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GENTLE-PACE — A multicenter, randomized, double-blinded research study comparinG the Efficacy and safety of cardioNeuroablaTion vs. permanent pacing in patients with an implantabLE PACEmaker for symptomatic bradycardia

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STUDY PROTOCOL

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INTRODUCTION

Background

Pacemaker (PM) therapy remains a cornerstone in the management of sinus node disease (SND) and atrioventricular blocks (AVB) [1, 2]. It is recommended by international cardiac societies and has spread across the globe. European epidemiological data shows a wide range of PM implantation rates, varying from 25 to 1000 per million inhabitants, with

significantly higher rates in affluent countries. Globally, approximately one million PM implants are estimated annually. Notably, about 20% of this population comprises individuals below 65 years of age.

Prolonged PM therapy is associated with various limitations (such as social discrimination and professional constraints, especially in high-risk professions as well as restricted sports activities) and complications include life-threating ones. In a Dutch cohort study, FOLLOWPACE, the incidence of device-related complications (DRC) increased with the time of follow-up, and it was 19.7% at 5 years [3]. These findings and those of other studies highlight the importance of continuous reassessment of indications for continuing the PM therapy and the search for reversible causes of SND or AVB, especially in younger subjects, who are the most vulnerable to long-term complications [4].

New therapeutic strategies

Increasing evidence supports the effectiveness of an alternative approach, cardioneuroablation (CNA), in functional bradycardia associated with excessive vagal nerve activation [5, 6]. This method leads to the alleviation or complete resolution of bradycardia symptoms and the disappearance of reflex fainting episodes, providing the option to forgo pacemaker therapy [7, 8]. CNA involves the radiofrequency ablation of extrinsic cells of the parasympathetic system located in the atrial walls, known as ganglionated plexi (GP). Its effect is the modulation of the sinoatrial node (SAN) and/or the atrioventricular node (AVN).

Certain types of SND and AVB might be previously undiagnosed and directly related to vagal nerve hypersensitivity, and they can be effectively treated by CNA. It is also possible that in cases of organic SAN and/or AVN damage, reducing or eliminating the inhibitory influence of the vagal nerve using CNA could delay or even avoid pacemaker therapy.

In some observational registry-based studies, CNA accompanied by broad electrophysiological assessment led to the discontinuation of PM therapy [9, 10]. However, the role of CNA in the decision-making on discontinuing PM therapy has never been assessed in randomized clinical trials. The GENTLE-PACE study, is intended to test the strategies involving CNA in order to discontinue PM therapy and compare them to continuous PM therapy in young patients with SND and/or AVB.

STUDY DESIGN

GENTLE-PACE is a non-commercial, multicenter, randomized, double-blinded, head-to-head comparative research experiment comparing the effectiveness and safety of cardioneuroablation (CNA) with a comparator in continuous cardiac stimulation therapy in patients with symptomatic bradycardia due to an implanted PM (Figure 1).

STUDY GOALS

The null hypothesis of this non-inferiority study is the claim that CNA is worse than continuing PM therapy in terms of syncopal and bradycardic events. The hypothesis is based on the current ESC Guidelines on Syncope from 2018 and on Cardiac Pacing from 2021, in which the authors recommend pacemaker (PM) implantation for recurrent syncope attributed to vagal bradycardia irrespective of the sinoatrial or atrioventricular origin. There is insufficient data on CNA to prove that vagal tone reduction is no worse than PM therapy in terms of syncope reduction. To falsify the null hypothesis, two therapeutic strategies were compared among patients with SND and/or AVB after PM implantation in a randomized control trial, comparing the effectiveness and safety of CNA and continued PM therapy. The primary goal includes an assessment of the therapeutic efficacy and safety of CNA allowing the discontinuation of PM therapy in patients with SND or AVB.

The secondary goals consist of assessing the efficacy and safety of CNA as a therapy, allowing optimization of the use of PM in patients with SND/AVB, and ambition for the development of a diagnostic algorithm allowing the qualification of patients with SND and/or AVB for CNA and discontinuation of PM and TLE therapy.

STUDY POPULATION

Based on the sample size calculation, the plan is to recruit 99 patients with SND and/or atrioventricular block, who underwent PM implantation before the age of 50 years and

who had a functional cause or a significant functional component of SND and/or AVB in non-invasive tests during the first visit.

Patients must meet the following criteria:

Inclusion criteria:

1. Patients implanted with a PM before the age of 50 due to SND and/or AVB
2. Positive response to atropine test (as defined in Supplementary material)
3. Age between 18 and 65 years
4. Signing informed consent for participation in the study

Exclusion criteria:

1. Intrinsic heart rate < 30/min.
2. Syncope after initiation of cardiac stimulation therapy
3. Persistent and sustained atrial fibrillation
4. History of myocarditis
5. History of myocardial infarction
6. History of cardiac surgery
7. History of ablation procedures
8. Congenital heart defects
9. Congenital AVB
10. Neuromuscular and neurodegenerative disorders
11. Indication for upgrading the PM to ICD/CRT-D

12. Pregnancy

13. Renal insufficiency with GFR < 30 mL/min/1.73m^2

14. Age below 18 and above 65 years

15. HAS-BLED score ≥ 3 points

METHODS

The study will utilize a blocked randomization method with stratification. Enrolled patients will be randomly assigned into three parallel arms with a 1:1:1 allocation ratio using a web-based randomization system.

- At the screening, the patients will have an electrocardiogram (ECG), pacemaker (PM) check, non-invasive electrophysiological study (NI-EPS) if available, and atropine and laboratory tests (Table 1). Inclusion and exclusion criteria will be analyzed. After passing the initial screening, patients will be randomized to one of the 3 groups. Groups 1 and 2 will be blinded and receive intervention. Group 3 will only be observed for the study and will not be hospitalized.
- During the first hospitalization:
    - Group 1 — will undergo the electrophysiology study (EPS), extracardiac vagal stimulation (ECVS), and CNA (along with study protocol available in Supplementary Material) with continuous PM therapy and implantable loop recorder (ILR) implantation.

- Group 2 will undergo the EPS and ECVS with continuous PM therapy and ILR implantation but without CNA.

- During the second visit, 2 months after the first invasive procedure, the secondary endpoint, the percentage of PM stimulation in all groups will be assessed.
  - In Group 1, NI-EPS will be conducted to assess the CNA effectiveness; moreover, any events of Morgagni-Adams-Stokes syndrome (MAS) symptoms, para-MAS will be noted, and the stimulation percentage will be assessed.
  - In Group 2, patients will undergo NI-EPS and an assessment of the para-MAS and MAS symptoms; the stimulation percentage will be noted.
  - Patients in Group 3 will be evaluated for the stimulation percentage and para-MAS and MAS symptoms.
- After another month — during the second hospitalization:
  - In Group 1, EPS and ECVS will be performed. Based on the ECVS result, repeated CNAs will be performed if cardiac parasympathetic denervation is not proven.
  - In Group 2, EPS, ECVS, and CNA will be performed.
  - In Groups 1 and 2, PM will be set to VVI or AAI pacing mode at 30/min.
- At the third visit — one month after the second invasive procedure – the stimulation percentage will be assessed in patients in Groups 1 and 2. Patients with zero stimulation percentage in PM will be set to ODO/OVO/OAO mode. Patients with a

stimulation percentage greater than zero will have PM set to the optimal mode. Patients in Group 3 will be evaluated for stimulation percentage and para-MAS and MAS symptoms.

- Over the next 12 months, patients will be observed. During this period, Groups 1 and 2 will undergo 4 subsequent visits every 3 months to evaluate the CNA's effectiveness with non-invasive procedures and to assess bradycardia symptoms. Group 3 will be evaluated for MAS symptoms, para-MAS, and stimulation percentage.

- During the final, seventh visit, patients from Groups 1 and 2 will be qualified to discontinue cardiac stimulation therapy, with possible transvenous lead extraction (TLE) qualification. TLE and follow-up after the procedure are planned as a new prospective study.

Patients in Groups 1 and 2 will be monitored regularly for at least 12 months after the last invasive procedure. If, during this time, the symptomatic bradycardia returns, another CNA — with the patient's consent - will be performed shortly after the study. Patients in Group 3 will be observed for the entire study duration. The study flowchart is shown in Table 1. The interventions and assessments for the GENTLE-PACE study are outlined in Supplementary Material. The operators do not participate in a patient’s follow-up.

The GENTLE-PACE study protocol received approval from the independent Ethics Committee of the Institutional Review Board (Bioethics Committee at the Lower Silesian Medical Chamber, Wroclaw, Poland, KBE 01/BN/2023). The study was registered at clinical-trials.gov [https://www.clinicaltrials.gov/], identifier NCT05896592. Enrolment will commence on August 1, 2024 (Figure 1).

ENDPOINTS

- The primary efficacy endpoints comprise a composite endpoint, including non-traumatic loss of consciousness AND/OR presyncope symptoms AND/OR asymptomatic significant bradycardia identified in the loop recorder (defined as a second-degree AVB type II, 2:1 or higher AVB AND/OR sinus bradycardia < 40/min during patient wakefulness AND/OR sinus pause > 3 seconds during patient wakefulness AND/OR cardiac pacing despite the PM setting in AAI/VVI mode 30/min after the second intervention).
- On the safety front, the primary endpoints encompass a composite outcome, including death from any cause periprocedural in-hospital and in the follow-up period combined AND/OR non-fatal periprocedural damage to cardiac or vascular structures requiring surgical intervention AND/OR non-fatal ischemic stroke AND/OR pulmonary veins stenosis AND/OR phrenic nerve palsy AND/OR lead-related infective endocarditis AND/OR pocket infection

AND/OR electrode dysfunction requiring replacement AND/OR bleeding of BARC Grade 2 or 3 during post-procedure anticoagulant therapy.

- The secondary efficacy endpoints include various scenarios such as non-traumatic loss of consciousness, syncope in documented bradyarrhythmia, presyncope symptoms, presyncope in documented bradyarrhythmia, asymptomatic bradycardia requiring permanent cardiac pacing (defined by specific criteria), deactivation of permanent cardiac pacing at Visit 3, statistically significant reduction in pacing percentage in the CNA group compared to those continuing PM therapy without CNA, and qualification for removal of the PM system and TLE.
- The secondary safety endpoints include outcomes such as death from any cause, periprocedural damage to cardiac or vascular structures requiring surgical intervention, non-fatal ischemic stroke, symptomatic damage to pulmonary veins, damage to the phrenic nerve, lead-related infective endocarditis, pocket infection, electrode dysfunction, the occurrence of atrial tachyarrhythmias, symptoms of heart failure, symptoms of inappropriate sinus tachycardia, hospitalization for any cause, and bleeding of BARC Grade 2 or 3 during the post-procedural anticoagulant therapy.

STATISTICAL ANALYSIS

SAMPLE SIZE: The sample size was determined a priori, based on both primary endpoints – efficacy and safety. The percentage of patients experiencing an episode qualified as a primary endpoint (composite endpoints of efficacy and safety) is compared between randomized groups (non-inferiority trial). It was assumed that the risk of serious complications, largely constituting elements of the primary safety endpoint, is 1% in the case of cardioneuroablation. This is based on literature data available for a similar ablation procedure – pulmonary vein isolation. [11] In terms of the primary efficacy endpoint, the risk of syncope recurrence after the ablation procedure was set at 1% — it should be noted that due to the lack of randomized clinical trials in this area, it is difficult to predict the expected efficacy of the tested intervention. Literature data for vasovagal syncope speaks of an efficacy of about 95%, which is similar to the result of permanent pacemaker therapy [12, 13]. Therefore, excluding patients with syncope recurrence after pacemaker implantation, a safe assumption is to consider the expected efficacy of CNA at 99%.

The experimental therapy is better than, the same as, or only slightly worse than standard treatment (by no more than d) — the new treatment in this situation is not inferior.

Proposed herein is a sample size of 78 patients considering a 5% non-inferiority margin (based on clinical judgment), alpha of 5%; a beta of 20%; and a statistical power of 80%. A dropout rate of 25% will be used to adjust the sample size to 99 patients for balancing

33 patients per treatment arm (using the Sealed Envelope Ltd. software 20124 (London, UK) [14, 15].

The first step involves a description of the variables to be used in the analysis, including efficacy and safety. After data collection, statistical analysis will be conducted to demonstrate that the new treatment is not worse than the other groups within the established non-inferiority margin (primary objective). The choice of the statistical test will depend on the type of data to be analyzed and the study assumptions. For this non-inferiority trial, an equivalence test may be performed to compare the selected treatment methods and determine if their differences are small enough to be considered equivalent. If the difference between the methods is smaller than the predefined equivalence limit, the alternative hypothesis is accepted, and the methods are deemed equivalent. Additionally, Bland-Altman analysis will assess the agreement between the new and standard methods. The limit of agreement will be used to determine if the results from the new method are sufficiently close to the results of the standard method. As for secondary objectives, a time-to-event analysis will be conducted to assess specific event occurrences. FA's predefined procedures for handling missing data will be established, and data quality assurance procedures (data verification, analysis validation) will be outlined. A schedule of planned activities, including primary and secondary analyses, review of results, and reporting, will be specified. Analyses will be performed on an intention-to-treat basis. The precise, comprehensive analysis plan, accessible to the entire research

team, may be updated if necessary. All analyses will be performed using the statistical software STATA 17 (StataCorp LLC, USA) or an equivalent tool [10–13].

DISCUSSION

Implantation of cardiac pacemakers for constant heart stimulation remains the recommended treatment for symptomatic bradycardia resulting from sinus node dysfunction (SND) or atrioventricular block (AVB), as endorsed by the European Society of Cardiology (ESC) and the American Heart Association (AHA) [1, 2]. Despite the increasingly prevalent use of physiological cardiac pacing and the introduction of leadless pacemakers, this approach still has significant limitations. The cumulative risk of long-term complications associated with continuous cardiac stimulation is challenging to estimate, particularly in younger patients. Several small, non-randomized studies and case reports have demonstrated the effectiveness of cardioneuroablation (CNA) in treating functional bradycardia due to vagal hyperactivity. To date, only small observational studies have shown the utility of CNA in patients previously treated with continuous stimulation, allowing for the termination of pacing therapy and pacemaker removal [9, 10]. Ending continuous heart stimulation and removing unnecessary pacemakers have been linked to reduced mortality rates [16]. To date, the only randomized trials investigating CNA are the ROMAN [7] and ROMAN 2 [17] studies, which have established its efficacy in vasovagal syncope (VVS) and focused on the technical aspects

of the procedure. The effectiveness of CNA in treating functional SND and AVB requires validation through multicenter randomized trials. According to the ClinicalTrials registry (as of October 2023), there are 4 ongoing studies evaluating CNA efficacy in functional SND [18–20], one in functional AVB [21], 4 in vasovagal syncope [22–25], and one in atrial fibrillation [26]. However, only the GENTLE-PACE trial addresses patients with existing pacemakers, aiming to assess the effectiveness of CNA as an alternative to continuing permanent cardiac pacing therapy.

CONCLUSIONS

GENTLE-PACE will provide data on the efficacy of safety of CNA as an alternative to PM therapy in SND/AVB patients. Moreover, it will potentially contribute to the development of PM therapy discontinuation algorithms after CNA.

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Conflict of interests: Sebastian Stec is a co-founder/stockholder of Medinice S.A. and co-author of patents (Pace-Press, Cryoapplicator, Cathaio, Ep-Bioptom catheter, Mini-Max for nonfluoroscopic navigation and procedures). The products of this company have not been used in this study and are not related to CNA procedures. There are no other potential conflicts of interest related to this article. The other authors declare no conflict of interest.

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26. Cardioneuroablation vs Pulmonary Vein Isolation in Treatment of Paroxysmal Atrial Fibrillation. NCT06058468.

Figure 1. Graphical abstract

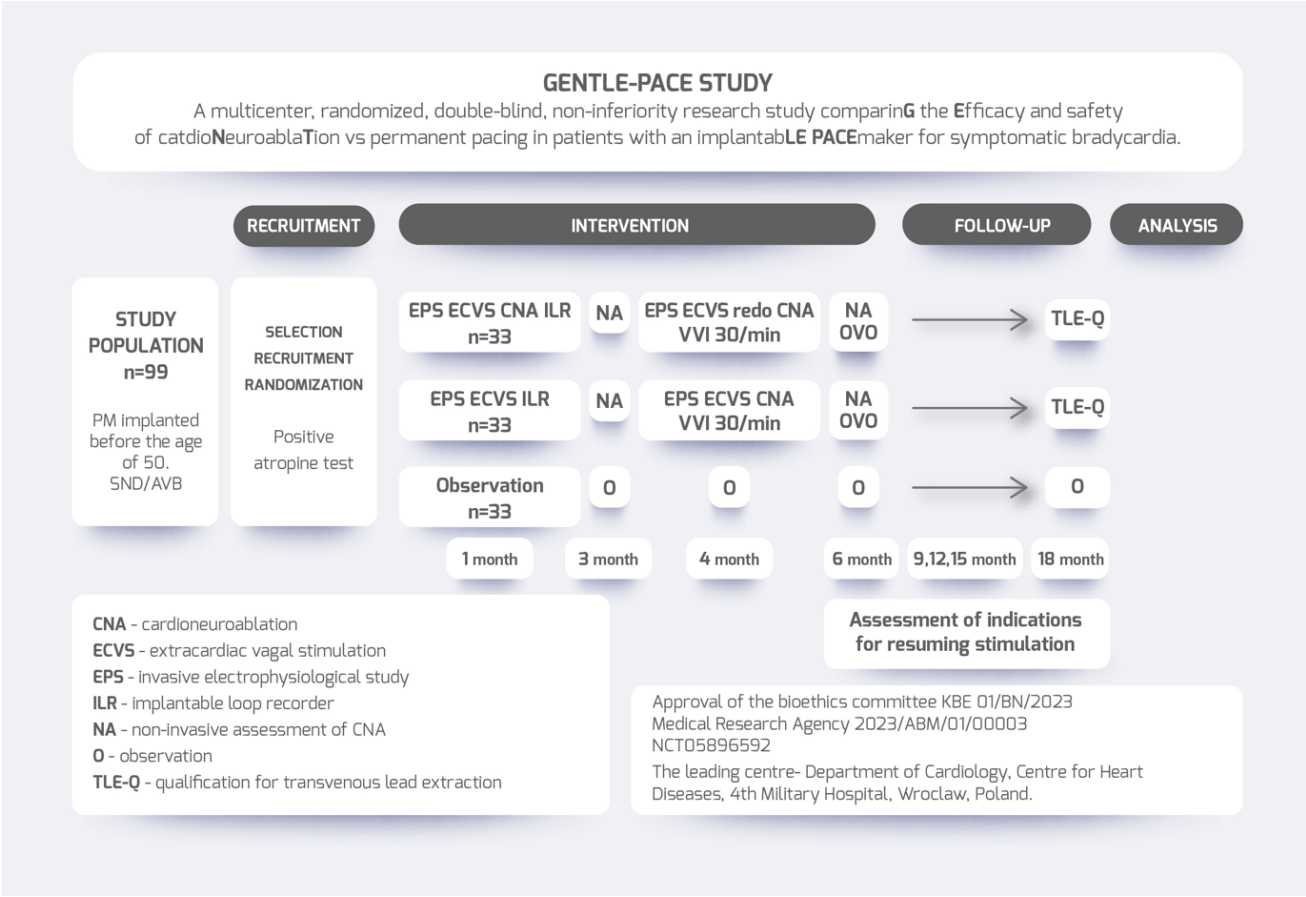

Table 1. Study flow-chart

HOSPITALIZATIONS FLOW-CHART

	TREATMENT PERIOD	
Hospitalisation	H1	H2
Day	30	120
Visit window (days)	+/- 15	+/-30
12-lead ECG	x	x
EPS	x	x
ECVS	x	x
CNA	x	x
ILR implantation	x	
ILR control		x
Setting PM stimulation to VVI 30/min. or AAI 30/min after a successful CNA		x
CBC	x	x
Creatinine	x	x
Na+, K+	x	x
CRP	x	x
INR	x	x
APTT	x	x
Pregnancy test if necessary	x	x
Transthoracic echocardiogram	x	x
24h Holter ECG	x	
Adverse event assessment	x	x

APTT - activated partial thromboplastin time
CBC - complete blood count
CNA – cardioneuroablation
CRP – C-reactive protein
ECG - electrocardiogram
ECVS - extracardiac vagal stimulation
EPS -electrophysiological study
ILR - implantable loop recorder
INR - international normalised ratio
K+ - potassium
Na+ - sodium
PM - pacemaker

VISITS FLOW-CHART

Visit	V1	V2	V3	V4	V5	V6	V7
Day	0	90	180	270	360	450	540
Visit window (days)		+/-30	+/-30	+/-30	+/-30	+/-30	+/-30
Informed Consent	x						
In-/exclusion criteria	x						
Randomisation	x						
Demographics	x						
Medical History/ Comorbidities	x						
Physical exam	x	x	x	x	x	x	x
Assessing the intrinsic rhythm's performance during pacemaker check. Subsequent reprogramming pacemaker in DDD mode at 50 beats per minute with an AV interval of 220 milliseconds or in AAI/VVI mode at 50 beats per minute.	x	x					
Assessing the intrinsic rhythm's performance during pacemaker check. Subsequent reprogramming pacemaker in ODO/OVO/OAO mode.			x				
PM check	x	x	x	x	x	x	x
ILR check		x	x	x	x	x	x
Optimization of stimulation settings for patients requiring pacing.			x	x	x	x	x
Qualification for discontinuation of permanent pacing therapy.							x
TLE qualification							x
12-lead ECG of native rhythm	x	x	x	x	x	x	x
NI-EPS with PM	x	x	x	x	x	x	x
Transthoracic echocardiogram							x
Atropine test	x						x
24h Holter ECG		x	x	x	x	x	x
EP heart team							x
CBC	x						
Creatinine	x						
Na+, K+	x						
AST	x						
ALT	x						
TSH	x						
fT3 i fT4	x						
NT-proBNP	x						
Pregnancy test	x						
Biobanking of blood samples.	x						
Assessment of adverse events	x	x	x	x	x	x	x