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Rationale and design of SAN.OK randomized clinical trial and registry: Comparison of the effects of evidence-based pacemaker therapy and cardioneuroablation in sinus node dysfunction

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Background

Sinus node dysfunction (SND) is considered a progressive, incurable, but manageable disease and has conventionally been treated with definitive pacemaker (PM) implantation, according to current European Society of Cardiology (ESC) guidelines [1–3]. However, there is lack of evidence that PM therapy results in improved prognosis and increased expectancy of life [1]. Moreover, the essential number of complications of PM implantation and relatively high rate of rejection by young patients constitute a common clinical dilemma in SND management [4].

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**Sebastian Stec and Beata Jankowska-Polańska are co-primary investigators of the study.*

Cardioneuroablation (CNA) is an emerging treatment, a novel method of bradyarrhythmia management [5–8], which is by endocardial radiofrequency (RF) catheter ablation, causing targeted neuromodulation of the cardiac autonomic nervous system, enabling a sudden postprocedural increase in sinus rhythm, thereby providing an attractive treatment option without the necessity for PM implantation in SND, atrioventricular blocks (AVB) and vasovagal syncope (VVS).

The main principle of CNA is a catheter-based destruction of parasympathetic postganglionic neurons of vagal nerve located in ganglionated plexi (GP) in atrial myocardium and epicardium, which induces cardio-neuromodulation of the sino-atrial node (SAN) and/or atrio-ventricular node (AVN), as it has been proven that SAN dysfunction and AVB can be directly related to vagal nerve hyperactivity [5–9].

The CNA technique was introduced by Jose Carlos Pachon over two decades ago and has been refined and improved along the way [5–8]. Currently many investigators worldwide reproduce CNA results with the immediate CNA endpoints including total abolition of atropine response and elimination or significant reduction of vagal response, confirmed by a vagal stimulation [9–16].

The implementation of comprehensive diagnostic assessment including the atropine challenge test, autonomic tests (head-up tilt test, Valsalva maneuver, carotid sinus massage, forced breathing test) and extracardiac vagal nerve stimulation (ECVS), with recently introduced ultrasound-guided ECVS (US-ECVS), enables validation of early and late success rate of vagal nerve ablation and positive impact on automaticity of SAN and conduction of the heart [15].

Despite promising results and relatively high (92%) short- and long-term efficacy of CNA and low risk of complications of the procedure (1–3% vs. 3–5% in PM implantation) [4–7], concerns about the performance of the new non-standardized method, its safety and clinical benefits still exist. In the 2018 ESC guidelines on the diagnosis and management of syncope and 2021 ESC guidelines on cardiac pacing CNA was considered an experimental method and did not receive ESC recommendations, mainly due to the lack of randomized clinical trials.

Therefore, a prospective randomized clinical trial (RCT) evaluating CNA application in SND management and feasibility of non-invasive and invasive diagnostic techniques to facilitate patients for CNA may influence the decision-making process to avoid long-term PM therapy and may have a major impact on future recommendations.

This manuscript is the study protocol of SAN.OK trial and registry, one of the first prospective randomized trials, designed to compare the effects of PM implantation and CNA in patients with SND.

Methods

Study design

SAN.OK study is a multicenter, noncommercial, physician-initiated, proof-of-concept, prospective, randomized, controlled, unblinded clinical trial and registry designed to compare two methods of SND treatment: optimized guideline-recommended PM therapy and a novel method, CNA, preceded by autonomic and interdisciplinary assessment, electrophysiological study (EPS) and ECVS with the goal of achieving post-procedure and maintaining a target heart rate > 50 beats per minute. Subjects who will choose to opt-out of randomization will be included in the registry and will undergo patient-tailored intervention through shared decision-making with a possibility of either PM implantation, CNA or observation only. The study design is presented in Figure 1.

Recruitment will take place in four study sites (**Suppl. Table S1**), in two distinct phases. First, the investigators will identify potential participants. Their medical records will be analyzed by the Scientific Committee (symptoms evaluation, physical examination, documentation of bradyarrhythmia). In the second phase eligible patients will be invited by the investigator to participate in the trial during medical consultation. After detailed explanations describing the study protocol, including the risk and benefits, they will sign the written informed consent to participate in the study or will choose to opt-out of randomization to be included in the registry only. Informed consent will be obtained only if it is clear that the patient truly understands the nature of the study. Alternatively, the patient will be encouraged to take a copy of the consent form home to contemplate enrolment in the study. Only patients who voluntarily consent will be included. Patients will be able to withdraw at any time without compromising their medical care. All measured parameters, as well as demographic and clinical data will be recorded in the study database.

Patients enrolled in the SAN.OK trial will be randomized in a 1:1 allocation to either an optimized guideline-recommended PM therapy (group A) or CNA (group B). Randomization will

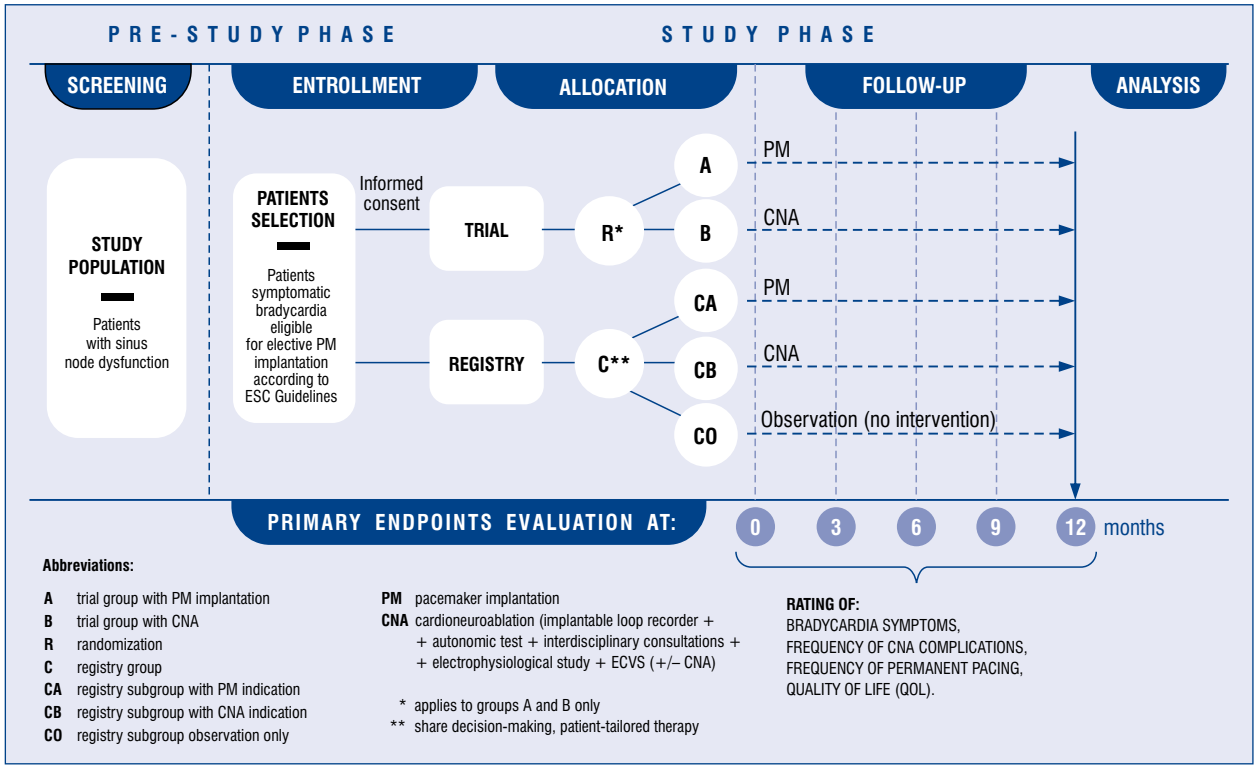

Figure 1. Study design of SAN.OK trial and registry; ECVS — extracardiac vagal nerve stimulation; ESC — European Society of Cardiology.

be performed centrally and assigned automatically to each patient via the internet. The randomization list will be blocked per center, with randomly varying block sizes of 2 and 4. The centers will not be aware of the block sizes. The PM implantation and treatment allocation will not be blinded to the patient or follow-up physician.

Patients in either arm of the study will be followed-up at regular intervals for a minimum of 12 months. The schedule of interventions and assessments of the SAN.OK study and registry is summarized in **Supplementary Tables S2 and S3**. During the 12-month study duration, the use of effective contraception will be recommended for women of child-bearing age.

The SAN.OK study protocol was approved by the independent Ethics Committee of Institutional Board Review (Bioethics Committee at the Lower Silesian Medical Chamber, Wroclaw, Poland, KBE 6/BOBD/2021). The study is registered at clinicaltrials.gov [https://www.clinicaltrials.gov/], identifier NCT05196126. Enrolment began on June 1, 2022. The SAN.OK trial is independently managed by KCRI (www.kcri.org), Krakow, Poland and the Scientific Steering Committee. Members of the latter are the exclusive authors of this manuscript.

Study population

SAN.OK trial will enroll a minimum of 29 patients in each group, 18–75 years old with indications for elective PM implantation according to 2021 ESC guidelines on cardiac pacing. The registry is expected to include up to 120 patients. The recruitment will take place at four study sites in Poland by medical referral (**Suppl. Table S1**). Patient enrollment time is anticipated to last 1 year. Inclusion and exclusion criteria are summarized in Table 1. The population of elderly patients > 75 years, frequently with concomitant heart disease, is excluded, since the demonstration of a clear cause–effect relationship between symptoms and SND is difficult to achieve.

Interventions

Patients in group A (PM, n = 29) will receive care on the basis of the 2021 ESC guidelines on cardiac pacing recommendations. They will be implanted with PM.

Patients in group B (CNA, n = 29) will be implanted with the same type of implantable loop recorder (ILR) device (Biotronic, Biomonitor 3m) with remote tele-monitoring, with the same thresholds for automatic episode recording. A central

Table 1. Inclusion and exclusion criteria of SAN.OK trial and registry.

Inclusion criteria
Male and female patients, age 18–75 years
Sinus node dysfunction/disease fulfilling criteria for elective pacemaker implantation according to current ESC guidelines (I, IIa, and IIb)
Optimization of chronic disease treatment
Ability to provide informed consent to participate in the study
Ability to understand patient information
Exclusion criteria
Contraindications to invasive and non-invasive procedures used in the study
Uncontrolled systemic and endocrine disorders
Persistent atrial fibrillation
Dilated cardiomyopathy
Severe congenital heart valve disease or cardiomyopathy
Functional NYHA class III/IV
Left ventricular ejection fraction < 35%
Left atrial diameter > 50 mm
Previous catheter ablation
Contraindications to anticoagulant treatment
Contraindications to catheter ablation
Chronic advanced (II or III degree) AV block associated with structural heart disease
Contraindications to non-invasive tests
Pregnancy and lactation
Previous cardiac surgery
Implanted pacemaker device
Neck and chest abnormalities
Myocardial infarction in the previous 6 months
Percutaneous coronary intervention in the previous 3 months
Estimated survival < 24 months
Participation in another drug or medical device program
Limited capacity to understand the study protocol or psychological disorders precluding informed consent to participate in the study
Any other uncontrolled chronic diseases, neck and chest abnormalities, or disorders that constitute a contraindication to catheter ablation, antiarrhythmic treatment, general anesthesia, or ECVS
Severe obesity (BMI ≥ 40 kg/m^2)

AV — atrioventricular; BMI — body mass index; ECVS — extracardiac vagal nerve stimulation; ESC — European Society of Cardiology; NYHA — New York Heart Association

committee will be responsible for remote tele-monitoring. The major reason for ILRs implantation is to provide electrocardiogram documentation of clinical bradycardia, as well as monitoring of patients before and after CNA (or PM implantation, if accepted). In case of severe bradycardia, the emergency system will always be called. Patients in group B will be accepted for CNA (or PM implantation) based on complex data including ILRs interrogation and multidisciplinary assessment.

Multidisciplinary assessment in group B will include: a) symptoms evaluation on VAS; b) documentation of bradyarrhythmias on ILR with remote monitoring; c) autonomic tests: atropine challenge, Valsalva maneuver, carotid sinus massage, head-up tilt test, forced breathing test; d) interventional assessment: EPS, ECVS; e) interdisciplinary consultations: sleep medicine, otolaryngology, vascular surgery, bruxism-orthodontic.

Cardioneuroablation will be performed in group B under general anesthesia by highly trained operators according to previous case reports [14, 15]. After EPS biatrial, binodal, anatomically-guided CNA will be performed with ECVS guidance, with demonstration of vagal response by ECVS at the beginning of CNA and its complete disappearance after successful CNA. Additional substrates for ablation will also be investigated. If CNA is unsuccessful, a second session of CNA is planned. In case of an inefficient second attempt, patients will be referred for PM implantation. They will cross-over to the PM arm.

Patients in the registry (group C) will undergo patient-tailored intervention through shared decision-making with a possibility of either PM implantation (subgroup CA), CNA (subgroup CB), or observation only (subgroup CO).

All patients in the trial and registry will be asked to complete questionnaires on health-related quality of life; (QOL) (EQ-5D-5L, SF-36), bradycardia symptoms; (Visual Analog Scale [VAS]), fatigue; (Modified Fatigue Impact Scale [MFIS]), depression (Modified Hospital Anxiety and Depression Scale; [HADS-M]) and sleep disorders (Epworth Sleep Scale [ESS]; Athens Insomnia Scale-8 [AIS-8]).

The safety of the interventions will be assessed weekly, with monitoring of major adverse cardiovascular events (MACE). All outcome events will be adjudicated by The Central Adjudication Committee, which does not include members of the Scientific Steering Committee.

Endpoints

The primary endpoint is to determine the efficacy of CNA in the treatment of bradyarrhythmia in comparison to PM therapy within 6 months of PM implantation/CNA procedure.

The secondary endpoints include: 1) occurrence of MACE, defined as peri-procedural and long-term complications: death, stroke, myocardial infarction, pericardial effusion requiring drainage, AVB, venous thrombosis, infection, hemorrhage, hematoma, fistula, pseudoaneurysm, surgical intervention; 2) assessment of the effect of CNA and PM implantation on bradycardia symptoms on VAS, health-related QOL (EQ-5D-5L, SF-36 questionnaires), fatigue (MFIS), depression/anxiety (HADS-M), sleep disorders questionnaire (ESS, AIS-8) at 0, 3, 6, 12 months (**Suppl. Table S4**).

Statistical analysis

Statistical analysis includes descriptive analysis of the primary and secondary endpoints. There are two types of endpoints in this study concerning the nature of the parameters tested: objective and subjective.

The objective endpoint examining the onset of bradyarrhythmia episodes after PM/CNA will be assessed at 6 months. It will specify the number of pauses > 3.0 s in the ILR for group B (occurrence of > 1 pause or the need for earlier (0–6 months) PM implantation will be an indicator of the failure of the CNA procedure), assuming the presence of PM stimulation in group A at the level between 93–100% (equates to the continued duration of the bradyarrhythmia treated with PM).

The subjective endpoint examining symptoms such as QOL, fatigue, depression/anxiety, sleep disorders using questionnaires will be assessed at 0, 3, 6, 12 months.

For both endpoints descriptive statistics (parametric and non-parametric) will be determined for the parameters tested. In addition, a comparative analysis between groups for the objective parameters at timepoints 0, 6 months and the subjective parameters at timepoints 0, 3, 6, 9, 12 months will be carried out with non-parametric tests of statistical significance using the Bonferroni correction.

The effectiveness of CNA vs. PM will be considered statistically significant at the level of $p < 0.01$ if there is an absence of pauses > 3.0 s within 6 months after the CNA procedure in 33% of patients (12/30) — assuming 90% statistical power, with simultaneous assumption of the presence of PM and 100% effectiveness of stimulation in group A. Such a result will mean a reduction in the need for PM implantation in 33% of respondents.

Statistical significance is expected in the difference between groups A and B in both objective and subjective endpoints, meaning:

- reduction in the number of patients requiring PM implantation in group B compared to group A (all patients with implanted PM);
- a significant improvement in the quality of life of patients in group B as measured by bradycardia symptoms on VAS, QOL (EQ-5D-5L, SF-36), fatigue (MFIS), depression/anxiety (HADS-M), sleep disorders (ESS, AIS-8) questionnaires.

Assuming the incidence of PM implantation at 6-month follow-up as 28/30 (93%) and 18/30 (60%) in groups A and B, respectively, and statistical power of 90%, the group size should be 29 patients each to obtain a statistical level of 0.01. This translates into a 33% reduction of the need for PM implantation.

Discussion

The autonomic nervous system plays a distinctive role in the pathophysiology of bradyarrhythmia [8]. Neuraxial modulation of vagal nerve is an important avenue of scientific inquiry and novel therapeutic intervention [5–18]. Treatment of SND by ablation technique seems a very attractive method, especially in young patients in whom a prosthesis is highly undesirable. Therefore, CNA has a potential to revolutionize cardiac electrophysiology and become a minimally invasive method of functional bradycardia and SND treatment. According to available research, SAN.OK RCT is one of the first clinical studies investigating optimal decisions on invasive strategy in SND and/or chance to avoid PM therapy with the use of ECVS as the most rational peri-procedural endpoint of CNA [19, 20]. In comparison to other registered ongoing trials, such as GAPS [19] and DINERVAPACE [20], in the SAN.OK study patients allocated to the CNA group will be monitored by ILR and ECVS. Moreover, the SAN.OK study is the first to compare measurable indicators of QOL and associated symptoms before and after CNA and PM implantation. According to current ESC guidelines quality of life is an essential metric for measuring a patient's clinical status and outcome, and provides a holistic picture of clinical treatment effectiveness [1]. In summary, SAN.OK prospective trial may influence the decision-making process to avoid long-term PM therapy, provided that an alternative treatment is available with demonstrated non-inferiority.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov/; unique identifier: NCT05196126.

Limitations of the study

Owing to differences in techniques of PM implantation and CNA the present study is unable to be blinded.

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Conflict of interest: Sebastian Stec is the author of several patents and shareholder of Medicine S.A. and Tracess A.B. No specific product of any company will be used in this trial. Artur Fedorowski has received speaker fees from Medtronic Inc, Biotronik, Finapres Medical Systems, and Bristol-Myers-Squibb, and is a consultant to Medtronic Inc. and Argenx B.V. All other authors declare that they have no conflicts of interest.

References

1. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021; 42(35): 3427–3520, doi: 10.1093/eurheartj/ehab364, indexed in Pubmed: 34455430.
2. Brignole M, Moya A, de La, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. ESC Scientific Document Group. Eur Heart J. 2018; 39: 1883–1948, doi: 10.1093/eurheartj/ehy037, indexed in Pubmed: 29562304.
3. Brignole M, Moya A, de Lange FJ, et al. ESC Scientific Document Group. Practical Instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018; 39(21): e43–e80, doi: 10.1093/eurheartj/ehy071, indexed in Pubmed: 29562291.
4. Tułecki Ł, Polewczyk A, Jacheć W, et al. A study of major and minor complications of 1500 transvenous lead extraction procedures performed with optimal safety at two high-volume referral centers. Int J Environ Res Public Health. 2021; 18(19), doi: 10.3390/ijerph181910416, indexed in Pubmed: 34639716.
5. Pachon JC, Pachon EI, Pachon JC, et al. „Cardioneuroablation"--new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. Europace. 2005; 7(1): 1–13, doi: 10.1016/j.eupc.2004.10.003, indexed in Pubmed: 15670960.
6. Pachon JC, Pachon EI, Cunha Pachon MZ, et al. Catheter ablation of severe neurally meditated reflex (neurocardiogenic or vasovagal) syncope: cardioneuroablation long-term results. Europace. 2011; 13(9): 1231–1242, doi: 10.1093/europace/eur163, indexed in Pubmed: 21712276.
7. Pachon M JC, Pachon M EI, Santillana P TG, et al. Simplified method for vagal effect evaluation in cardiac ablation and electrophysiological procedures. JACC Clin Electrophysiol. 2015; 1(5): 451–460, doi: 10.1016/j.jacep.2015.06.008, indexed in Pubmed: 29759475.
8. Shivkumar K, Ajijola OA, Anand I, et al. Clinical neurocardiology defining the value of neuroscience-based cardiovascular therapeutics. J Physiol. 2016; 594(14): 3911–3954, doi: 10.1113/JP271870, indexed in Pubmed: 27114333.
9. Yao Y, Shi R, Wong T, et al. Endocardial autonomic denervation of the left atrium to treat vasovagal syncope. Circ Arrhythm Electrophysiol. 2012; 5(2): 279–286, doi: 10.1161/circep.111.966465.
10. Aksu T, Golcuk E, Yalin K, et al. Simplified cardioneuroablation in the treatment of reflex syncope, functional AV block, and sinus node dysfunction. Pacing Clin Electrophysiol. 2016; 39(1): 42–53, doi: 10.1111/pace.12756, indexed in Pubmed: 26411271.
11. Qin Mu, Zhang Yu, Liu Xu, et al. Atrial ganglionated plexus modification: a novel approach to treat symptomatic sinus bradycardia. JACC Clin Electrophysiol. 2017; 3(9): 950–959, doi: 10.1016/j.jacep.2017.01.022, indexed in Pubmed: 29759719.
12. Piotrowski R, Baran J, Kułakowski P, et al. Cardioneuroablation using an anatomical approach: a new and promising method for the treatment of cardioinhibitory neurocardiogenic syncope. Kardiol Pol. 2018; 76(12): 1736–1738, doi: 10.5603/KP.a2018.0200, indexed in Pubmed: 30338504.
13. Aksu T, Erdem Guler T. Cardioneuroablation in the management of vasovagal syncope, sinus node dysfunction and functional atrioventricular block: patient selection based on supporting evidence. J Atr Fibrillation. 2020; 13(1): 2396, doi: 10.4022/jafib.2396, indexed in Pubmed: 33024497.
14. Stec S, Dobaj Ł, Śledź A, et al. Cardioneuroablation for management of cardioinhibitory vasovagal syncope and pacemaker complications. HeartRhythm Case Rep. 2020; 6(8): 531–534, doi: 10.1016/j.hrcr.2020.04.021, indexed in Pubmed: 32817835.
15. Wileczek A, Polewczyk A, Kluk M, et al. Ultrasound-guided imaging for vagus nerve stimulation to facilitate cardioneuroablation for the treatment of functional advanced atrioventricular block. Indian Pacing Electrophysiol J. 2021; 21(6): 403–406, doi: 10.1016/j.ipej.2021.06.008, indexed in Pubmed: 34186197.
16. Aksu T, De Potter T, John L, et al. Procedural and short-term results of electroanatomic-mapping-guided ganglionated plexus ablation by first-time operators: A multicenter study. J Cardiovasc Electrophysiol. 2022; 33(1): 117–122, doi: 10.1111/jce.15278, indexed in Pubmed: 34674347.
17. Rivasi G, Ungar A, Moya A, et al. Syncope: new solutions for an old problem. Kardiol Pol. 2021; 79(10): 1068–1078, doi: 10.33963/KP.a2021.0138, indexed in Pubmed: 34668180.
18. ROMAN registry (Cardioneuroablation for Reflex Syncope (ROMAN): NCT 03903744. www.clinicaltrials.com.
19. Cardiac Ganglionated Plexus Ablation Before Permanent Pacemaker Implantation in Patients With Sick Sinus Syndrome (GAPS): NCT 04149886. www.clinicaltrials.com.
20. Cardioneuroablation versus pacemaker implantation for the treatment of symptomatic sinus node dysfunction (DINERVA-PACE): NCT 051862. www.clinicaltrials.com.