ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 3700–3709
Published online 20 September 2023 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14488

STUDY DESIGN

Conduction system pacing and atrioventricular node ablation in heart failure: The PACE-FIB study design

Daniel Rodríguez Muñoz[1,2]*, María Generosa Crespo-Leiro[3,4,5], Ignacio Fernández Lozano[6,7], José Luis Zamorano Gómez[8,9], Rafael Peinado Peinado[7,10], Luis Manzano Espinosa[9,11], Javier de Juan Bagudá[1,2,4,12], Álvaro Marco del Castillo[1,2], Fernando Arribas Ynsaurriaga[1,2,4,13] and Rafael Salguero Bodes[1,2,4]

[1]*Cardiology Department, Hospital Universitario 12 de Octubre, Madrid, Spain;* [2]*Research Institute Hospital Universitario 12 de Octubre (i + 12), Madrid, Spain;* [3]*Cardiology Department, Complexo Hospitalario Universitario A Coruña (CHUAC), A Coruña, Spain;* [4]*Centro de Investigación Biomedica en Red Cardiovascular (CIBERCV), Madrid, Spain;* [5]*Faculty of Medicine, Universidade da Coruña (UDC), A Coruña, Spain;* [6]*Arrhythmia Unit, Department of Cardiology, University Hospital Puerta de Hierro, Majadahonda, Spain;* [7]*Faculty of Medicine, Universidad Autónoma de Madrid, Madrid, Spain;* [8]*Cardiology Department, University Hospital Ramón y Cajal, Madrid, Spain;* [9]*Faculty of Medicine, University of Alcalá, Alcalá de Henares, Spain;* [10]*Arrhythmia Unit, Cardiology Department, University Hospital La Paz, Madrid, Spain;* [11]*Department of Medicine and Medical Specialities, Madrid, Spain;* [12]*Faculty of Medicine, European University of Madrid, Madrid, Spain; and* [13]*Faculty of Medicine, University Complutense of Madrid, Madrid, Spain*

Abstract

Aims Atrial fibrillation (AF) worsens the prognosis of patients with heart failure (HF). Successful treatments are still very scarce for those with permanent AF and preserved (HFpEF) or mildly reduced (HFmrEF) ejection fraction. In this study, the long-term benefits and safety profile of heart rate regularization through left-bundle branch pacing (LBBP) and atrioventricular node ablation (AVNA) will be explored in comparison with pharmacological rate-control strategy.

Methods and results The PACE-FIB trial is a multicentre, prospective, open-label, randomized (1:1) clinical study that will take place between March 2022 and February 2027. A total of 334 patients with HFpEF/HFmrEF and permanent AF will receive either LBBP followed by AVNA (intervention arm) or optimal pharmacological treatment for heart rate control according to European guideline recommendations (control arm). All patients will be followed up for a minimum of 36 months. The primary outcome measure will be the composite of all-cause mortality, HF hospitalization, and worsening HF at 36 months. Other secondary efficacy and safety outcome measures such as echocardiographic parameters, functional status, and treatment-related adverse events, among others, will be analysed too.

Conclusion LBBP is a promising stimulation mode that may foster the clinical benefit of heart rate regularization through AV node ablation compared with pharmacological rate control. This is the first randomized trial specifically addressing the long-term efficacy and safety of this pace-and-ablate strategy in patients with HFpEF/HFmrEF and permanent AF.

Keywords Atrial fibrillation; Heart failure; Atrioventricular node; Pacemaker; Left bundle branch pacing

Received: 12 January 2023; Revised: 30 June 2023; Accepted: 17 July 2023
**Correspondence to: Daniel Rodríguez Muñoz, Cardiology Department, Hospital Universitario 12 de Octubre, Avda de Córdoba s/n, 28041 Madrid, Spain. Email: daniel.rodriguez.mnz@gmail.com*

Introduction

Atrial fibrillation in patients with heart failure

Concomitant heart failure (HF) and atrial fibrillation (AF) are found in up to 6% of patients with New York Heart Association (NYHA) class I, and 15 to 35% of those with classes II to IV.[1–4] The presence of AF in these patients is associated with a worse prognosis compared with those in sinus rhythm,[1,2,5] regardless of their ejection fraction (EF),[6] although the prevalence of AF is higher in patients with HF and preserved [left ventricular EF (LVEF) $\geq$ 50%; HFpEF] or mildly reduced (LVEF = 41–49%; HFmrEF) EF than those with reduced EF. Moreover, in patients with HFpEF and AF, mortality risk increases independently of heart rate (HR).[7] Restoring and maintaining sinus rhythm rather than an HR control

strategy alone has shown significant benefits in HF patients,[8,9] but the efficacy of rhythm control strategies is limited in a relatively large subgroup of these patients in whom permanent AF must be assumed.

Current treatment for heart failure and atrial fibrillation

Treatment recommendations for HF with reduced EF (LVEF ≤40% HFrEF) are broad and well-defined.[10] However, only sodium-glucose co-transporter 2 (SGLT2) inhibitors have shown prognostic benefits in patients with HFpEF or HFmrEF.[11–13] Until recently, diuretics have been the mainstay of treatment to control congestion and alleviate symptoms in HFpEF. In addition, other drugs such as angiotensin-receptor blockers and mineralocorticoid receptor antagonists may be considered, although there is very little robust evidence, especially in patients with permanent AF.[10] Lenient [resting HR ≤ 110 beats per minute (bpm)] instead of strict (resting HR ≤ 80 bpm) rate control is currently recommended as first-line treatment in these patients.[14,15] Combination of rate-controlling drugs when a single drug does not achieve the target resting HR and the addition of digoxin/digitoxin or amiodarone are to be considered before cardiac resynchronization therapy pacemaker (CRT-P), defibrillator (CRT-D) or pacemaker implantation followed by atrioventricular (AV) node ablation (AVNA).[16]

Mechanisms and deleterious effects of irregular heartbeat in patients with heart failure

Constant beat-to-beat irregularity due to permanent AF decreases cardiac output and worsens haemodynamic performance.[17–19] Several root causes have been suggested, such as failure to adapt cardiac contractility for each heartbeat due to incomplete compensation by the Frank-Starling mechanism, ventricular mechanical inefficiency due to low cardiac filling and reduced myocardial perfusion and coronary blood flow, as well as other vasomotor and neurohormonal factors.[17–19] Moreover, irregular rhythm is associated with altered sarco/endoplasmic reticulum ATPase 2a pump (SERCA) and phospholamban (PLB) proteins expression, leading to a decrease in the amplitude of intramyocardial calcium currents and an increase in cell oxidation and peroxidation.[20,21]

The impact of these deleterious effects has been shown in randomized clinical trials and long-term observational studies of patients who underwent AVNA and permanent pacing. In these studies, haemodynamic and clinical outcomes, including NYHA functional class, activity, and quality of life scores, use of diuretics, hospital readmission, worsening HF, and mortality, among others, improved upon rhythm regularization.[22–27]

A collateral effect of AVNA is the prevention of episodes of rapid ventricular response (RVR) that not infrequently occur in patients with adequate baseline HR control, especially in the context decompensated HF and aggravating such episodes.

Cardiac stimulation modes: advantages of left-bundle branch pacing

Right ventricular apical (RVA) pacing can cause ventricular dilatation and left ventricular (LV) systolic dysfunction due to pacing-induced ventricular dyssynchrony.[28,29] This may be overcome by more physiological cardiac stimulation modes such as CRT (biventricular pacing) or different modalities of conduction system pacing (CSP) at different locations of the His-Purkinje system [His-bundle pacing (HBP) or left-bundle branch pacing (LBBP)].[23–26,30,31] The APAF-CRT trial with elderly patients with HF, permanent AF and a broad range of EF values showed a significant reduction of a composite of all-cause mortality, HF hospitalizations (HFH) and worsening HF in patients treated with AVNA and CRT compared with pharmacological rate control.[27] The observed benefit led to early termination of recruitment, which yielded a small population with EF > 35% to obtain definitive conclusions among patients with preserved or only modestly reduced LV function.[32] Other studies have reported significant improvement in echocardiographic parameters, NYHA functional class, and reduced use of diuretics after AVNA and HBP in patients with normal LV function and AF.[25,26,28]

HBP simultaneously stimulates both His bundle branches and provides a physiological contraction pattern with intra and interventricular synchrony. However, several technical weaknesses restrict its wide application, including a higher capture threshold (which reduces the battery life of pacemaker generators) and significant increase in threshold during follow-up, which may lead to loss of capture in some cases.[33,34]

LBBP, targeting the left branch of the His bundle, has appeared as a physiological pacing alternative and is associated with reduced long-term HFH and mortality compared with RVA pacing.[35] Furthermore, LBBP achieves more favourable pacing parameters (lower and more stable capture threshold) as well as shorter procedural and fluoroscopy durations.[30] Specifically among patients undergoing subsequent AVNA, LBBP leads to higher success rates and decreased incidence of acute and chronic lead-related complications compared with HBP.[36] Recent observational data and a small randomized clinical trial have suggested that LBBP may be superior to conventional biventricular pacing even in patients with CRT indication.[31,37–39] This may potentially influence outcomes of patients with HFmrEF following AVNA.

Study rationale and aim

The beneficial effects of LBBP in patients with permanent AF and HFpEF or HFmrEF remain unsettled to date. Hence, the purpose of the PACE-FIB trial is to assess the long-term patient prognosis of heart rhythm regularization by CSP (LBBP) and AVNA in this patient population compared with optimal pharmacological HR control.

PACE-FIB trial design

Study design

PACE-FIB is a multicentre, prospective, open-label, randomized (1:1) clinical study on LBBP and subsequent AVNA in Spain. It has been notified to the Spanish Agency of Medicines and Medical Devices (AEMPS), registered on https://www.clinicaltrials.gov with unique identifier NCT05029570 and is being conducted in accordance with the Declaration of Helsinki ethical standards[40] and the rules and regulations of the approving Ethics Committee (EC) at the core hospital (Clinical Research EC of *Hospital Universitario 12 de Octubre*, CEI 21-454, Madrid, Spain; approved on 12/08/2021). Patient data are handled according to the current General Data Protection Regulation 2016/679 of the European Parliament (EU-GDPR) and the Council of 27 April 2016 on Personal Data Protection, the Spanish Organic Law 3/2018 of 5 December 2018 on Personal Data Protection and Guarantee of Digital Rights, and the 41/2002 Law of 14 November 2002 on Patient Autonomy and Rights and Obligations in terms of information and clinical documentation.

Participants and study settings

Eligible participants are adults aged 18 or older with HF with NYHA functional Status II to IV, permanent AF with resting HR ≤110 bpm and LVEF >40% (i.e. HFmrEF or HFpEF) measured by the Simpson's method of disks summation in either echocardiogram or cardiac magnetic resonance imaging within the three months prior to inclusion.[41,42] In the event of disparities between different techniques or repeated exams in this period, the lower LVEF value would be considered. Other inclusion criteria are at least one HFH or worsening HF (requiring intravenous diuretics and/or inotropes) during the previous year, basal N-terminal pro-brain natriuretic peptide (NT-proBNP) levels ≥900 pg/mL in the 30 days prior to enrolment, capacity to understand the nature of the study and providing signed informed consent using the EC-approved consent form. Exclusion criteria are severe frailty (Clinical Frailty Scale[43] ≥7) or comorbidity reducing life expectancy to <12 months, acute HF at enrolment or systolic blood pressure <80 mmHg in the absence of inotropic agents, severe chronic kidney disease [estimated glomerular filtration rate (eGFR) < 20 mL/1.73m^2], severe mitral or aortic valvular heart disease, anaemia (haemoglobin <10 g/dL), morbid obesity (body mass index ≥35), severe chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease[44] ≥3), presence of a clinical indication for pacemaker of implantable cardioverter-defibrillator implantation, obstructive hypertrophic cardiomyopathy, infiltrative cardiomyopathy (amyloidosis, sarcoidosis, Fabry disease, or others), simultaneous participation in a different trial, pregnancy or expected pregnancy, and breastfeeding during 18 months after enrolment. No sex- or ethnicity-based criteria will be applied.

The following events are considered study withdrawals: cardiac surgery (coronary artery bypass grafting, valve surgery or pulmonary vein isolation) or cardiac transplant during the study period, residential relocation far away from the centre where the device was implanted, invalidation of the informed consent, investigator's decision to exclude a patient, and patient's decision to withdraw their consent to participate in the study. In these cases, patients may allow the analysis of their cumulative data until withdrawal.

The study took place in 16 Spanish tertiary centres since March 2022, and it is planned to end in May 2027 (inclusive). Patient recruitment started in March 2022 and will finish in February 2024 (inclusive). The patient follow-up period will be 36 months (until February 2027 for the last recruited patient). For those reaching it before the study completion, additional follow-up visits every 6 months will continue until February 2027 (*Figure 1*).

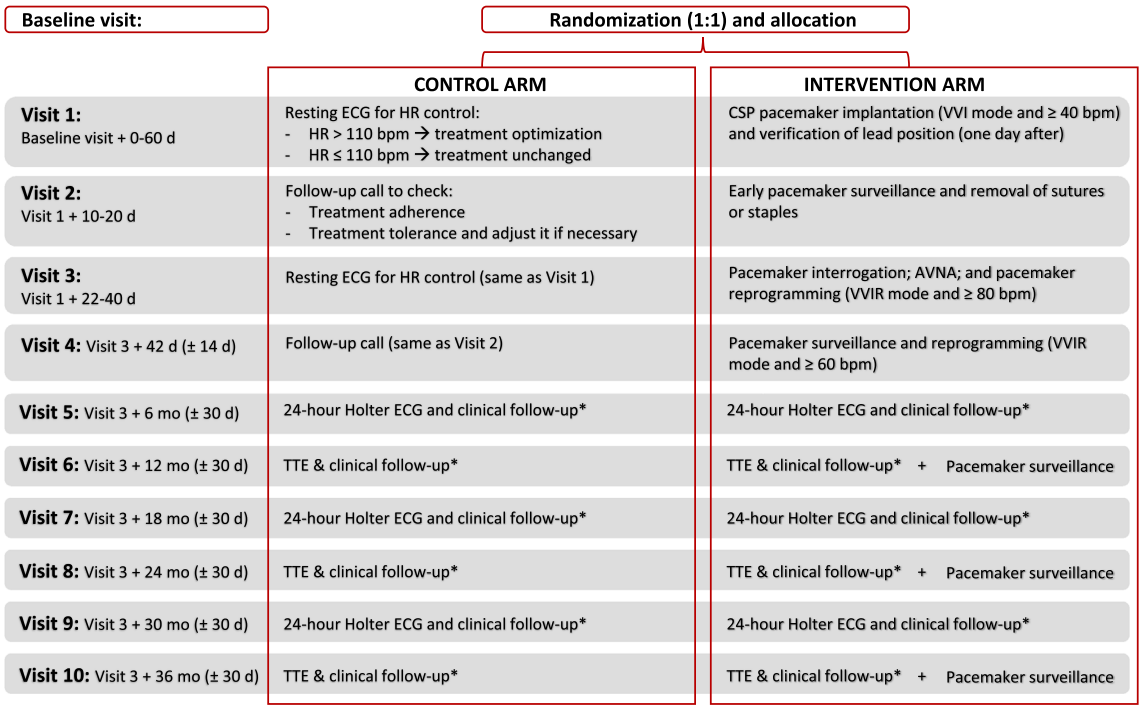
Interventions

Patients are assessed for eligibility during the first visit (baseline visit). Included patients are randomly allocated to either pharmacological HR control strategy (control arm) or CSP (LBBP) and subsequent AVNA (intervention arm) (*Figure 1*).

Control arm

Within 60 days after the baseline visit (Visit 1), resting HR is determined by electrocardiogram (ECG). HR control strategy for these patients will be based on the ESC pharmacological treatment algorithm[16] to maintain resting HR below 110 bpm and achieve the highest possible clinical stability for the patient and the best prognosis. Within 10–20 days after Visit 1 (Visit 2), treatment adherence and tolerance are assessed by telephone visit, and it may be adjusted if necessary. Follow-up Visit 3 is scheduled 22–40 days after Visit 1. According to the ECG, HR control treatment is fine-tuned if resting HR is >110 bpm. Within 25–50 days after Visit 3 (Visit 4), telephone treatment follow-up will be

Figure 1 Intervention scheme and visit schedule. The flow chart summarizes the study interventions and the number and frequency of follow-up visits from patient allocation to study completion. Patients in the intervention arm will be subject to AVNA and CSP (LBBP). Patients in the control arm will receive optimal rate control pharmacological treatment. Duration of patient follow-up: 36 months minimum. After that, patients will be followed up every 6 months until the end of the study. *ECG and clinical variables will be registered during every visit. If necessary, pharmacological treatment in the control arm will be adjusted to reach optimal resting HR (≤110 bpm). AVNA, atrioventricular node ablation; bpm, beats per minute; CSP, conduction system pacing; d, days; ECG, electrocardiogram; HR, heart rate; LBBP, left-bundle branch pacing; mo, months; TTE, transthoracic echocardiogram; VVI, ventricular demand pacing; VVIR, rate-responsive VVI.



carried out by telephone as the previous one. The subsequent visits (Visits 5–10) are scheduled every 6 months (±30 days) for 36 months. During this follow-up period, a 24 h Holter ECG or routine transthoracic echocardiogram (TTE) is performed every other visit. Moreover, treatment may be optimized in Visits 5–10 if resting HR is >110 bpm (*Figure 1*).

Intervention arm

Patients in the intervention arm will not receive medication specifically aimed at HR control. However, they will receive pharmacological treatment according to their HF status and other comorbidities. This may potentially include the use of beta-blockers or calcium-channel blockers for other indications such as angina, hypertension, or HF when appropriate.

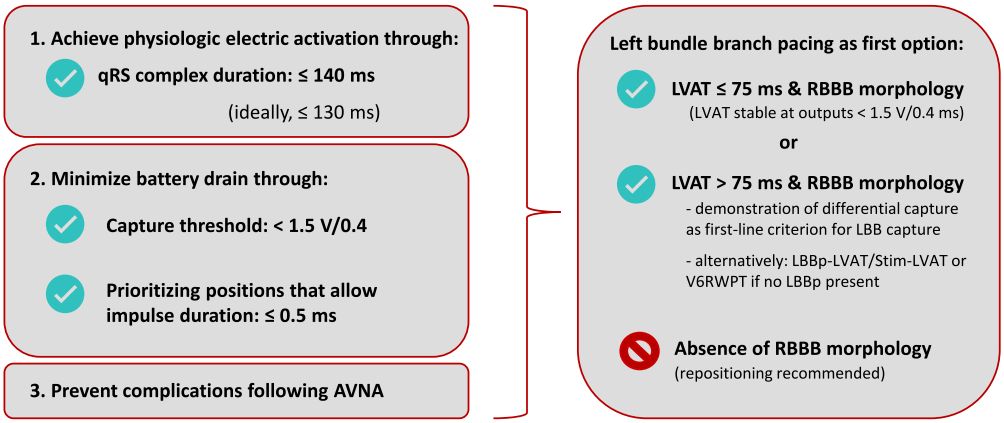
At Visit 1, patients undergo single-chamber pacemaker implantation with lead implantation aimed at LBB capture using dedicated CSP sheaths according to current standard practice. Implant recommendations and optimization guidance are summarized in *Figure 2*. The pacemaker is initially programmed to operate in ventricular demand (VVI) pacing mode and at a 40 bpm minimal rate until AVNA is performed. Following device implantation, the position of the electrode is confirmed by posteroanterior and lateral chest X-ray (*Figure 1*).

Suture and staple removal and early surveillance of pacemaker will take place during Visit 2. Specifically, device functioning (electrogram amplitude detection, signal stability, impedance, and threshold, among others) is checked, with special attention to the detection of potential early implantation-related adverse events (AE).

In Visit 3, after pacemaker interrogation to ensure adequate pacemaker performance, AVNA is performed via transfemoral venous access according to standard protocols in each centre. It is strongly advised not to discontinue anticoagulant treatment. In any case, bridging therapy using LMWHs is not recommended. Ultrasound-guided venous cannulation is also strongly recommended. Primary target for ablation is the compact AV node, aiming to preserve a stable escape rhythm. Afterwards, the pacemaker is reinterrogated and programmed at rate-responsive VVI (VVIR) mode with minimum HR of 80 bpm (*Figure 1*).

During Visit 4, a minimum rate of 60 bpm is set. The maximum rate depends on the age and physical condition of the patient, not exceeding 130 bpm. Follow-up Visits 5–

Figure 2 Optimization of pacemaker programming. Recommendations for pacing fulfilling LBB capture criteria followed by AVNA are shown. AVNA, atrioventricular node ablation; LBB, left-bundle branch; LBBp, LBB potential; LVAT, left-ventricular activation time; Stim-LVAT, interval from stimulation to left-ventricular activation time; RBBB, right-bundle branch block; V6RWPT, V6 R-wave peak time.



10 alternate 24-h Holter ECG with routine TTE and pacemaker surveillance. If necessary, minimum rate and rate response values may be adjusted according to exercise tolerance and HR histograms (*Figure 1*).

Variable description and outcome measures

Demographic data, patients' medical history related to cardiovascular (CV) health and relevant comorbidities are collected during the baseline visit. Clinical parameters and echocardiographic variables related to the primary and secondary outcome measures are collected by the investigators and their teams during the follow-up visits (*Figure 1*) using an electronic case report form (eCRF): Deaths, hospital admissions, LVEF (assessed by the Simpson's method of disks summation in either echocardiogram or cardiac magnetic resonance imaging[41]), end-diastolic and end-systolic volumes, mitral regurgitation degree, NYHA class,[45] eGFR, HR and levels of brain natriuretic peptide (BNP) and NT-proBNP (*Table 1*). Electric parameters registered at 200 mm/s in Visits 1, 3, and 10 (including here the stimulated qRS features and LVAT), together with all pacemaker surveillance measurements will be stored in the eCRF as anonymized digital imaging files and will be subsequently analysed by the core lab. (Serious) AE (SAE/AE), (serious) adverse device effects (SADE/ADE), unanticipated serious adverse device effects (USADE), and device deficiencies (DD) will be also reported using the eCRF according to ISO 14155:2020 standard 'Clinical investigation of medical devices for human subjects- Good clinical practice' (*Table S1*).[46]

The eCRF is linked to an internet database to which only designated personnel have access. Clinical study monitors are in charge of contrasting data entries in every participating centre and confirm that all investigators adhere to the study protocol, ISO 14155:2020 standard, the US Food and Drug Administration (FDA) Code of Federal Regulation (CFR) [21 CFR Parts 50 (Informed Consent), 54 (Financial Disclosure), 56 (Institutional Review Board) and 812 (Investigational Device Exemption)], local laws, and ethical principles that have their origin in the Declaration of Helsinki. In addition, all events related to the primary and secondary outcome measures are reviewed by the data monitoring committee, composed of three medical experts in the electrophysiology and HF fields and not directly participating in the study.

The study's primary outcome measure is the composite of all-cause mortality, HFH, and worsening HF (i.e. unplanned HF hospitalizations or urgent visits requiring intravenous diuretics and/or inotropics) during a 36 month follow-up period in both arms. Other secondary efficacy and safety outcome measures are described in *Table 1*.

Sample size

Results from several observational studies and one single randomized clinical trial point towards a survival benefit and improved HF prognosis associated with AVNA and physiological stimulation, both in patients with LVEF ≤40% and LVEF >40%.[25–27] Although no study has specifically addressed the effect of this strategy in patients with LVEF >40%, we anticipated an incidence of the primary outcome of 30%[27] and 15%[26] in the control and intervention arms, respectively. Therefore, to detect differences between study arms with a 5% significance level and a power of 80%, a sample size of 152 patients per group (304 patients in total) is necessary. Assuming a dropout rate of 10%, 167 patients will be included in each arm (334 patients in the study sample), with no minimum or maximum number of patients per centre. A 24 month inclusion period was estimated to recruit this number of patients.

Table 1 Study outcome measures (efficacy and safety) with time points and definitions

Outcome measures	Time frame	Variable description
Primary efficacy outcome		
Composite of all-cause mortality, HFH, and worsening HF	36 months	Number and percentage of deaths due to any cause, hospitalized subjects due to HF decompensation and/or subjects presenting an episode of HF, which will be diagnosed by symptoms, signs, imaging techniques and/or analytical criteria and require unexpected medical attention and intravenous diuretic therapy.
Secondary efficacy outcomes		
All-cause mortality	36 months	Number and percentage of deaths due to any cause.
CV mortality	36 months	Number and percentage of deaths due to CV causes.
All-cause hospitalization	36 months	Number and percentage of hospitalized subjects due to any cause.
HFH	36 months	Number and percentage of hospitalized subjects due to HF decompensation.
Worsening HF	36 months	Number and percentage of subjects presenting an episode of HF, which will be diagnosed by symptoms, signs, imaging techniques and/or analytical criteria and require unexpected medical attention and intravenous diuretic therapy.
Unplanned CV hospitalization	36 months	Number and percentage of hospitalized subjects due to unexpected CV causes.
LVEF	36 mo	Assessed by Simpson's method of disks summation.
LV dimension	36 months	Mean change in end-diastolic and end-systolic volumes.
Mitral regurgitation	36 months	Mean change in mitral regurgitation degree.
Functional status	36 months	Number and percentage of subjects in each NYHA class.
Renal function	12 months	Mean change in eGFR.
Natriuretic peptides	12 months	Mean change in NT-proBNP or BNP.
Secondary safety outcomes		
AE after pacemaker implantation	30 days	Number and percentage of subjects suffering one of the following events during the first 30 days after pacemaker implantation: Death, cardiac tamponade, perforation requiring cardiac surgery, pneumothorax, haemothorax, device infection, endocarditis, femoral artery pseudoaneurysm, femoral arteriovenous fistula and lead displacement and haematoma related to pacemaker implantation that require re-intervention.
AE after AV node ablation	30 days	Number and percentage of subjects suffering one of the following events during the first 30 days after AV node ablation: Death, cardiac tamponade, perforation requiring cardiac surgery, puncture site vascular complications requiring vascular surgery.

Abbreviations: AE, adverse event; AV, atrioventricular; BNP, brain natriuretic peptide; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; HR, heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, basal N-terminal pro-BNP; NYHA, New York Heart Association.

Interim analysis and stopping guidelines

The study may be halted prematurely for benefit if the interim analysis, which will be performed after recruiting 50% of the estimated sample size, shows significant superiority of either arm regarding the primary outcome, that is, if the percentage of patients in the composite of all-cause mortality, HFH, and worsening HF is significantly lower. Other stopping rules include the withdrawal of >10% of patients from the study (withdrawal of the informed consent or due to medical reasons) and not having recruited >50% of the total patient sample after 24 months.

Randomization

Before starting patient recruitment, the random allocation sequence will be generated by the biostatistics team with SAS® PROC PLAN and will subsequently be included in the eCRF. The four-patient block design and stratification by centre will ensure a correct balance between the study arms (1:1). Data from patients that fulfil the eligibility criteria are uploaded by the investigators to the eCRF. Then, patients are automatically assigned to either arm according to the previously generated random allocation list.

Statistical methods

Data will be presented by descriptive-univariate statistics. Qualitative variables will be described by absolute and relative frequencies. Measures of central tendency and dispersion will be used for quantitative variables. An intention to treat approach will be applied to analyse the primary efficacy outcome, although a pre-specified analysis per treatment received will be performed assuming that some patients may swap study arms, especially from the pharmacological approach (control arm) to the AVNA and stimulation one (intervention arm). A second pre-specified outcome measure will consider cardiac stimulation outcomes, according to

DOI: 10.1002/ehf2.14488

fulfilment of conduction system capture criteria and paced qRS [qRS <135 ms and LV activation time (LVAT) ≤80 ms (successful capture) vs. qRS >135 ms and LVAT >80 ms (not successful)].

Other pre-specified subgroup analyses will be performed to test the following hypotheses: (i) patients in the intervention arm with pacing fulfilling LBB capture criteria are associated with better clinical and echocardiographic prognosis than those with LV septal pacing with no LBB capture; (ii) AVNA in patients with recent (4 weeks) CSP implant is an efficacious and safe procedure; (iii) the pharmacological rate control strategy does not prevent CV hospitalizations, emergency visits and episodes of fast ventricular rate despite frequent dose adjustments; (iv) electric parameters related to the stimulation of the conduction system and measured in each participating centre (capture threshold, impedance, stimulated qRS width and LVAT) are stable during a 3 year follow-up period. These parameters will be compared with those collected in the core laboratory by using the electrocardiographic and endocavitary registry at 200 mm/s, which will be included in every eCRF; and (v) both patients with HFmrEF and HFpEF benefit from this strategy.

Discussion

AVNA followed by the best possible stimulation seems a promising strategy for patients with HF and permanent AF. Recent studies have suggested a superiority in clinical and echocardiographic results of CSP over conventional biventricular pacing through CRT in a variety of scenarios including patients with conventional indication for CRT,[31] patients with failed CRT implantation or non-response to CRT,[47] or patients having undergone AVNA.[48] Among the different CSP modes, evidence points to a higher safety and long-term performance of LBBP over HBP in patients with HF and permanent AF.[36] Consequently, a randomized controlled trial evaluating the benefit of CSP (prioritizing LBB pacing) and subsequent AVNA over current first-line therapy is of interest in a prevalent population as that of HF patients with mildly reduced of preserved systolic function and permanent AF.

A potential limitation of the study is the use of different commercially available pacemakers and leads. No device bias is expected because this study aims to assess the advantages of the AVNA procedure followed by CSP, and all devices have shown high implantation success rates and adequate long-term performance.

Conclusions

HR regularization through AVNA with subsequent stimulation seems a promising strategy in patients with HF and permanent AF. However, the role of CSP in this scenario and, more specifically, for patients with HFpEF and HFmrEF remains to be established. The PACE-FIB trial is the first large-scale study specifically addressing it while comparing LBBP and AVNA interventions to regulate heart rhythm with pharmacological HR control. Hence, it may significantly contribute to redefining and broadening the limited therapeutic strategies for this subset of patients.

Declaration of Interest

IFL has received honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Medtronic and participated on Data Safety Monitoring Board and Advisory Board for Abbott.

DRM and FAY have received honoraria for lectures and educational events from Medtronic and research funding from Medtronic and Biotronik.

Acknowledgements

The authors thank Neus Cantariño (Trialance SCCL, Spain) for providing medical writing services.

Conflict of interest

None declared.

Funding information

The study has received funding from the Spanish Heart Rhythm Association and the Spanish Ministry of Science and Innovation through the Carlos III Institute for Healthcare, without interfering with the study design, preparation of this article or the decision to submit it for publication.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Definition of safety endpoints. AE, adverse event; ADE, adverse device effect; CIP, clinical investigation plan; DD, device deficiencies; SAE, serious adverse event; SADE, adverse device effect; USADE, unanticipated serious adverse device effects.

References

1. Chamberlain AM, Redfield MM, Alonso A, Weston SA, Roger VL. Atrial fibrillation and mortality in heart failure: a community study. *Circ Heart Fail [Internet]*. 2011 [cited 2022 Jun 13];**4**:740–6. Available from: https://pubmed.ncbi.nlm.nih.gov/21920917/. Accessed Jun, 2022.
2. Zafrir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, *et al*. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J [Internet]*. 2018 [cited 2022 Jun 13];**39**:4277–4284. Available from: https://pubmed.ncbi.nlm.nih.gov/30325423/. Accessed Jun, 2022.
3. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006 [cited 2022 Jun 13];**355**:251–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16855265/. Accessed Jun, 2022.
4. Bhatia RS, Tu J V., Lee DS, Austin PC, Fang J, Haouzi A, *et al*. Outcome of heart failure with preserved ejection fraction in a population-based study. [Internet]. 2006 Jul 20 [cited 2022 Jun 13];355(3):260–9. Available from: https://doi-org.sire.ub.edu/101056/NEJMoa051530. Accessed Jun, 2022.
5. Dries DL, Exner D V., Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *J Am Coll Cardiol [Internet]*. 1998 [cited 2022 Jun 13];**32**:695–703. Available from: https://pubmed.ncbi.nlm.nih.gov/9741514/. Accessed Jun, 2022.
6. Zhang P, Chamberlain AM, Hodge DO, Cai C, Xiao PL, Han J, *et al*. Outcomes of incident atrial fibrillation in heart failure with preserved or reduced ejection fraction: a community-based study. *J Cardiovasc Electrophysiol [Internet]* 2020 [cited 2022 Jun 14];**31**:2275–2283. Available from: https://pubmed.ncbi.nlm.nih.gov/32584498/. Accessed Jun, 2022.
7. Sartipy U, Savarese G, Dahlström U, Fu M, Lund LH. Association of heart rate with mortality in sinus rhythm and atrial fibrillation in heart failure with preserved ejection fraction. *Eur J Heart Fail [Internet]*. 2019 [cited 2022 Jun 14];**21**:471–9. Available from: https://pubmed.ncbi.nlm.nih.gov/30698317/. Accessed Jun, 2022.
8. Packer DL, Piccini JP, Monahan KH, al-Khalidi HR, Silverstein AP, Noseworthy PA, *et al*. Ablation versus drug therapy for atrial fibrillation in heart failure. *Circulation [Internet]*. 2021 [cited 2022 Jul 8];**143**:1377–90. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.120.050991. Accessed Jul, 2022.
9. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, *et al*. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med [Internet]* 2018 [cited 2022 Jul 8;**378**:417-427. Available from: https://www-nejm-org.sire.ub.edu/doi/full/10.1056/nejmoa1707855. Accessed Jul, 2022.
10. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J [Internet]*. 2021 [cited 2022 Jun 14];**42**:3599–726. Available from: https://pubmed.ncbi.nlm.nih.gov/34447992/. Accessed Jun, 2022.
11. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, *et al*. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med [Internet]* 2021 [cited 2022 Jul 8];**385**:1451–1461. Available from: https://www-nejm-org.sire.ub.edu/doi/full/10.1056/NEJMoa2107038. Accessed Jul, 2022.
12. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, *et al*. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med [Internet]*. 2022 [cited 2022 Oct 3];**387**:1089–1098. Available from: https://pubmed.ncbi.nlm.nih.gov/36027570/. Accessed Oct, 2022.
13. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, *et al*. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet (London, England) [Internet]*. 2022 [cited 2022 Oct 3];**400**:757–67. Available from: https://pubmed.ncbi.nlm.nih.gov/36041474/. Accessed Oct, 2022.
14. Groenveld HF, Tijssen JGP, Crijns HJGM, van den Berg MP, Hillege HL, Alings M, *et al*. Rate control efficacy in permanent atrial fibrillation: successful and failed strict rate control against a background of lenient rate control. *J Am Coll Cardiol [Internet]*. 2013 [cited 2022 Jun 16];**61**:741–8. Available from: https://research.rug.nl/en/publications/rate-control-efficacy-in-permanent-atrial-fibrillation-successful. Accessed Jun, 2022.
15. van Gelder I, Groenveld HF, Crijns HJGM, Tuininga YS, Tijssen JGP, Alings AM, *et al*. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med [Internet]*. 2010 [cited 2022 Jun 16];**362**:1363–73. Available from: https://pubmed.ncbi.nlm.nih.gov/20231232/. Accessed Jun, 2022.
16. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, *et al*. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European. *Eur Heart J [Internet]*. 2021 [cited 2022 May 31];**42**:373–498. Available from: https://academic-oup-com.sire.ub.edu/eurheartj/article/42/5/373/5899003. Accessed May, 2022.
17. Naito M, David D, Michelson EL, Schaffenburg M, Dreifus LS. The hemodynamic consequences of cardiac arrhythmias: evaluation of the relative roles of abnormal atrioventricular sequencing, irregularity of ventricular rhythm and atrial fibrillation in a canine model. *Am Heart J [Internet]* 1983 [cited 2022 Jun 14];**106**:284–291. Available from: https://pubmed.ncbi.nlm.nih.gov/6869209/. Accessed Jun, 2022.
18. Daoud EG, Weiss R, Bahu M, Knight BP, Bogun F, Goyal R, *et al*. Effect of an irregular ventricular rhythm on cardiac output. *Am J Cardiol [Internet]*. 1996 [cited 2022 Jun 14];**78**:1433–6. Available from: https://pubmed.ncbi.nlm.nih.gov/8970422/. Accessed Jun, 2022.
19. Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol [Internet]*. 1997 [cited 2022 Apr 29];**30**:1039–45. Available from: https://pubmed-ncbi-nlm-nih-gov.sire.ub.edu/9316536/. Accessed Apr, 2022.
20. Pabel S, Knierim M, Stehle T, Alebrand F, Paulus M, Sieme M, *et al*. Effects of atrial fibrillation on the human ventricle. *Circ Res [Internet]*. 2022 [cited 2022 Jun 15];**130**:994–1010. Available from: https://pubmed.ncbi.nlm.nih.gov/35193397/. Accessed Jun, 2022.
21. Ling LH, Khammy O, Byrne M, Amirahmadi F, Foster A, Li G, *et al*. Irregular rhythm adversely influences calcium handling in ventricular myocardium: implications for the interaction between heart failure and atrial fibrillation. *Circ Heart Fail [Internet]*. 2012 [cited 2022 Jun 15];**5**:786–93. Available from: https://pubmed.ncbi.nlm.nih.gov/23014130/. Accessed Jun, 2022.
22. Ueng KC, Tsai TP, Tsai CF, Wu DJ, Lin CS, Lee SH, *et al*. Acute and long-term effects of atrioventricular junction ablation and VVIR pacemaker in symptomatic patients with chronic lone atrial fibrillation and normal ventricular response. *Journal of electrophysiology* 2001 [cited 2022 Jun 15];**12**:303–309. Available from: https://pubmed.ncbi.

nlm.nih.gov/11291803/. Accessed Jun, 2022.
23. Simantirakis EN, Vardakis KE, Kochiadakis GE, Manios EG, Igoumenidis NE, Brignole M, *et al*. Left ventricular mechanics during right ventricular apical or left ventricular-based pacing in patients with chronic atrial fibrillation after atrioventricular junction ablation. *J Am Coll Cardiol [Internet]*. 2004 [cited 2022 Jun 15];**43**:1013–8. Available from: https://pubmed.ncbi.nlm.nih.gov/15028360/. Accessed Jun, 2022.
24. Vijayaraman P, Subzposh FA, Naperkowski A. Atrioventricular node ablation and His bundle pacing. *EP Eur [Internet]*. 2017 [cited 2022 Jun 15];**19**:iv10–6. Available from: https://pubmed.ncbi.nlm.nih.gov/29220422/. Accessed Jun, 2022.
25. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, *et al*. Benefits of permanent his bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. *J Am Heart Assoc [Internet]*. 2017 [cited 2022 Jun 13];**6**. Available from: https://pubmed.ncbi.nlm.nih.gov/28365568/. Accessed Jun, 2022.
26. Su L, Cai M, Wu S, Wang S, Xu T, Vijayaraman P, *et al*. Long-term performance and risk factors analysis after permanent His-bundle pacing and atrioventricular node ablation in patients with atrial fibrillation and heart failure. *EP Eur [Internet]*. 2020 [cited 2022 Jun 13];**22**:ii19–26. Available from: https://academic-oup-com.sire.ub.edu/europace/article/22/Supplement_2/ii19/6054243. Accessed Jun, 2022.
27. Brignole M, Pokushalov E, Pentimalli F, Palmisano P, Chieffo E, Occhetta E, *et al*. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J [Internet]*. 2018 [cited 2022 Jun 13];**39**:3999–4008. Available from: https://pubmed.ncbi.nlm.nih.gov/30165479/. Accessed Jun, 2022.
28. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. *J Am Coll Cardiol [Internet]*. 2009 [cited 2022 Jun 15];**54**:764–76. Available from: https://pubmed.ncbi.nlm.nih.gov/19695453/. Accessed Jun, 2022.
29. Khurwolah MR, Yao J, Kong X-Q. Adverse consequences of right ventricular apical pacing and novel strategies to optimize left ventricular systolic and diastolic function. *Curr Cardiol Rev [Internet]* 2019 [cited 2022 Jun 15];**15**:145–155. Available from: https://pubmed.ncbi.nlm.nih.gov/30499419/. Accessed Jun, 2022.
30. Hua W, Fan X, Li X, Niu H, Gu M, Ning X, *et al*. Comparison of left bundle branch and his bundle pacing in bradycardia patients. *JACC Clin Electrophysiol [Internet]*. 2020 [cited 2022 Jun 16];**6**:1291–9. Available from: https://pubmed.ncbi.nlm.nih.gov/33092757/. Accessed Jun, 2022.
31. Vijayaraman P, Zalavadia D, Haseeb A, Dye C, Madan N, Skeete JR, *et al*. Clinical outcomes of conduction system pacing compared to biventricular pacing in patients requiring cardiac resynchronization therapy. *Hear Rhythm [Internet]*. 2022 [cited 2023 Jun 5];**19**:1263–71. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1547527122019476. Accessed Jun, 2022.
32. Brignole M, Pentimalli F, Palmisano P, Landolina M, Quartieri F, Occhetta E, *et al*. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. *Eur Heart J [Internet]* 2021 [cited 2022 Jun 17];**42**:4731–4739. Available from: https://pubmed.ncbi.nlm.nih.gov/34453840/. Accessed Jun, 2022.
33. Abdelrahman M, Subzposh FA, Beer D, Durr B, Naperkowski A, Sun H, *et al*. Clinical outcomes of his bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol [Internet]*. 2018 [cited 2022 Jun 17];**71**:2319–30. Available from: https://pubmed.ncbi.nlm.nih.gov/29535066/. Accessed Jun, 2022.
34. Su L, Wu S, Wang S, Wang Z, Xiao F, Shan P, *et al*. Pacing parameters and success rates of permanent his-bundle pacing in patients with narrow QRS: a single-centre experience. *Europace [Internet]* 2019 [cited 2022 Jun 17];**21**:763–770. Available from: https://pubmed.ncbi.nlm.nih.gov/30561576/. Accessed Jun, 2022.
35. Sharma PS, Patel NR, Ravi V, Zalavadia D V, Dommaraju S, Garg V, *et al*. Clinical outcomes of left bundle branch area pacing compared to right ventricular pacing: results from the Geisinger–Rush Conduction System Pacing Registry. *Hear Rhythm [Internet]*. 2022 [cited 2022 Jun 18];**19**:3–11. Available from: https://pubmed.ncbi.nlm.nih.gov/34481985/. Accessed Jun, 2022.
36. Pillai A, Kolominsky J, Koneru JN, Kron J, Shepard RK, Kalahasty G, *et al*. Atrioventricular junction ablation in patients with conduction system pacing leads: a comparison of His-bundle vs left bundle branch area pacing leads. *Hear Rhythm [Internet]*. 2022 [cited 2022 Jun 18]; S1547–5271. Available from: https://pubmed.ncbi.nlm.nih.gov/35351624/. Accessed Jun, 2022.
37. Diaz JC, Sauer WH, Duque M, Koplan BA, Braunstein ED, Marín JE, *et al*. Left bundle branch area pacing versus biventricular pacing as initial strategy for cardiac resynchronization. *JACC Clin Electrophysiol [Internet]*. 2023 [cited 2023 Jun 5]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S2405500X23002682. Accessed Jun, 2022.
38. Wang Y, Zhu H, Hou X, Wang Z, Zou F, Qian Z, *et al*. Randomized trial of left bundle branch vs biventricular pacing for cardiac resynchronization therapy. *J Am Coll Cardiol [Internet]*. 2022 [cited 2023 Jun 5];**80**:1205–16. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109722056704. Accessed Jun, 2022.
39. Vijayaraman P, Sharma PS, Cano Ó, Ponnusamy SS, Herweg B, Zanon F, *et al*. Comparison of left bundle-branch area pacing to biventricular pacing in candidates for resynchronization therapy. *J Am Coll Cardiol [Internet]*. 2023 [cited 2023 Jun 5];Available from: http://www.ncbi.nlm.nih.gov/pubmed/37220862, **82**, 228, 241. Accessed Jun, 2022.
40. World medical association declaration of Helsinki. *JAMA [Internet]*. 1997 [cited 2022 May 31];**277**:925. Available from: https://jamanetwork-com.sire.ub.edu/journals/jama/fullarticle/414713. Accessed May, 2022.
41. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, *et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiograph. *J Am Soc Echocardiogr [Internet]* 2005 [cited 2022 Jun 3];**18**:1440–1463. Available from: https://pubmed.ncbi.nlm.nih.gov/16376782/. Accessed Jun, 2022.
42. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, di Salvo G, *et al*. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Hear journal Cardiovasc Imaging [Internet]* 2017 [cited 2022 Oct 3];**18**:1301–1310. Available from: https://pubmed.ncbi.nlm.nih.gov/29045589/. Accessed Oct, 2022.
43. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ [Internet]* 2005 [cited 2022 May 31];**173**:489–95. Available from: https://www.cmaj.ca/content/173/5/489. Accessed May, 2022.
44. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Pocket guide to COPD diagnosis, management, and prevention. A guide for health care professionals. 2018 Report [Internet]. 2018 [cited 2022 May 31]. Available from: www.goldcopd.org. Accessed May, 2022.
45. *The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the*

Heart and Great Vessels. 9th ed. Boston: Little Brown & Co.; 1994:253-256.
46. ISO 14155: 2020, Clinical investigation of medical devices for human subjects —good clinical practice [Internet]. [cited 2023 Jun 5]. Available from: https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-3:v1:en. Accessed Jun, 2022.
47. Vijayaraman P, Herweg B, Verma A, Sharma PS, Batul SA, Ponnusamy SS, *et al*. Rescue left bundle branch area pacing in coronary venous lead failure or non-response to biventricular pacing: results from International LBBAP Collaborative Study Group. *Hear Rhythm [Internet]* 2022 [cited 2022 Aug 24];**19**:1272–1280. Available from: https://pubmed.ncbi.nlm.nih.gov/35504539/. Accessed Aug, 2022.
48. Huang W, Wang S, Su L, Fu G, Su Y, Chen K, *et al*. His-bundle pacing vs biventricular pacing following atrioventricular nodal ablation in patients with atrial fibrillation and reduced ejection fraction: a multicenter, randomized, crossover study—the ALTERNATIVE-AF trial. *Hear Rhythm [Internet]*. 2022 [cited 2022 Aug 24]; Available from: https://pubmed.ncbi.nlm.nih.gov/35843465/, **19**, 1948, 1955. Accessed Aug, 2022.