendix

Quality Appraisal of systematic review using the AMSTAR-2 assessment tool

Table A-1: AMSTAR-2 assessment: Permanent His-bundle pacing: a systematic literature review and meta-analysis [4, 38]

Author, year	**Zanon et al., 2018 [4]**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? RCTs	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCTs	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes
Overall Confidence	**Low**
Reasoning	Many small single arm studies, patient selection bias very likely. Missing risk of bias assessment in individual studies, no publication bias investigation for quantitative synthesis. Systematic review still considered for identification of studies published before 2017, as no critical flaw in literature search strategy, study selection or data extraction detected.

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-2: His-bundle pacing: Results from randomised controlled trials

Author, year	Li et al., 2021 [43]	Vinther et al., 2021 [46]	Upadhyay et al., 2019 [44, 45]
Country	China	Denmark	USA
Sponsor	Not reported	Research grant from the Clinical Research Unit at the Heart Center, Rigshospitalet, Copenhagen, Denmark	None
Intervention/ Product	His bundle pacing Medtronic C304 His-sheath®, lead type not reported	His bundle pacing Medtronic C315 His-sheath®, 3830 SelectSecure lead®	His bundle pacing Medtronic C304 sheath®, 3830 SelectSecure lead®
Comparator	Right ventricular apex pacing	Biventricular pacing	Biventricular pacing
Indication	Heart failure, Atrial fibrillation	Heart failure	Heart failure
Study design	Randomised controlled trial	Randomised controlled trial	Randomised controlled trial
Number of pts	72 (36 HBP and 36 RVAP)	50 (25 His-CRT and 25 BiV-CRT)	41[34] (21 His-CRT and 20 BiV-CRT)
Inclusion criteria	■ Age between 40 and 80 ■ Diagnostic criteria for heart failure and atrial fibrillation (Chinese guidelines) ■ Indication for permanent pacemaker ■ Patients who signed the informed consent voluntarily ■ Cardiac function (NYHA) grade II-III ■ Patients with good compliance and cooperation with researchers	■ Age ≥18 years ■ Systolic heart failure with LVEF ≤35% as assessed by transthoracic echocardiography ■ Symptoms of heart failure (NYHA functional class II-IV) despite optimization of medical therapy and an ECG with sinus rhythm ■ LBBB according to Strauss' criteria: QRS-width >130 ms for women and >140 ms for men, QS or rS pattern in leads V1 and V2, and mid-QRS plateau phase and/or notching in at least 2 of leads V1, V2, V5, V6, I, and aVL.	■ Age ≥18 years ■ Patients with heart failure ■ American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society class I or class II guideline indications for CRT
Exclusion criteria	■ Severe heart valve disease ■ Patients who received cardiac resynchronisation therapy ■ Unstable angina pectoris ■ Acute myocardial infarction ■ Expected survival time less than 12 months	■ Existing biventricular pacing system ■ Permanent atrial fibrillation ■ Severe kidney disease with estimated glomerular filtration rate <30 ml/min ■ Acute myocardial infarct or coronary artery bypass graft within 3 months before assessment ■ Unwillingness to participate	■ Existing CRT device ■ Pregnancy ■ Inability of the patient to provide consent for himself or herself owing to either medical or psychiatric co-morbidity
Age of patients (yrs)	Total: 59.0 ± 3.4 Study group: 59.1 ± 3.6; Control group: 58.7 ± 3.3 p=0.588	*Intention-to-Treat:* Study group: 63.8 ± 9.4; Control group: 67.7 ± 9.0 *Per-Protocol:* Study group: 63.2 ± 9.2; Control group: 67.4 ± 9.1	Total: 64.6 ± 12.6 Study group: 63.4 ± 13.3; Control group: 65.5 ± 12.4 p=0.61
Gender (%)	Study group: 64% male, 36% female Control group: 53% male, 47% female p=0.339	*Intention-to-treat:* Study group: 56% male; Control group: 72% male *Per-Protocol:* Study group: 42%; Control group: 77%; p<0.05	Total: 62% male, 38% female Study group: 56% male, 44% female Control group: 67% male, 33% female p=0.51

[34] One patient withdrawal prior to device implantation in the Control group (BiV-CRT)

Author, year	Li et al., 2021 [43]	Vinther et al., 2021 [46]	Upadhyay et al., 2019 [44, 45]
Baseline characteristics and comorbidities	*Course of disease (years)* Study group: 7.4 ± 1.8; Control group: 7.7 ± 1.6 p=0.511 *NYHA classification (II/III)* Study group: 47%/53%; Control group: 42%/58% p=0.635 *Hypertension/Diabetes/Others* Study group: 50%/39%/25% Control group: 47%/33%/31% p=0.815	***Intention-to-treat:*** *BMI, kg/m²* Study group: 26.5 ± 4.6; Control group: 26.1 ± 4.4 *CHA_2DS_2-VASc Score* Study group: 2.8 ± 1.4; Control group: 3.4 ± 1.5 *eGFR <45 ml/min, %* Study group: 8; Control group: 28 *Nonischemic cardiomyopathy, %* Study group: 80; Control group: 76 *NYHA baseline* Study group: 2.4 ± 0.4; Control group: 2.4 ± 0.4 *QRS, ms* Study group: 165 ± 14; Control group: 167 ± 16 *LVEF, %* Study group: 30 ± 6; Control group: 30 ± 8 *Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor, %* Study group: 88; Control group: 96 *Beta-blockers, %* Study group: 80; Control group: 92 *Aldosterone antagonist, %* Study group: 64; Control group: 72 *Oral anticoagulation, %* Study group: 12; Control group: 12 ***Per-Protocol:*** *BMI, kg/m²* Study group: 27.2 ± 4.6; Control group: 25.8 ± 4.4 *CHA_2DS_2-VASc Score* Study group: 2.7 ± 1.3; Control group: 3.3 ± 1.5 *eGFR <45 ml/min, %* Study group: 11; Control group: 23 *Nonischemic cardiomyopathy, %* Study group: 84; Control group: 74 *NYHA baseline* Study group: 2.4 ± 0.4; Control group: 2.4 ± 0.4 *QRS, ms* Study group: 163 ± 14; Control group: 167 ± 15 *LVEF, %* Study group: 31 ± 6; Control group: 29 ± 8 *ACEI/ARB/ARNI, %* Study group: 84; Control group: 97	***Intention-to-treat:***[35] *LVEF (median %, IQR %):* Study group: 26.3% (21.3%-28.3%); Control group: 30.5% (27.1%-33.9%); p=0.011 ***Per-protocol:*** *BMI, kg/m²* Study group: 28.8 (26.4-33.2); Control group: 29.7 (26.2-31.3) p=0.99 *Hypertension:* Study group: 69%; Control group: 79%; p=0.48 *Coronary artery disease:* Study group: 62.5%; Control group: 67%; p=0.80 *History of CABG:* Study group: 12.5%; Control group: 21%; p=0.68 *Atrial fibrillation:* Study group: 25%; Control group: 37.5%; p=0.42 *COPD:* Study group: 25%; Control group: 25%; p=1.00 *Diabetes Mellitus Type 2:* Study group: 50%; Control group: 46%; p=0.80 *Chronic kidney disease:* Study group: 50%; Control group: 46%; p=0.80 *End-stage renal disease:* Study group: 7%; Control group: 8%; p=1 *NYHA class:* Study group: 3.0 (2.25-3.0); Control group: 2.75 (2.25-3.0); p=0.66 *QRS, ms* Study group: 174 ± 18; Control group: 165 ± 17; p=0.12 *LVEF, %* Study group: 28.0 (23.0-34.0); Control group: 27.7 (23.6-30.7) p=0.81

[35] Intention-to-treat baseline characteristics only published as research letter; the authors state that no differences except LVEF significantly lower among patients in the study group identified.

Author, year	Li et al., 2021 [43]	Vinther et al., 2021 [46]	Upadhyay et al., 2019 [44, 45]
Baseline characteristics and comorbidities *(continuation)*		*Beta-blockers, %* Study group: 74; Control group: 94 *Aldosterone antagonist, %* Study group: 47; Control group: 81; p<0.05 *Oral anticoagulation, %* Study group: 11; Control group: 13	
Follow-up (months)	12 months	6 months	6 months (QRS duration, LVEF change) 12 months (cardiovascular hospitalisation or death)
Loss to follow-up, n (%)	0 (0%)	0 (0%)	1 (2.4%)
Cross-over	NA	*Intention-to-treat:* Study group: 25 patients; Control group: 25 patients *Per-Protocol:* Study group: 19 patients (18 with randomization to His-CRT, 1 with randomization to BiV-CRT) Control group: 31 patients (24 with randomization to BiV-CRT, 7 to randomization to His-CRT)	*Intention-to-treat:* Study group: 21 patients; Control group: 20 patients[36] *Per-Protocol:* Study group: 16 patients (11 with randomization to His-CRT, 5 with randomization to BiV-CRT) Control group: 24 patients (14 with randomization to BiV-CRT, 10 with randomization to His-CRT)
Outcomes			
Efficacy			
Quality-of-life	SF-36 quality-of-life scale was referred to and a questionnaire was designed: ***Physiological function*** *Before operation:* Study group: 33.39 ± 2.42 Control group: 33.25 ± 2.36; p=0.805 *12 months after operation:* Study group: 41.02 ± 2.58[37] Control group: 37.50 ± 2.47[37]; p=0.000 ***Psychological function*** *Before operation:* Study group: 34.37 ± 2.81 Control group: 34.18 ± 2.63; p=0.768 *12 months after operation:* Study group: 43.05 ± 2.92[37] Control group: 39.42 ± 2.72[37]; p=0.000 ***Social relations*** *Before operation:* Study group: 34.87 ± 2.32 Control group: 35.03 ± 2.19; p=0.764	NR	NR

[36] One patient withdrawal after randomization

[37] Compared with that before operation in this group, p<0.01

Author, year	Li et al., 2021 [43]	Vinther et al., 2021 [46]	Upadhyay et al., 2019 [44, 45]
Quality-of-life *(continuation)*	*12 months after operation:* Study group: 44.17 ± 2.84[37] Control group: 39.06 ± 2.51[37]; p=0.000 ***Physical pain*** *Before operation:* Study group: 34.57 ± 2.58 Control group: 34.85 ± 2.61; p=0.649 *12 months after operation:* Study group: 44.56 ± 2.72[37] Control group: 40.25 ± 3.06[37]; p=0.000		
New York Heart Association Class (NYHA)	*NYHA Baseline:* Study group: 2.47 ± 0.38 Control group: 2.58 ± 0.35; p=0.206 *NYHA 12 months*: Study group: 1.57 ± 0.26[37] Control group: 2.03 ± 0.34[37]; p=0.000	***Intention-To-Treat:*** *NYHA:* Study group Baseline: 2.4 ± 0.4 Study group 6 months: 1.8 ± 0.4; p<0.01 Control group Baseline: 2.4 ± 0.4 Control group 6 months: 1.9 ± 0.6; p<0.01 Between Study group and Control group 6 months: p=0.56 *Δ NYHA ≥1, %* Study group: 12 (48%); Control group: 10 (40%) ***Per-Protocol:*** *NYHA, %* Study group Baseline: 2.4 ± 0.4 Study group 6 months: 1.8 ± 0.4; p<0.01 Control group Baseline: 2.4 ± 0.4 Control group 6 months: 1.9 ± 0.5; p<0.01 *Δ NYHA ≥1, %* Study group: 9 (47%); Control group: 13 (42%)	*NYHA Baseline:* Study group: 3.0 (2.25-3.0); Control group: 2.75 (2.25-3.0); p=0.66 *Improvement NYHA ≥1, %* 6 months:Study group: 53%; Control group: 39%; p=0.41 12 months: Study group: 25%; Control group: 31%; p=0.89 *Decline NYHA ≥1, %* 6 months: Study group: 0%; Control group: 0% 12 months: Study group: 6%; Control group: 0%; p=1.0
Implant success	NR[38]	Implantation with capture of the left bundle sustained through 6 months of follow-up: *Intention-To-Treat:* Study group: 18/25 (72%); Control group: 24/25 (96%); p=NR *Per-Protocol:* Study group: 19/26 (73%); Control group: NR; p=NR **Reasons for failure:** Study group: His location found, but the threshold for capturing the left bundle was too high (>5-10 V, often intermittent capture): 6 (24%); His signal not identified, left bundle not captured: 1 (4%) Control group: Dissection in the coronary sinus ostium: 1 (4%)	Successful implantation with correction of QRS: *Intention-To-Treat:* Study group: 11/21 (52%); Control group: 14/20 (70%); p=NR **Reasons for failure:** Study group: Intraventricular conduction delay: 5 (24%) Failure to achieve QRS narrowing <130 ms: 3 (14%) Inability to map His: 2 (9%) Control group: Unable to cannulate: 2 (10%) Suboptimal coronary sinus target branch: 2 (10%) Vascular occlusion: 1 (5%) Withdrawal after randomization: 1 (5%)

[38] Not reported directly (data available 12 months after operation in all patients in both study (36/36) and control group (36/36)).

Author, year	Li et al., 2021 [43]	Vinther et al., 2021 [46]	Upadhyay et al., 2019 [44, 45]
Electrocardiographic parameters	*QRS, ms* Study group: 115.05 ± 18.96 Control group: 132.25 ± 21.25; p=0.000	***Intention-To-Treat*** *QRS, ms* Study group Baseline: 165 ± 14 Study group 6 months: 131 ± 20; p<0.01 Control group Baseline: 167 ± 16 Control group 6 months: 134 ± 15; p<0.01 Between Study group and Control group 6 months: p=0.51 ***Per-Protocol*** *QRS, ms* Study group Baseline: 163 ± 14 Study group 6 months: 129 ± 20; p<0.01 Control group Baseline: 167 ± 15 Control group 6 months: 135 ± 15; p<0.01	***Intention-To-Treat***[39] *QRS, ms* Study group: Baseline QRS: 172 ± 16 ms; Paced QRS: 144 ± 30 ms; p=0.002 Control group: Baseline QRS: 165 ± 18 ms; Paced QRS: 152 ± 30ms; p=0.11 Between Study group and Control group paced: p=0.42 ***On-treatment-analysis*** *QRS, ms* Study group: Baseline QRS: 174 ± 18 ms; Paced QRS: 125 ± 22 ms; p<0.01 Control group: Baseline QRS: 165 ± 17 ms; Paced QRS: 164 ± 25 ms; p=0.82 Study group paced vs. control group paced: 125 ± 22 ms vs. 164 ± 25 ms, p<0.01 **Per-Protocol** *QRS, ms* Study group: 124 ± 19 ms; Control group: 162 ± 24 ms; p<0.01
Echocardiographic parameters	*LVEF (%)* Before operation: Study group: 35.18 ± 2.09 Control group: 35.29 ± 2.12; p=0.825 12 months after operation: Study group: 45.37 ± 2.31[37] Control group: 39.57 ± 2.27[37]; p=0.000	***Intention-To-Treat*** *LVEF, %* Study group Baseline: 30 ± 6 Study group 6 months: 46 ± 9; p<0.01 Control group Baseline: 30 ± 8 Control group 6 months: 43 ± 7; p<0.01 Between Study group and Control group 6 months: p=0.27 *Δ LVEF, %* Study group: 16 ± 7; Control group: 13 ± 6; p=NR ***Per-Protocol*** *LVEF, %* Study group Baseline: 31 ± 6 Study group 6 months: 48 ± 8; p<0.01 Control group Baseline: 29 ± 8 Control group 6 months: 42 ± 8; p<0.01 Between Study group and Control group 6 months: p<0.05 *Δ LVEF, %* Study group: 17 ± 8; Control group: 13 ± 6; p=0.053	***Intention-To-Treat***[40] *LVEF, %* Study group Baseline: 26.3; Study group 6 months: 31.9; p<0.01 Control group Baseline: 30.5; Control group 6 months: 34.0; p<0.01 *Median change in LVEF, % (IQR %)* Study group:+9.1 (5.0-14.4); Control group: +5.2 (1.5 – 11.3); p=0.33 *Rate of echocardiographic response:* Study group: 76%; Control group: 53%; p=0.13 ***On-treatment-analysis*** *LVEF (%)* Study group: Baseline LVEF: 28.0%; Follow-Up LVEF: 34.6%; p<0.01 Control group: Baseline LVEF: 27.7%; Follow-Up LVEF: 32.0%; p<0.01 *Median change in LVEF:* Study group: +7.2%; Control group: +5.9%; p=0.17 *Rate of echocardiographic response:* Study group: 80%; Control group: 57%; p=0.14

[39] Intention-To-Treat measurements for QRS duration only published as research letter.

[40] Intention-to-treat measurements of change in LVEF only published as research letter.

Author, year	Li et al., 2021 [43]	Vinther et al., 2021 [46]	Upadhyay et al., 2019 [44, 45]
Echocardiographic parameters *(continuation)*			***Per-Protocol*** *Median change in LVEF:* Study group: +11.8; Control group: +5.2; p=0.11 Rate of echocardiographic response: Study group: 91%; Control group: 54%; p=0.78
Laboratory parameters	NR	***Intention-To-Treat*** *NT-proBNP, pmol/l* Study group Baseline: 139 ± 124 Study group 6 months: 59 ± 78; p<0.01 Control group Baseline: 86 ± 79 Control group 6 months: 44 ± 32; p<0.05 Between Study group and Control group 6 months: p=0.46 ***Per-Protocol*** *NT-proBNP, pmol/l* Study group Baseline: 107 ± 90 Study group 6 months: 45 ± 65; p<0.05 Control group Baseline: 115 ± 118 Control group 6 months: 56 ± 55; p<0.05	NR
Safety			
Mortality	NR[41]	Study group: 0 (0%) Control group: 0 (0%) p=NR	*Intention-to-treat:* Study group: NR; Control group: NR Total: 2 (5%)[42] p=NR *Per-Protocol:* Study group: 2 (12%); Control group: 0 (0%) p=NR
Major adverse cardiac events (MACE)	NR	NR	NR
Serious adverse events (SAE)	NR	NR	NR
Adverse events/ Complications	*Hemopneumothorax (%)* Study group: 0.00; Control group: 5.56; p=0.473 *Pericardial effusion* Study group: 2.78; Control group: 8.33; p=0.607 *Catheter electrode displacement* Study group: 2.78; Control group: 8.33; p=0.607 *Total* Study group: 5.56; Control group: 22.22; p=0.041	*Periprocedural complications* Study group: 1 (4%); Control group: 1 (4%); p=NR	***Per-Protocol*** *Ventricular tachycardia/ventricular fibrillation:* Study group: 2 (12%); Control group 0 (0%); p=0.16 *Periprocedural complications* Study group: 1 (6%); Control group: 3 (12%); p=NR *Infectious complications* Study group: 0 (0%); Control group: 0 (0%); p=NR

[41] Not reported directly (data available 12 months after operation in all patients in both study (36/36) and control group (36/36)).

[42] In research letter with intention-to-treat analysis, 2 deaths reported across groups with no information on study arm.

Author, year	Li et al., 2021 [43]	Vinther et al., 2021 [46]	Upadhyay et al., 2019 [44, 45]
Hospitalisations	NR	Study group: 0 (0%); Control group: 2 (8%); p=NR *Reasons for hospitalisations:* Dislodgement of the LV-lead: 1 (4%) Device endocarditis: 1 (4%)	Study group: NR; Control group: NR; p=NR Total: 6/41 hospitalisations[43] (15%) *Reasons for hospitalisations:* Heart failure: 3 (7%); Periprocedural: 2 (5%) Atrial fibrillation requiring cardioversion: 1 (2%)
Increase in capture threshold	*Pacing threshold (V)* During operation: Study group: 1.45 ± 0.52 Control group: 0.81 ± 0.41; p=0.000 12 month follow-up: Study group: 1.42 ± 0.61 Control group: 0.78 ± 0.43; p=0.000	***Intention-To-Treat*** *Threshold LV-/His-lead, V at 1 ms* Study group Baseline: 1.8 ± 1.2 Study group 6 months: 2.3 ± 1.4; p<0.05 Control group Baseline: 1.2 ± 0.8 Control group 6 months: 1.4 ± 0.5; p=NR Between Study group and Control group Baseline: p<0.05 Between Study group and Control group 6 months: p<0.05 ***Per-Protocol*** *Threshold LV-/His-lead, V at 1 ms* Study group Baseline: 2.2 ± 1.2 Study group 6 months: 2.4 ± 1.6; p=0.28 Control group Baseline: 1.1 ± 0.7 Control group 6 months: 1.5 ± 0.6; p<0.05 Between Study group and Control group Baseline: p<0.05 Between Study group and Control group 6 months: p<0.05	***Intention-To-Treat*** *Pacing threshold (V)* During operation: Study group: 1.7; Control group: 0.9; p=0.046 Follow-up: Study group: NR; Control group: NR; p=NR ***Per-Protocol*** *His or LV threshold (V)* During operation: Study group: 2.75 (1.25-3.38) Control group: 0.85 (0.73-1.31); p=0.002 6 month follow-up: Study group: 2.00 (1.00-3.25) Control group: 0.94 (0.75-1.25); p=0.004

Abbreviations: AVB – atrioventricular block, BiV-CRT – biventricular cardiac resynchronisation therapy, BMI – body mass index, CABG – coronary artery bypass graft surgery, CI – Confidence interval, COPD – chronic obstructive pulmonary disease, CRT – cardiac resynchronisation therapy, eGFR – estimated glomerular filtration rate, HBP – his bundle pacing, His-CRT – His bundle cardiac resynchronisation therapy, LBBB – left bundle branch block, LBBP – left bundle branch pacing, LV – left ventricle, LVEF – left ventricular ejection fraction, MACE – major adverse cardiac events, ms – milliseconds, NA – not applicable, NR – not reported, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, NYHA – New York Heart Association class, p – p-value, PCI – percutaneous coronary intervention, pts – patients, RVAP – right ventricular apex pacing, SAE – serious adverse events, SF-36 – short form 36 questionnaire, V – Volt, yrs – years

[43] Only total number of hospitalisations for both groups reported.

Table A-3: His-bundle pacing: Results from observational studies

Author, year	Abdelrahman et al., 2018 [3]
Country	USA
Sponsor	Not reported
Intervention/ Product	His bundle pacing Medtronic C315 and C304 His-sheath®, 3830 SelectSecure lead®
Comparator	Right ventricular pacing (RVP)
Indication	Bradycardia
Study design	Retrospective cohort study
Number of pts	765 (332 HBP and 433 RVP)
Inclusion criteria	■ Patients ≥ 18 years ■ Requirement for de novo permanent pacemaker implantation for bradycardia indications
Exclusion criteria	■ Younger than 18 years of age ■ Patients that had undergone cardiac resynchronisation therapy ■ Existing cardiac implantable electronic device
Age of patients (yrs)	Study group: 74.8 ± 11.0; Control group: 76.4 ± 11.3; p=0.053
Gender (%)	Study group: 60.2% male, 39.8% female Control group: 52.4% male, 47.6% female p=0.03
Baseline characteristics and comorbidities	*Active smokers* Study group: 6.6%; Control group: 4.6%; p=0.23 *Hypertension:* Study group: 85.2%; Control group: 82.7%; p=0.34 *Diabetes* Study group: 31.9%; Control group: 35.0%; p=0.39 *Hyperlipidemia* Study group: 71.7%; Control group: 72.7%; p=0.75 *Coronary artery disease* Study group: 21.4%; Control group: 17.8%; p=0.21 *Chronic kidney disease* Study group: 36.1%; Control group: 29.6%; p=0.056 *Ischemic stroke* Study group: 13.0%; Control group: 11.3%; p=0.49 *Heart failure* Study group: 25.6%; Control group: 31.2%; p=0.09 *Atrial fibrillation* Study group: 56.9%; Control group: 44.6%; p<0.01 *Baseline medical regimen, beta-blocker:*[44] Study group: 78.9%; Control group: 72.8%; p=0.049 *Baseline ejection fraction, %* Study group: 54.9 ± 8.5; Control group: 54.2 ± 10.2; p=0.28 *Baseline QRS duration, ms* Study group: 104.5 ± 24.5; Control group: 110.5 ± 28.4; p<0.01 *Ventricular pacing burden* Study group: 54.5 ± 45.2; Control group: 58.3 ± 43.8; p=0.24 *Sinus node dysfunction* Study group: 36.0%; Control group: 35.0%; p=0.90 *AV conduction disease* Study group: 64.0%; Control group: 65.0%; p=0.80 *Dual-chamber permanent pacemaker* Study group: 81.3%; Control group: 85.2%; p=0.15 *Single-chamber permanent pacemaker* Study group: 15.4%; Control group: 14.8%; p=0.82

[44] For angiotensin-converting-enzyme, angiotensin-receptor-blocker, loop diuretics, spironolactone, antiarrhythmics (including amiodarone), no statistically significant baseline characteristics were identified.

Author, year	Abdelrahman et al., 2018 [3]
Baseline characteristics and comorbidities *(continuation)*	*Subgroup of patients with baseline LVEF <50%:*[45] Study group: 37 patients; Control group: 62 patients; *Subgroup atrial fibrillation:* Study group: 81%; Control group: 58%; p<0.05 *Subgroup baseline ejection fraction, %:* Study group: 38 ± 7; Control group: 36 ± 8; p<0.01
Follow-up (months)	Mean follow-up entire cohort: 725 ± 423 days (23.9 ± 13.9 months) Median follow-up study group: 754 days (24.8 months) Median follow-up control group: 648 days (21.3 months) p=0.01
Loss to follow-up, n (%)	Study group: 16 (4.8%); Control group: 15 (3.5%)
Cross-over	NA
Quality-of-life	NR
New York Heart Association Class (NYHA)	NR
Implant success	Study group: 304/332 (91.6%); Control group: 433/433 (100%) *Reasons for failure:* Study group: Inability to map the His bundle: 8 patients Inability to successfully fix the lead: 3 patients Inability to recruit distal His-Purkinje conduction: 11 patients Inability to correct high thresholds: 6 patients Control group: NA
Electrocardiographic parameters	*QRS, ms* Study group implantation: 104.5 ± 24.5 Study group follow-up: 128 ± 27.7 Control group implantation: 110.5 ± 28.4 Control group follow-up: 166 ± 21.8 Between Study group and Control group implantation, p<0.01 Between Study group and Control group follow-up, p<0.01
Echocardiographic parameters	*LVEF, %*[46] Study group: 51.3 ± 10.4; Control group: 44.2 ± 15; p=0.01
Laboratory parameters	NR
Mortality	*Mortality* Study group: 17.2%; Control group: 21.4% Univariate analysis: Hazard ratio: 0.728 (95% CI: 0.523–1.014); p=0.06 Multivariate analysis: NA
Major adverse cardiac events (MACE)	NR
Serious adverse events (SAE)	NR
Adverse events/Complications	*Composite* *(all-cause mortality, heart failure hospitalisations or upgrade to biventricular pacing):* Study group: 25%; Control group: 31.6%; Hazard ratio: 0.71; p=0.02 Study subgroup, baseline LVEF <50%: 14/37 (37.8%) Control subgroup, baseline LVEF <50%: 33/62 (53.2%) Univariate analysis Hazard ratio: 0.349 (95% CI: 0.138-0.883); p=0.03 Multivariate analysis Hazard ratio: 0.384 (95% CI: 0.146-1.013); p=0.053 Study subgroup, baseline LVEF <50%: 14/37 (37.8%) Study subgroup, baseline LVEF ≥50%: 69/295 (23.3%)

[45] For the subgroup of patients with baseline LVEF <50%, the baseline differences for age, gender, hypertension, diabetes, coronary artery disease requiring intervention, chronic kidney disease, ventricular pacing burden, sinus node dysfunction or atrioventricular conduction disease were statistically not significant.

[46] Echocardiograms were only available for 34 (11.2%) patients in the study group and 71 (16.4%) patients in the control group.

Author, year	Abdelrahman et al., 2018 [3]
Adverse events/Complications *(continuation)*	Univariate analysis Hazard ratio: 2.92 (95% CI: 1.429-5.965); p<0.01 Multivariate analysis Hazard ratio: 1.966 (95% CI: 0.928-4.168); p=0.08 Control subgroup, baseline LVEF <50%: 33/62 (53.2%) Control subgroup, baseline LVEF ≥50%:104/371 (28.0%) Univariate analysis Hazard ratio: 2.699 (95% CI: 1.631-4.467); p<0.01 Multivariate analysis Hazard ratio: 1.785 (95% CI: 1.054-3.023); p=0.03 *Upgrade to biventricular pacing:* Study group: 0.3%; Control group: 1.4% Hazard ratio: 0.211 (95% CI: 0.025-1.752); p=0.15 *Ventricular lead revision required:* Study group: 4.2%; Control group: 0.5%; p=NR *Pericardial effusion:* Study group: 0 (0%); Control group: 3 (0.7%); p=NR *Infection necessitating device or lead removal:* Study group: 1 (0.3%); Control group: 1 (0.2%); p=NR *Premature battery depletion:* Study group: 1 (0.3%); Control group: 0 (0%); p=NR
Hospitalisations	*Heart failure hospitalisations:* Study group: 12.4%; Control group: 17.6% Hazard ratio: 0.642 (95%CI: 0.439-0.939) p=0.02
Increase in capture threshold	*Capture threshold, V* Study group implantation: 1.30 ± 0.85 Study group follow-up: 1.56 ± 0.95 Control group implantation: 0.59 ± 0.42 Control group follow-up: 0.76 ± 0.29 Between Study group and Control group implantation, p<0.01 Between Study group and Control group follow-up, p<0.01 *Change in threshold, V* Study group: 0.28 ± 1.1; Control group: 0.16 ± 0.5; p=0.09

Abbreviations: AVB – atrioventricular block, BiV-CRT – biventricular cardiac resynchronisation therapy, BMI – body mass index, CABG – coronary artery bypass graft surgery, CI – Confidence interval, COPD – chronic obstructive pulmonary disease, CRT – cardiac resynchronisation therapy, eGFR – estimated glomerular filtration rate, HBP – his bundle pacing, His-CRT – His bundle cardiac resynchronisation therapy, LBBB – left bundle branch block, LBBP – left bundle branch pacing, LV – left ventricle, LVEF – left ventricular ejection fraction, MACE – major adverse cardiac events, ms – milliseconds, NA – not applicable, NR – not reported, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, NYHA – New York Heart Association class, p – p-value, PCI – percutaneous coronary intervention, pts – patients, RVAP – right ventricular apex pacing, SAE – serious adverse events, SF-36 – short form 36 questionnaire, V – Volt, yrs – years

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [55] and in the Guidelines of EUnetHTA [56, 57].

Table A-4: Risk of bias – study level (randomised studies), see [56]

Trial	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Li et al. 2021 [43]	Some concerns[47]	Low	Low	High[48]	Low	High
Vinther et al., 2021 [46]	Low	High[49]	Low	High[48]	Low	High
Upadhyay et al., 2019 [44, 45]	Some concerns[47, 50]	High[49]	High[51]	High[48]	Low	High

[47] No detailed information for the randomization process provided.

[48] The knowledge of the assigned intervention could have influenced the participant-reported outcomes (e.g. the NYHA classification or the quality-of-life questionnaire).

[49] Unbalanced deviations from intended intervention between groups, with a likely effect on the reported outcomes.

[50] Statistically significant difference for LVEF at baseline.

[51] Only total number of hospitalisations for both groups reported, with missing individual measurements of each group.

Table A-5: Risk of bias of non – randomised studies comparing HBP versus other types of pacing (e.g. RVP, BVP) [57]

Study reference/ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Michalik et al., 2021 [58]	Serious[52]	Moderate[53]	Low	Moderate[54]	Serious[55]	Moderate[56]	Low	Serious	Funding: no external funding Conflict of interest: none declared.
Abdelrahman et al., 2018 [3]	Moderate[57]	Moderate[58]	Low	Low	Some concerns[59]	Moderate[56]	Low	Moderate	Funding: not reported Conflict of interest: three authors received speaker or consultant fees or research support from Medtronic. One author is a consultant for Boston Scientific and Abbott.
Zanon et al., 2011 [59]	Serious[60]	Moderate[61]	Moderate[62]	Low	Serious[63]	Moderate[56]	Low	Serious	Funding: not reported Conflict of interest: three authors are employees of Medtronic Inc.

AF – atrial fibrillation; AVB – atrioventricular block; HBP – his-bundle pacing; LBBP – left bundle branch pacing; RBBB – right bundle branch block

[52] 8/26 patients in group 1 were diagnosed with permanent AF and high-degree AVB compared to 13/24 patients in group 2. Sinus rhythm and AVB was present for 18/26 patients in group 1 compared to 11/24 patients in group 2; further possible baseline confounding cannot be ruled out.

[53] Single-center study, unclear if all participants who would have been eligible for the target trial were included in the study.

[54] HBP was failed in 2/26 patients leading to bias due to deviation from intended intervention.

[55] Not all echocardiogram results included in study (only echocardiograms of good quality and with frame rates between 40 and 80 frames per second were included).

[56] For some of the outcomes, the measure was potentially subjective (e.g. influenced by knowledge of the intervention received by study participants).

[57] Statistically significant baseline differences present for gender, atrial fibrillation, use of beta-blockers and QRS duration at baseline. Additional possible baseline confounding cannot be ruled out.

[58] Two-center study, with all attempted HBP in the first center and all attempted RVP in the second center, start of follow up and start of intervention do not coincide for all participants.

[59] Loss to follow-up in 4.8% in study group and 3.5% in control group.

[60] Baseline confounding present, additional residual/unmeasured confounding cannot be ruled out.

[61] Multi-center study, unclear if all participants who would have been eligible for the target trial were included in the study.

[62] The classification of intervention status could have been affected by knowledge of the outcome or risk of the outcome (the choice of the specific target pacing site was left to physician decision).

[63] Comparisons between follow-up data were made only for patients with at least 24 months of follow-up and data of all scheduled visits available (in the HBP group, data available for 213/307 participants).

Table A-6: Evidence profile: efficacy and safety of His bundle pacing in patients requiring a pacemaker or cardiac resynchronisation [40]

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBP	SoC Pacing (RVP or BVP)		
EFFICACY (Randomised controlled trials)										
Quality-of-life										
1 [43]	RCT	Very serious[a]	Not serious	Serious[b]	Very serious[c]	none	36	36	*Physiological function:* 41.02 ± 2.58 vs. 37.50 ± 2.47; p=0.000 *Psychological function:* 43.05 ± 2.92 vs. 39.42 ± 2.72; p=0.000 *Social relations:* 44.17 ± 2.84 vs. 39.06 ± 2.51; p=0.000 *Physical pain:* 44.56 ± 2.72 vs. 40.25 ± 3.06; p=0.000	⨁◯◯◯ Very low
New York Heart Association Class (NYHA) 6 months										
2 [44-46]	RCT	Very serious[a]	Not serious	Not serious	Very serious[c]	none	46	45	*NYHA (1 study, n=50)* 1.8 ± 0.4 vs. 1.9 ± 0.6; p=0.56 *Δ NYHA ≥1, % (1 study, n=50)* 12 (48%) vs. 10 (40%); p=NR *Improvement NYHA ≥1, % (1 study, n=41)* 53% vs. 39%; p=0.41 *Decline NYHA ≥1, % (1 study, n=41)* 0% vs. 0%; p=NR	⨁◯◯◯ Very low
New York Heart Association Class (NYHA) 12 months										
2 [43-45]	RCT	Very serious[a]	Serious[d]	Not serious	Very serious[c]	none	57	56	*NYHA (1 study, n=72)* 1.57 ± 0.26 vs. 2.03 ± 0.34; p=0.000 *Improvement NYHA ≥1, % (1 study, n=41)* 25% vs. 31%; p=0.89 *Decline NYHA ≥1, % (1 study, n=41)* 6% vs. 0%; p=1.0	⨁◯◯◯ Very low
Implant success										
2 [44-46]	RCT	Not serious	Serious[d]	Serious[f]	Very serious[c]	none	46	45	*Implant success (2 studies, n=91)* 18/25 (72%) vs. 24/25 (96%); p=NR 11/21 (52%) vs. 14/20 (70%); p=NR	⨁◯◯◯ Very low

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBP	SoC Pacing (RVP or BVP)		
Electrocardiographic parameters										
3 [43-46]	RCT	Not serious	Serious[d]	Serious[g]	Very serious[c]	none	82	81	*QRS, ms (3 studies, n=163)* 115.05 ± 18.96 vs. 132.25 ± 21.25; p=0.000 131 ± 20 vs. 134 ± 15; p=0.51 144 ± 30 ms vs. 152 ± 30 ms; p=0.42	⨁◯◯◯ Very low
Echocardiographic parameters										
3 [43-46]	RCT	Not serious	Serious[d]	Serious[g]	Very serious[c]	none	82	81	*LVEF, % (3 studies, n=163)* 45.37 ± 2.31 vs. 39.57 ± 2.27: p=0.000 46 ± 9 vs. 43 ± 7; p=0.27 31.9% vs. 34.0%; p=NR	⨁◯◯◯ Very low
Laboratory parameters										
1 [46]	RCT	Not serious	Not serious	Not serious	Very serious[c]	none	25	25	*NT-proBNP, pmol/l (1 study, n=50)* 59 ± 78 vs. 44 ± 32; p=0.46	⨁⨁◯◯ Low
SAFETY (Randomised controlled trials)										
Mortality										
2 [44-46]	RCT	Not serious	Serious[d]	Serious[h]	Very serious[c]	none	46	45	Mortality (2 studies, n=91) 0 (0%) vs. 0 (0%); p=NR 2 (12%) vs. 0 (0%); p=NR	⨁◯◯◯ Very low
Adverse events/Complications										
3 [43-46]	RCT	Not serious	Serious[d]	Serious[h]	Very serious[c]	none	82	81	*Periprocedural complications (2 studies, n=91)* 1 (4%) vs. 1 (4%); p=NR 1 (6%) vs. 3 (12%); p=NR *Hemopneumothorax (%) (1 study, n=72)* 0.00 vs. 5.56; p=0.473 *Pericardial effusion (1 study, n=72)* 2.78 vs. 8.33; p=0.607 *Catheter electrode displacement (1 study, n=72)* 2.78 vs. 8.33; p=0.607 *Total (1 study, n=72)* 5.56 vs. 22.22; p=0.041 *Ventricular tachycardia/ventricular fibrillation (1 study, n=41)* 2 (12%) vs. 0 (0%); p=0.16 *Infectious complications (1 study, n=41)* 0 (0%) vs. 0 (0%); p=NR	⨁◯◯◯ Very low

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBP	SoC Pacing (RVP or BVP)		
Hospitalisations										
2 [44-46]	RCT	Serious[a]	Serious[e]	Not serious	Very serious[c]	In one study, only total values (across both groups) for hospitalisations were reported	46	45	*Hospitalisations per group (1 study, n=50)* 0 (0%) vs. 2 (8%); p=NR *Hospitalisations across groups (1 study, n=41)* 6 (15%)	⨁◯◯◯ Very low
Increase in capture threshold										
3 [43-46]	RCT	Not serious	Not serious	Not serious	Very serious[c]	none	82	81	*Pacing threshold, V (3 studies, n=163)* 1.42 ± 0.61 vs. 0.78 ± 0.43; p=0.000 2.3 ± 1.4 vs. 1.4 ± 0.5; p<0.05 2.00 (1.00-3.25) vs. 0.94 (0.75-1.25); p=0.004	⨁⨁◯◯ Low
SAFETY (Observational studies)										
Mortality										
1 [3]	Retrospective cohort study	Serious[i]	Not serious	Not serious	Not serious	none	304	433	*Mortality (1 study, n=707)* 17.2% vs. 21.4% Hazard ratio: 0.728 (95% CI: 0.523–1.014); p=0.06	⨁◯◯◯ Very low
Adverse events/Complications										
1 [3]	Retrospective cohort study	Serious[i]	Not serious	Not serious	Not serious	none	304	433	*Composite: all-cause mortality, heart failure hospitalisations or upgrade to biventricular pacing (1 study, n=707)* 25% vs. 31.6% Hazard ratio: 0.71; p=0.02 *Upgrade to biventricular pacing (1 study, n=707)* 0.3% vs. 1.4% Hazard ratio: 0.211 (95% CI: 0.025-1.752); p=0.15 *Ventricular lead revision required (1 study, n=707)* 4.2% vs. 0.5%; p=NR *Pericardial effusion (1 study, n=707)* 0% vs. 0.7%; p=NR *Infection necessitating device or lead removal (1 study, n=707)* 0.3% vs. 0.2%; p=NR *Premature battery depletion (1 study, n=707)* 0.3% vs. 0%; p=NR	⨁◯◯◯ Very low

Quality assessment							Summary of findings			
							Number of analysed patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HBP	SoC Pacing (RVP or BVP)		
Hospitalisations										
1 [3]	Retrospective cohort study	Serious[i]	Not serious	Not serious	Not serious	none	304	433	*Heart failure hospitalisations (1 study, n=707)* 12.4% vs. 17.6% Hazard ratio: 0.642 (95%CI: 0.439-0.939); p=0.02	⨁◯◯◯ Very low
Increase in capture threshold										
1 [3]	Retrospective cohort study	Serious[i]	Not serious	Not serious	Not serious	none	304	433	*Capture threshold, V (1 study, n=707)* 1.56 ± 0.95 vs. 0.76 ± 0.29; p<0.01 *Change in threshold, V (1 study, n=707)* 0.28 ± 1.1 vs. 0.16 ± 0.5; p=0.09	⨁◯◯◯ Very low

Abbreviations: BVP – biventricular pacing, HBP – His bundle pacing, LBBP –,left bundle branch pacing, ms – milliseconds, NR – not reported, NRCT – non-randomised controlled trial, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, NYHA – New York Heart Association (Classification), p – p-value, RCT – randomised-controlled trial, RVP – right ventricular pacing

Explanations:

[a] *Participants and carers had knowledge of the assigned intervention, potentially influencing the measurement of this outcome.*

[b] *Not enough information on what kind of variation from the SF-36 questionnaire was used for the measurement.*

[c] *Small number of patients, studies were potentially statistically underpowered to detect a difference in this outcome.*

[d] *Variation in effect size present for this outcome.*

[e] *Unclear if inconsistency present, as one study only provided total values of this outcome across both groups.*

[f] *The definitions for implant success were differing across studies (e.g. capture of the left bundle branch vs. correction of QRS).*

[g] *Comparison of this outcome before and after pacing, but difference in timing of measurement across studies.*

[h] *Insufficient length of follow-up for measurement of this outcome.*

[i] *Retrospective data collection; statistically significant baseline differences in gender, atrial fibrillation, use of beta-blockers and QRS duration at baseline.*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Applicability table

Table A-7: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Within the included studies, not all indications for HBP were fully covered. The use of HBP in patients with heart failure was assessed by all three RCTs. However, for the use of HBP in cardiac conduction system disease, there was no randomised evidence available. Patients with atrial fibrillation were included in addition to heart failure in one RCT, while another RCT listed atrial fibrillation as exclusion criterion. The "pace and ablate" strategy for atrial fibrillation was not assessed in the included studies. These differences in inclusion and exclusion criteria across the studies could limit the applicability to the target population.
Intervention	All of the included studies used HBP as an intervention. In all included studies, the products used were the Medtronic C315 or C304 His-sheath®, and the Medtronic 3830 SelectSecure lead®. In none of the included studies, the Agilis HisPro® by Abbott Laboratories was used for HBP.
Comparators	BVP was the comparator in two of the included RCTs. RVP was the comparison in one of the included RCTs, as well as in the observational cohort study. Other forms of physiological pacing, such as left bundle branch pacing, were excluded from the evidence synthesis of this systematic review. The use of different comparators may affect the included comparative trial results.
Outcomes	The most frequently reported crucial outcome was NYHA functional class, which was reported in all three included RCTs. The other crucial effectivenss outcome, health-related quality-of-life, was reported in one RCT. The most frequently reported safety outcomes, QRS duration, change of LVEF, adverse events as well as increase in capture threshold, were reported in all three RCTs as well as the observational cohort study. Mortality rates and hospitalisations were reported in two RCTs and the cohort study. Follow-ups ranged from six to twelve months (in the RCTs) and 24 months (in the observational cohort study). Due to small sample sizes in the RCTs and short follow-up times in all included studies, the presented data in the studies is limited.
Setting	The studies were published between 2018 and 2021. The inpatient settings of the included studies reflect the clinical setting in which the technology is intended to be used appropriately. The included RCTs were carried out in China, Denmark and the USA. The included cohort study was carried out in the USA. It is not expected that the results from these studies are limited by the geographical settings, with no applicability issues identified.

Abbreviations: BVP – Biventricular pacing; HBP – His-bundle pacing; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; RCT – randomised controlled trial; USA – United States of America

List of ongoing randomised controlled trials

Table A-8: List of ongoing randomised controlled trials of His-bundle pacing

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Number of patients planned	Primary completion date	Sponsor
NCT04529577/ HIS-PrEF	Heart failure	HBP first (cross-over design)	RVP first (cross-over design)	Difference in LVEF after 6 months	40	12/2022	Region Skane University Hospital
NCT04672408/ His-PACE	Standard pacing indication with >20% ventricular pacing, baseline LVEF >40%	HBP	RVP	Difference in LVEF after 6 months	50	02/2023	Geneva University Hospital
NCT04544345	AV-block	HBP	Backup VVI (ventricular only) pacing	Changes in exercise capacity, left ventricular stroke volume and quailty of life after 6 months	16	07/2022	Ljubljana University Medical Center
NCT04093414/ LEFTBASH	Bradycardia, Sinus node dysfunction, AV-block	HBP	LBBAP	Ventricular capture threshold after 3 months	26	12/2023	William Beaumont Hospitals
NCT03685617	Slow arrhythmia	HBP	BVP	Changes of QRS and QT duration, threshold value, changes in BNP, echocardiographic parameters	84	03/2020	Hebei Medical University
NCT02671903/ HOPE-HF	Heart failure	CRT with HBP first (cross-over design)	CRT without HBP first (cross-over design)	Changes in exercise capacity	198	10/2020	Imperial College London
NCT04512586/ His-PAAF	Atrial fibrillation	HBP and AV node ablation	Atrial fibrillation ablation by pulmonary vein isolation	Health-related quality-of-life after 12 months	90	12/2021	Region Skane University Hospital
NCT04546555/ PACE-HFpEF	Heart failure	Bachmann's bundle pacing without HBP; Bachmann's bundle pacing with HBP	No pacing	Change in composite Minnesota-Living-with-Heart-Failure Questionnaire score Percent change in NT-proBNP	20	02/2022	University of Vermont
NCT04409119/ HIS-alt_2	Heart failure, left bundle branch block	HBP/LBBP	LV pacing	Change in LVEF and implant success at 6 months	125	12/2023	Rigshospitalet, Denmark
NCT04482816/ PHYS-TAVI	Pacing indication after TAVI	Physiological pacing (His or branch)	RVP	Survival; Improvement >1 point in NYHA class or >25% increase in distance covered in the 6-minute walking test at 12 months	24	09/2023	Hospital Clinic of Barcelona
NCT05187611/ CONSYST-CRT	Heart failure, Cardiac conduction system disease	Conduction system pacing (Pacing the His-Purkinje system)	BVP	All-cause mortality, cardiac transplant, heart failure hospitalisation and LVEF improvement <5 points at 12 months	130	01/2023	Hospital Clinic of Barcelona

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Number of patients planned	Primary completion date	Sponsor
ChiCTR1900020817	Bradycardia	HBP	RVP	Ventricular synchronisation, LVEF, LVOT-VTI, Valve regurgitation, QRS duration	100	06/2022	Shanghai Chest Hospital
NCT04054895/ LEVEL-AT	AV-block, indication for resynchronisation therapy	Physiological pacing (Pacing the His-Purkinje system)	BiV-CRT	Left ventricular activation time at 45 days	70	06/2022	Hospital Clinic of Barcelona
NCT05029570/ PACE-FIB	Heart failure, atrial fibrillation	Conduction system pacing and AV node ablation	Medical treatment for rate control of atrial fibrillation	All-cause mortality, heart failure hospitalisation and worsening heart failure at 36 months	334	11/2026	University Hospital Madrid

Abbreviations: AV – atrioventricular; BiV-CRT – Biventricular cardiac resynchronisation therapy; BNP – B-type natriuretic peptide; BVP – Biventricular pacing; HBP – His-bundle pacing; LBBAP – left bundle branch area pacing; LBBP – left bundle branch pacing; LV – left ventricular; LVEF – left ventricular ejection fraction; RVP – rightventricular pacing; TAVI – transcatheter aortic valve implantation

Research questions

Table A-9: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table A-10: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-11: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0003	What is the effect of the technology on the mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality-of-life?
D0013	What is the effect of the technology on disease-specific quality-of-life?
D0017	Was the use of the technology worthwhile?

Table A-12: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

Literature search strategies

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 16, 2021>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2017 to December 16, 2021>	
Search date: 17.12.2021	
ID	Search
1	exp Heart Failure/ (164076)
2	exp Cardiomyopathy, Dilated/ (18478)
3	exp Shock, Cardiogenic/ (12060)
4	cardiogenic shock.mp. (18099)
5	exp Ventricular Dysfunction/ (48821)
6	exp Cardiac Output, Low/ (5752)
7	((heart* or cardiac* or myocardial or cardio* or ventric*) adj4 (failure* or de?compensat* or de-compensat* or insufficient* or dysfunct* or stand?still or stand-still)).mp. (400914)
8	((congestive or chronic) adj4 heart failure*).mp. (76222)
9	((dilated or congestive) adj4 (cardio?myopath* or cardio-myopath*)).mp. (30610)
10	((left ventricular or left ventricle) adj4 (failure* or insufficien* or dysfunction*)).mp. (35582)
11	(lvsd or hf or chf).ti,ab. (94516)
12	exp Bundle-Branch Block/ (10572)
13	(LBBB or RBBB).ti,ab. (3431)
14	exp Atrioventricular Block/ (4045)
15	AV-Block*.mp. (5086)
16	((bundle?branch* or bundle-branch* or fascic* or atrio?ventricular or atrio-ventricular) adj4 block*).mp. (30251)
17	((prolong* or delay*) adj4 PR adj4 interval*).mp. (931)
18	exp Cardiac Conduction System Disease/ (107573)
19	(cardiac conduction adj4 (failure* or disease*)).mp. (2642)
20	exp Atrial Fibrillation/ (81863)
21	((atrial or auricular) adj2 fibrillat*).mp. (128598)
22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (677508)
23	exp "Bundle of His"/ (4609)
24	(Bundle* of His or His Bundle* or Para-His).mp. (7104)
25	23 or 24 (7104)
26	exp Cardiac Pacing, Artificial/ (29817)
27	pacing*.mp. (51012)
28	26 or 27 (55604)
29	25 and 28 (2713)
30	HBP.ti,ab. (3915)
31	((His-bundle* or (bundle* adj4 His) or His?bundle* or para?his* or para-his*) adj4 pacing).mp. (1331)
32	His pacing*.mp. (53)
33	29 or 30 or 31 or 32 (6321)
34	22 and 33 (2215)
35	limit 34 to dt=20170505-20211217 (1038)
36	limit 35 to (english or german) (1026)
37	remove duplicates from 36 (522)
Total hits: 522	

Search strategy for Embase

Search Name: His bundle pacing (MEL 2022)		
Comment: MEL 2022 (RJ/BW)		
Search date: 17.12.2021		
No.	Query Results	Results
#39.	#37 NOT #38	662
#38.	#37 AND 'Conference Abstract'/it	417
#37.	#36 AND ([english]/lim OR [german]/lim)	1,079
#36.	#35 AND [5-5-2017]/sd NOT [18-12-2021]/sd	1,09
#35.	#22 AND #34	2,311
#34.	#29 OR #30 OR #31 OR #32 OR #33	7,111
#33.	hbp:ti,ab	4,434
#32.	'his pacing*'	96
#31.	('his-bundle*' OR 'bundle* of his' OR his*bundle* OR para*his* OR 'para-his*') NEAR/3 pacing*	1,257
#30.	'his bundle pacing'/exp	176
#29.	#25 AND #28	3,137
#28.	#26 OR #27	85,791
#27.	pacing*	72,548
#26.	'heart pacing'/exp	46,318
#25.	#23 OR #24	8,41
#24.	(his NEAR/1 bundle*) OR 'para-his*'	8,41
#23.	'his bundle'/exp	4,565
#22.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	982,497
#21.	(atrial OR auricular) NEAR/1 fibrillat*	196,68
#20.	'atrial fibrillation'/exp	183,189
#19.	('cardiac conduction' OR 'heart conduction') NEAR/3 (failure* OR disease*)	536
#18.	'heart muscle conduction disturbance'/exp	114,65
#17.	(prolong* OR delay*) NEAR/3 pr NEAR/3 interval*	1,329
#16.	(bundle*branch* OR 'bundle branch*' OR fascic* OR atrio*ventricular OR 'atrio ventricular') NEAR/3 block*	56,021
#15.	'av-block*'	8,16
#14.	'atrioventricular block'/exp	33,162
#13.	lbbb:ti,ab OR rbbb:ti,ab	6,678
#12.	'heart bundle branch block'/exp OR 'his bundle block'/exp	32,503
#11.	lvsd:ti,ab OR hf:ti,ab OR chf:ti,ab	117,491
#10.	('left ventricular' OR 'left ventricle') NEAR/3 (failure* OR insufficien* OR dysfunction*)	61,296
#9.	(dilated OR congestive) NEAR/3 (cardio*myopath* OR 'cardio myopath*')	44,046
#8.	(congestive OR chronic) NEAR/3 'heart failure*'	140,76
#7.	(heart* OR cardiac* OR myocardial OR cardio* OR ventric*) NEAR/3 (failure* OR de*compensat* OR 'de compensat*' OR insufficient* OR dysfunct* OR stand*still OR 'stand still')	559,676
#6.	'forward heart failure'/exp	6,236
#5.	'heart left ventricle failure'/exp	35,854
#4.	'cardiogenic shock*'	35,623
#3.	'cardiogenic shock'/exp	31,763
#2.	'congestive cardiomyopathy'/exp	34,585
#1.	'heart failure'/exp	579,38
Total hits: 662		

Search strategy for Cochrane

Search Name: His Bundle pacing	
Last Saved: 20.12.2021 14:17:42	
Comment: MEL 2022 (RJ/BW)	
ID	Search
#1	MeSH descriptor: [Heart Failure] explode all trees
#2	MeSH descriptor: [Cardiomyopathy, Dilated] explode all trees
#3	MeSH descriptor: [Shock, Cardiogenic] explode all trees
#4	("cardiogenic shock") (Word variations have been searched)
#5	MeSH descriptor: [Ventricular Dysfunction] explode all trees
#6	MeSH descriptor: [Cardiac Output, Low] explode all trees
#7	((heart* OR cardiac* OR myocardial OR cardio* OR ventric*) NEAR (failure* OR de?compensat* OR insufficient* OR dysfunct* OR stand?still OR stand-still)) (Word variations have been searched)
#8	((congestive OR chronic) NEAR "heart failure*") (Word variations have been searched)
#9	((dilated OR congestive) NEAR (cardio?myopath* OR cardio-myopath*)) (Word variations have been searched)
#10	(("left ventricular" OR "left ventricle") NEAR (failure* OR insufficien* OR dysfunction*)) (Word variations have been searched)
#11	((lvsd OR hf OR chf)):ti,ab,kw (Word variations have been searched)
#12	MeSH descriptor: [Bundle-Branch Block] explode all trees
#13	((LBBB OR RBBB)):ti,ab,kw (Word variations have been searched)
#14	MeSH descriptor: [Atrioventricular Block] explode all trees
#15	(AV-Block*) (Word variations have been searched)
#16	((bundle?branch* OR bundle-branch* OR fascic* OR atrio?ventricular OR atrio-ventricular) NEAR block*) (Word variations have been searched)
#17	((prolong* OR delay*) NEAR PR NEAR interval*) (Word variations have been searched)
#18	MeSH descriptor: [Cardiac Conduction System Disease] explode all trees
#19	("cardiac conduction" NEAR (failure* OR disease*)) (Word variations have been searched)
#20	MeSH descriptor: [Atrial Fibrillation] explode all trees
#21	((atrial OR auricular) NEXT fibrillat*) (Word variations have been searched)
#22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	((His-bundle* OR (bundle* NEAR His) OR His?bundle* OR para?his* OR para-his*) NEAR pacing*) (Word variations have been searched)
#24	MeSH descriptor: [Bundle of His] explode all trees
#25	(His NEAR pacing*) (Word variations have been searched)
#26	#23 OR #24 OR #25
#27	#22 AND #26 with Publication Year from 2017 to 2021, in Trials
#28	#22 AND #26 with Cochrane Library publication date Between May 2017 and Dec 2021
#29	#27 OR #28
#30	(conference abstract):pt (Word variations have been searched)
#31	(abstract):so
#32	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR CT.gov OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#33	#30 OR #31 OR #32
#34	#27 NOT #33
#35	#28 NOT #33
#36	#34 OR #35
Total hits: 27	

Search strategy for HTA-INAHTA

Search Name: His bundle pacing (MEL 2022)	
Date of search: 17.12.2021	
Comment: MEL 2022 (RJ/BW)	
ID	Search query,"Hits","Searched At"
#3	("Bundle* of His" OR "His Bundle*" OR "Para-His") OR ("Bundle of His"[mhe]),"0","2021-12-17T19:35:13.000000Z"
#2	"Bundle* of His" OR "His Bundle*" OR "Para-His","0","2021-12-17T19:32:07.000000Z"
#1	"Bundle of His"[mhe],"0","2021-12-17T19:30:50.000000Z"
Total Hits: 0	

Search strategy for Systematic reviews and Meta-analyses in Embase

Search Name: His bundle pacing (MEL 2022)		
Date of search: 20.12.2021		
Comment: MEL 2022 (RJ/BW)		
No.	Query Results	Results
#4.	(#1 OR #2) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	32
#3.	#1 OR #2	4,680
#2.	'his bundle pacing'/exp	176
#1.	'his bundle'/exp	4,565
Total Hits: 32		

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH