

The CONDUCT-AF trial: Rationale and design of a prospective, randomized, multicentre study comparing conduction system and biventricular pacing in patients undergoing atrioventricular node ablation for heart failure with atrial fibrillation

Maja Ivanovski^{1,2}, Miha Mrak¹, Anja Zupan Mežnar¹, Matevž Jan³, Catalin Pestrea⁴, Sandro Brusich^{5,6}, Peter Bogyi^{7,8}, Sebastiaan Dhont^{9,10}, Zrinka Jurišić¹¹, Vassil Traykov¹², Borka Pezo Nikolić¹³, Wilfried Mullens^{9,10}, and David Žižek^{1,2}*¹⁰

¹Cardiology Department, University Medical Centre Ljubljana, Ljubljana, Slovenia; ²University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia; ³Department of Cardiovascular Surgery, University Medical Centre Ljubljana, Ljubljana, Slovenia; ⁴Department of Interventional Cardiology, Brasov County Emergency Clinical Hospital, Brasov, Romania; ⁵Clinic for Cardiovascular Diseases, Clinical Hospital Centre Rijeka, Rijeka, Croatia; ⁶University of Rijeka, Department of Internal Medicine, Medical Faculty, Rijeka, Croatia; ⁷Central-Hospital of Northern Pest - Military Hospital, Budapest, Hungary; ⁸Semmelweis University, Centre for Translational Medicine, Budapest, Hungary; ⁹Department of Cardiology, Ziekenhuis Oost-Limburg A.V., Genk, Belgium; ¹⁰Hasselt University, Faculty of Medicine and Life Sciences, Diepenbeek, Belgium; ¹¹Department of Cardiology, University Hospital Center Split, Split, Croatia; ¹²Department of Invasive Electrophysiology, Clinic of Cardiology, Acibadem City Clinic Tokuda University Hospital, Sofia, Bulgaria; and ¹³University Hospital Centre Zagreb, Zagreb, Croatia

Received 19 April 2025; revised 1 July 2025; accepted 28 July 2025; online publish-ahead-of-print 8 September 2025

-	•		
\boldsymbol{D}	м	n	36
_	м		-

There is a lack of data from randomized clinical trials comparing treatment outcomes between conduction system pacing (CSP) modalities and biventricular pacing (BVP) in symptomatic patients with refractory atrial fibrillation (AF) scheduled for atrioventricular node ablation (AVNA). The CONDUCT-AF investigates whether CSP is non-inferior to BVP in improving left ventricular ejection fraction (LVEF) and clinical outcomes in heart failure (HF) patients with symptomatic AF undergoing AVNA.

Methods

This study is an investigator-initiated, prospective, randomized, multicentre clinical trial conducted across 10 European centres, enrolling 82 patients with symptomatic AF, HF with reduced LVEF, and narrow QRS. Participants will be randomized 1:1 to CSP or BVP with subsequent AVNA and followed for at least 24 months. The primary endpoint is the change in LVEF after 6 months. Secondary endpoints will include time to the first occurrence of worsening HF or cardiovascular death and its individual components, total number of HF hospitalizations, change in quality of life, N-terminal pro-B-type natriuretic peptide, 6-min walk test distance, and safety outcomes.

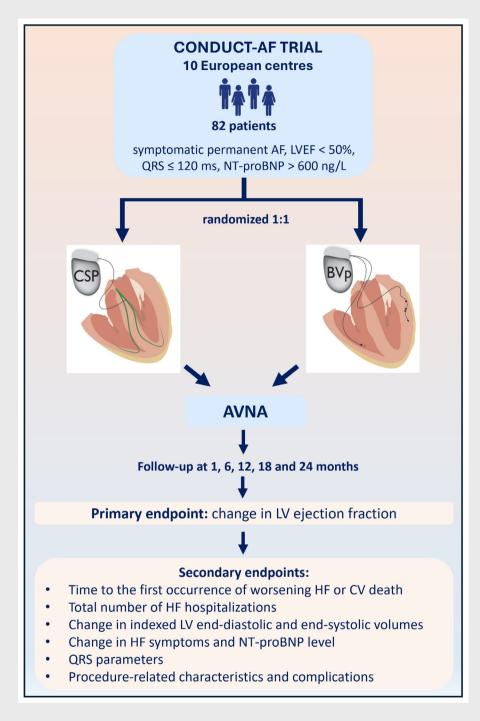
Conclusions

The CONDUCT-AF trial will provide critical insights into the optimal pacing modality for patients with HF and refractory AF undergoing AVNA. Recruitment is expected to conclude in 2025, with the first study results anticipated in 2026.

^{*}Corresponding author. Department of Cardiology, University Medical Centre Ljubljana, Zaloška 7, 1000 Ljubljana, Slovenia. Tel: +386 1 5228534, Email: david.zizek@kclj.si

18790844, 2025, 10, Dov

Graphical Abstract



The CONDUCT-AF trial. AF, atrial fibrillation; AVNA, atrioventricular node ablation; BVp, biventricular pacing; CSP, conduction system pacing; CV, cardiovascular; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Atrioventricular node ablation ● Atrial fibrillation ● Conduction system pacing ● Biventricular pacing ● Heart failure

The CONDUCT-AF trial 1929

Introduction

Atrial fibrillation in heart failure

Disorganized atrial activity during atrial fibrillation (AF) has many deleterious haemodynamic effects contributing to cardiac remodelling and induction of fibrosis. 1-3 Early studies proved that irregularity and loss of atrial contribution to left ventricular (LV) filling decreased cardiac output (CO).4 Further exploration revealed that independent of rate, irregular ventricular rhythm disables cardiac contractility to adapt during beat-to-beat changes in ventricular filling. In addition, AF leads to insufficient coronary flow, molecular LV remodelling, and disrupted Ca²⁺ homeostasis, which eventually may induce contractile dysfunction.^{3,5} In brief, deleterious haemodynamic effects of AF on cardiac function can be attributed to loss of atrial contraction, reduced CO, and irregular and often rapid heart rate.^{2,6} Considering these facts, removing irregularity and fast ventricular response alone can increase CO and prevent long-term deleterious effects of AF culminating in arrhythmia-induced cardiomyopathy.

Treatment strategies

Catheter ablation enables restoration of sinus rhythm and several studies have recently demonstrated its prognostic benefit.⁷⁻⁹ Therefore, current guidelines recommend CA as a first-line treatment when arrhythmia-induced cardiomyopathy is highly probable (class I, level of evidence B, European and US guidelines). 10,11 However, these benefits might be less distinct in patients with long-standing, persistent AF in whom lower interventional success rates might be expected. 12 Additionally, most trials do not specify ablation outcomes in persistent AF or elderly patients with more comorbidities in whom recurrences may be particularly problematic. Therefore, even though the guidelines recommend CA as a treatment of choice, alternative therapeutic strategies may be considered. Atrioventricular node ablation (AVNA) with permanent pacemaker implantation (pace and ablate strategy) is a feasible rate control option that offers more robust control of ventricular rate over medical therapy alone, as well as definitive rhythm regularization. 13 A recent meta-analysis compared the efficacy and safety endpoints among five major approaches for AF. Although CA performed best in reducing AF recurrence, the pace and ablate strategy showed superiority in reducing mortality and rehospitalization.¹⁴ Current 2024 European Society of Cardiology guidelines recommend AVNA in patients unresponsive or intolerant to intensive rate and rhythm control therapy, and not eligible for rhythm control by CA (class IIa, level of evidence B). The choice of pacing modality depends on patient characteristics and the presence of heart failure (HF).10

Pacing modalities in the pace and ablate strategy

Right ventricular pacing (RVP) combined with AVNA has demonstrated its potential to effectively improve clinical outcomes. ¹⁵ However, the beneficial effects of rate control and regularization

after AVNA could be hampered by non-physiological asynchronous contraction after RVP.¹⁶ Deleterious effects of RVP can be avoided with biventricular pacing (BVP). As demonstrated in the APAF-CRT study, BVP combined with AVNA significantly reduced mortality, HF hospitalizations, and improved LV function.^{17,18} However, the benefit was less distinct in symptomatic AF patients with moderately reduced left ventricular ejection fraction (LVEF) and narrow QRS. BVP circumvents the dyssynchrony induced by RVP but still induces abnormal epicardial activation that results in QRS prolongation and some extent of electrical and mechanical dyssynchrony.^{3,17,19}

In recent years, conduction system pacing (CSP) modalities, including His bundle pacing (HBP) and left bundle branch area pacing (LBBAP), have evolved as a promising alternative allowing the most physiological activation of the myocardium. Retrospective studies demonstrated both the feasibility and advantages of HBP in echocardiographic outcomes and time to death or HF hospitalization compared to conventional RVP.20 Although the His bundle appears to be the ideal physiological pacing site, its proven feasibility alongside AVNA must be considered in light of some significant limitations. The implant technique is challenging and requires advanced implantation tools and longer procedural and fluoroscopic times. Low sensing values could engender atrial oversensing in pacemaker-dependent patients. Moreover, higher pacing thresholds and their further rise after AVNA due to the proximity of the ablation site to the implanted HBP lead might be observed, necessitating a right ventricular (RV) backup lead and early battery replacement.^{21,22} In contrast, LBBAP lead is implanted in the region of the left bundle in the septum, which has an adequate distance from the AVNA site. Therefore, this modality could minimize the risk of an increase in capture threshold after AVNA. Additionally, the pacing parameters of LBBAP were stable in long-term follow-up studies, precluding the need for back-up pacing and early battery replacement. Therefore, compared to HBP, LBBAP may offer a more feasible physiological pacing option, especially in patients undergoing AVNA.²¹

Some observational studies have already shown superior symptomatic and echocardiographic improvement in symptomatic AF patients who underwent CSP, both HBP and LBBAP, compared to BVP after AVNA, especially in HF patients with narrow baseline QRS and reduced LVEF (<50%).^{23,24} Therefore, it is reasonable to assume that CSP, in conjunction with AVNA, could represent a promising alternative to BVP in refractory AF patients. Nevertheless, the 2021 guidelines give BVP a class Ila recommendation for those with mildly reduced and a class I for those with reduced LVEF. In contrast, HBP is allowed as an alternative with class Ilb, and recommendations for LBBAP remain to be formulated.²⁵

Study rationale and aim

Data from randomized clinical trials comparing treatment outcomes between CSP and BVP in combination with AVNA are lacking. The need for a comparison between both pacing modalities in the treatment of refractory symptomatic AF constituted the rationale for the CONDUCT-AF study.

Table 1 Inclusion and exclusion criteria in the study

Inclusion criteria

Symptomatic permanent AF refractory to drug therapy or failed catheter ablation

- Left ventricular ejection fraction <50%
- Narrow intrinsic ORS <120 ms
- NT-proBNP >600 ng/L
- Age between 18 and 85 years

Exclusion criteria

- Pre-existing permanent PM, ICD or CRT device with >5% of paced beats (i.e. backup pacing)
- Life expectancy <12 months
- · Severe concomitant non-cardiac disease
- Pregnancy
- Recent (<3 months) MI, percutaneous or surgical myocardial revascularization
- Significant heart valve disease (severe insufficiency or stenosis)
- Contraindication for oral anticoagulation
- Mechanical tricuspid valve replacement
- Unwillingness to participate or lack of availability for follow-up

AF, atrial fibrillation; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PM, pacemaker.

Study design

CONDUCT-AF is an investigator-initiated, prospective, multicentre, randomized, single-blinded, two-arm clinical trial conducted in 10 European centres (ClinicalTrials.gov: NCT05467163). Eighty-two patients with symptomatic AF, HF, and narrow QRS will be randomized in a 1:1 ratio to CSP or BVP with subsequent AVNA (*Graphical Abstract*) using a computer-generated randomization sequence stratified by centre, gender, and LVEF below or above 35%.

The study will follow the Declaration of Helsinki, Good Clinical Practice, and the applicable local regulatory requirements. It was initiated after approval from the institutional review and ethics board at each centre. The authors, who are responsible for writing this paper and its final content, designed the protocol.

Study population and enrolment

Patients with reduced LVEF (<50%), narrow intrinsic QRS (\leq 120 ms), initial N-terminal pro-B-type natriuretic peptide (NT-proBNP) >600 ng/L, and refractory symptomatic AF despite guideline-directed medical therapy or failed catheter ablation are candidates for participation in this study. Detailed inclusion and exclusion criteria are presented in *Table 1*. All patients will receive detailed clarification from local investigators and will provide their written informed consent before enrolment. A screening log with reasons for inclusion failure will be collected at each site.

Eligible patients will undergo baseline evaluation including clinical history, 12-lead electrocardiogram, assessment of New York Heart Association (NYHA) class and European Heart Rhythm Association score of AF (EHRA-AF), echocardiographic examination, assessment of quality of life, 6-min walk test (6MWT), and blood testing. Quality of life and symptoms will be evaluated with the Kansas City Cardiomyopathy Questionnaire (KCCQ). Subjects fulfilling all inclusion criteria, without meeting any exclusion criteria, will be automatically randomized in a 1:1 ratio to BVP + AVNA or CSP + AVNA. Randomization will be performed

automatically according to the previously generated random allocation list. Both groups will be treated identically in all respects except for the intervention being tested. There will be no restrictions on medical therapy adjustments during the study. Optimization of guideline-directed medical therapy following HF guidelines will be encouraged, but at the discretion of the treating physician.

Study objectives and endpoints

The CONDUCT-AF study aims to confirm the non-inferiority of CSP versus BVP in echocardiographic and clinical outcomes, during a 24-month follow-up in HF patients with symptomatic AF and narrow QRS scheduled for AVNA. The study primary endpoint is the LVEF change from baseline to 6 months. Changes in indexed LV end-diastolic and end-systolic volumes from baseline to 6 months will be reported as secondary endpoints. These will also include the composite of worsening HF or cardiovascular death and its individual components. Worsening HF was defined as an episode of HF that requires unplanned medical attention with an increase in diuretic dose or intravenous diuretic therapy or HF hospitalization. The total number of HF hospitalizations will be reported. Clinical parameters, including changes in functional NYHA class, NT-proBNP level, quality of life, and 6MWT distance, will be assessed after 6 months. Additional secondary endpoints are safety endpoints related to procedure success and adverse events. A detailed list of pre-specified study endpoints is provided in Table 2.

Study flow

After enrolment, both interventions will preferably be performed during the same hospitalization. Patients will be followed for a minimum of 24 months after randomization. Regular outpatient visits will be performed at 1, 6, 12, and every 6 months thereafter. Patients will be followed up for the occurrence of the primary and secondary endpoints, echocardiographic examination, and device interrogations. Symptoms will be evaluated with NYHA and EHRA-AF scores, while quality of life will be assessed using

The CONDUCT-AF trial

Table 2 Primary and secondary endpoints of the study

Outcomes	Time frame			
Primary outcome measure				
Change in left ventricular ejection fraction	Baseline and 6 M			
Secondary outcome measures				
Time to the first occurrence of worsening HF or cardiovascular death	At least 24 M			
Time to the first occurrence of worsening HF	At least 24 M			
Time to cardiovascular death	At least 24 M			
Total number of HF hospitalizations	At least 24 M			
Change in indexed LV end-diastolic and end-systolic volumes	Baseline and 6 M			
Improvement in clinical parameters (NYHA class, EHRA-AF, KCCQ score)	Baseline and 6 M			
Change in the 6-min walk test	Baseline and 6 M			
Laboratory parameters - NT-proBNP	Baseline and 6 M			
Procedural-related characteristics (total procedure and fluoroscopy time)	Peri-procedural			
Procedure-associated adverse events	30 days after the procedure			
Need for procedural reintervention	At least 24 M			
ECG parameters (QRS duration)	Baseline and after the procedure			
Pacing parameters (capture threshold, lead impedance)	At least 24 M			
Number of detected sustained VT/VF	At least 24 M			

ECG, electrocardiogram; EHRA-AF, European Heart Rhythm Association score of atrial fibrillation; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; M, months; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3 Time and events table of the CONDUCT-AF trial

	Enrolment (-7 to -1 days)	Implant (day 0)	Discharge	FU 1 (1 M ± 7 days)	FU 2 (6 M ± 10 days)	FU 3 (12 M ± 15 days)	FU 4 (18 M ± 30 days)	FU 5 (24 M ± 30 days)
Eligibility check	×							
Informed consent	x							
Demographics	x							
Comorbidities	x							
Medication	x			x	×	x	x	x
Randomization	x							
Device implantation and AVNA		x						
ECHO	x		x		×			
12-lead ECG	x		x	x	×	x	x	x
EHRA-AF score	x				×			
NYHA class	x				x			
KCCQ score	x				×			
6MWT	x				×			
Lab testing	x				x			
Review clinical outcome events ^a				x	x	x	x	x
Device interrogation				х	×	×	×	X

6MWT, 6-min walk test; AVNA, atrioventricular node ablation; ECG, electrocardiogram; ECHO, echocardiographic examination; EHRA-AF, European Heart Rhythm Association score of atrial fibrillation; FU, follow-up; KCCQ, Kansas City Cardiomyopathy Questionnaire; M, months; NYHA, New York Heart Association.

the KCCQ. Data regarding HF hospitalizations and cardiovascular deaths will be collected continuously as presented in *Table 3*.

Trial interventions

Device implantation will always precede AVNA. Crossover between pacing modalities will be permitted in cases of unfeasible

LBBAP implantation (due to high threshold, failure to penetrate the septum, or unmet criteria for conduction system capture) or failed BVP implantation due to anatomical constraints that preclude the LV lead from being placed in an acceptable position. The additional defibrillator lead will be implanted at the discretion of the implanting physician as indicated in the guidelines.²⁵

^aHospitalization for worsening heart failure, hospitalization for ventricular tachycardia/implantable cardioverter-defibrillator shock, need for reintervention, death.

Biventricular pacing

Implantation of the biventricular device will be performed using standard techniques. The RV lead will be positioned in the RV apex or septum, while the LV lead will be delivered to the most appropriate coronary sinus tributary, preferably the posterolateral or lateral vein. Optimal V-V delay and appropriate LV vector in a multipolar LV lead will be selected after the procedure to achieve the narrowest possible QRS complex.¹⁷

Conduction system pacing

Left bundle branch area pacing will be the preferred pacing technique in patients randomized to the CSP group. The implantation technique has been described elsewhere.24 In brief, after localizing the His bundle area (fluoroscopically or determined with intracardiac signal), the LBBAP lead will be positioned approximately 1-1.5 cm distally to the His bundle position in the RV septum. Before screwing the lead into the interventricular septum, the suitable position will be confirmed by fluoroscopic features and adequate paced QRS morphology ('w' pattern in lead V1, polarity discordance of leads II and III). Lead progression into the interventricular septum will be monitored using progressive change of paced QRS morphology, fixation beats, local endocardial electrogram, impedance, and current of injury. Confirmation of conduction system capture will be desired.²⁶ Given that the pacing parameters with LBBAP are typically low and stable, a backup RV lead will not be mandatory but can be implanted at the discretion of the operator.

If LBBAP is unobtainable, HBP implantation will be attempted. The procedural steps for delivering HBP were previously reported. In short, the same leads and dedicated delivery sheaths as with LBBAP will be used for HBP. His bundle potential mapping will be performed in a unipolar setting using the electrophysiological system at a sweep speed of $100 \, \text{mm/s}$ and under fluoroscopic guidance. Distal His bundle potential with large ventricular signal and small atrial signal (ventricular to atrial electrogram ratio >3:1) will be targeted before the pacing lead will be screwed into position. An acute HBP threshold $\leq 2 \, \text{V}$ at 1 ms will be considered acceptable. The additional backup lead will be mandatory for all patients receiving HBP devices.

Atrioventricular node ablation

Atrioventricular node ablation will be performed following pace-maker implantation (preferably during the same hospitalization), which will temporarily be set to 40 bpm for the duration of the procedure. After femoral vein access is obtained, the ablation catheter will be positioned to the presumed area of the atrioventricular node in the mid-septum under fluoroscopy and according to the intracardiac electrograms. Ablation will be performed in a temperature-controlled (40 W, non-irrigated tip catheter, up to 60 s) or power-controlled mode (40 W, irrigated tip catheter, up to 60 s). AVNA will be considered successful after clearly documented presence of a complete atrioventricular block that will persist after a mandatory 20-min waiting period. Each pacemaker will be tested after the procedure and at every follow-up at a lower pacing rate

(30 bpm) to check for any relevant escape ventricular rhythm. Any acute change in device lead position or pacing threshold following AVNA will be monitored. After AVNA, the pacemaker will be initially programmed to operate in VVI mode at 90 bpm base rate. At 1-month follow-up, the base rate will be decreased to 70 bpm.

Echocardiographic examination

An echocardiographic assessment will be obtained before enrolment, after AVNA, and at the 6-month follow-up visit. All participating centres will receive a detailed echocardiographic protocol. Transthoracic echocardiographic images will be obtained according to guidelines following the European Association of Cardiovascular Imaging (EACVI) recommendations.²⁷ Participating sites will follow a standardized imaging protocol, including specific image acquisition views in two-dimensional imaging, to ensure uniformity across all study participants. All videos should include five cardiac cycles. During echocardiographic examination heart rhythm and heart rate will be continuously monitored and recorded. As stated previously, at the 1-month follow-up, the base rate will be decreased to 70 bpm, and the echocardiographic examination at the 6-month follow-up will be performed at the uniform base rate. Images will be acquired using commercially available ultrasound systems and stored in Digital Imaging and Communications in Medicine (DICOM) format. All echocardiographic studies will be anonymized and securely transferred to the independent Core Laboratory (University Medical Centre Maribor, Maribor, Slovenia), which is blinded to treatment allocation. The core laboratory will provide standardized echocardiographic assessments, ensuring consistency in measurement and interpretation. Measurements of LV volumes and LVEF will be performed using Simpson's method of disk summation. To reduce inter-cycle variability, relevant echocardiographic measurements will be averaged over five subsequent cardiac cycles.

Study timeline

Recruitment began in July 2023 and is expected to be completed by the end of 2025. Follow-up is expected to be concluded by the end of 2027. The expected total study duration will be approximately 4.5 years, composed of 2.5 years of patient enrolment and 2 years of study follow-up. The short-term analysis of the primary outcome is expected in 2026, while secondary outcomes will be reported by the end of 2027.

Sample size and statistical considerations

The study is designed to test the two-sided hypothesis, at a type I error level of 0.05, that participants assigned to the CSP group would achieve a non-inferior improvement of LVEF compared to the participants assigned to the BVP group, with the non-inferiority margin of 5%. Additionally, an allowable absolute difference of 5% in echo measurement of LVEF with Simpson biplane was set to cover the intraobserver variability. To estimate the sample size and study power, we used the linear mixed model. Although there is an absence of robust estimation from the literature, according to

The CONDUCT-AF trial

the non-randomized study, the predicted mean change of LVEF in the population would be +12% in the CSP group and -1% in the BVP group. According to available data, the maximum standard deviation of measured LVEF in the CSP group was 13% and 15% in the BVP group. Therefore, the LVEF change in the CSP group would be distributed in the population as N (12, 13²) and in the BVP group as N (-1, 15²). Based on these assumptions, we calculated that the necessary sample size would be 70 participants (35 patients in each group) to achieve a power of 0.9996 and yield a statistically significant result. The dropout rate was assumed at 15% due to study withdrawal or loss to follow-up. Consequently, the target patient number was set as 82 participants.

Acknowledging limited data available in the literature, we conducted several sample size simulations to address the robustness of our assumptions across a plausible range of ejection fraction responses after both pacing modalities. Even in a more conservative scenario where the CSP group follows a N (7, 13^2) and BVP group a N (0, 15^2) distribution, the calculated power remains above 80%. The ALTERNATIVE-AF trial showed improvement in LVEF in both pacing modalities with only 5% absolute difference in favour of CSP. Even in this scenario (CSP mean ejection fraction change: +12%, BVP mean ejection fraction change: +7%), the calculated power would remain >95% to demonstrate the non-inferiority.

Data management will be performed using the Research Electronic Data Capture – REDCap (Vanderbilt, Nashville, TN, USA) and statistical analyses using the R programming language. The trial will follow an intention-to-treat analysis approach.

Adverse events

All adverse events and complications will be documented and reported. Interim safety analyses will be performed during the study. Early termination of the study will be permitted if BVP efficacy is superior to CSP or if significant harmful effects are documented with an implanted CSP over BVP.

Discussion

To the best of our knowledge, CONDUCT-AF will be the first multicentre, randomized trial to evaluate the efficacy and safety of CSP compared to BVP in patients with refractory symptomatic AF, HF with LVEF <50%, and narrow QRS after AVNA. To date, the only randomized, crossover study, ALTERNATIVE-AF, comparing BVP and HBP, demonstrated small but significant post-AVNA improvements in LVEF in a similar patient cohort, but with no conclusive data about clinical endpoints.²⁸ The APAF-CRT study reported a significant reduction in all-cause mortality, HF hospitalizations, and worsening HF in patients treated with AVNA and BVP.^{17,18} These results further established the potential of the pace and ablate strategy in conjunction with BVP. However, the need for precise tools and implant expertise, a complex device with additional lead and subsequent increased costs, and a longer procedure duration affected by anatomical variations of the coronary sinus limit its wider adoption in clinical practice. On the contrary, CSP might bring several advantages with high implant success rates, stable pacing parameters, and better cost-effectiveness.^{21,29} Therefore, we can reasonably assume that the positive results of the study might not only confirm CSP as a feasible alternative to BVP but will also further establish the pace and ablate strategy as an important therapeutic option in refractory AF treatment with HF when sinus rhythm is no longer pursued.

Among CSP modalities, LBBAP may be advantageous over HBP due to better pacing parameters and success rates.²¹ Therefore, adoption in clinical practice is attractive despite the lack of data from randomized trials and concerns regarding physiological activation compared to HBP. Namely, LBBAP is achieved by penetrating the interventricular septum to capture the left bundle branch and maintaining near-normal LV electrical activation with supposedly indirect RV recruitment.³⁰ These concerns may not be relevant as propensity score analysis matching 99 LBBAP with 86 HBP patients demonstrated comparable clinical benefits (echocardiographic and HF outcomes), higher implant success rate, better pacing parameters, and fewer complications in the LBBAP group compared with HBP.³¹ Therefore, LBBAP is a promising alternative to BVP that may foster the benefits of the pace and ablate strategy. Consequently, a randomized clinical trial comparing the outcomes of CSP and BVP in patients with HF and refractory symptomatic AF undergoing subsequent AVNA is of interest.

To conclude, the CONDUCT-AF study directly addresses clinical decision-making on optimal pacing modality in HF patients undergoing AVNA, potentially providing the data that will impact future guideline recommendations.

Study limitations

A potential limitation of this study is the small sample size that was calculated to achieve statistically significant results and prove the non-inferiority of CSP compared to BVP in the primary outcome — change in LVEF. Although our study may provide some insight into hard endpoints, adequately powered, large-scale randomized clinical trials with long-term follow-up will be required to confirm our findings regarding morbidity and mortality. As only patients with reduced LVEF and narrow QRS will be included, the results cannot be extrapolated to other subgroups of patients undergoing AVNA.

Funding

The CONDUCT-AF trial is an investigator-initiated, independent clinical trial. This work was partially supported by an institutional (UMC Ljubljana) research grant [TP 20220047]. No additional grants from funding agencies in the public, commercial, or non-profit sectors were obtained.

Conflict of interest: A.Z.M. reports receiving proctoring fees from Abbott. M.J. reports proctorship fees from Abbott and Johnson & Johnson. C.P. reports receiving travel and proctoring fees from Medtronic and Biotronik. S.B. reports receiving speaking honoraria, travel, and proctoring fees from Medtronic, Biotronik, and Abbott. P.B. reports receiving travel and proctoring fees from Biotronik. V.T. reports receiving speaking honoraria, travel grant, and proctoring fees from Medtronic, Abbott, and Biotronik. D.Ž. reports receiving proctoring fees and speaker honoraria from Medtronic, Biotronik, Abbott, and Boston Scientific. All other authors have nothing to disclose.

References

- Shoureshi P, Tan AY, Koneru J, Ellenbogen KA, Kaszala K, Huizar JF. Arrhythmia-induced cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2024;83:2214–2232. https://doi.org/10.1016/j.jacc.2024.03.416
- Tung R, Burri H. Role of conduction system pacing in ablate and pace strategies for atrial fibrillation. Eur Heart J Suppl 2023;25:G56-G62. https://doi.org/10.1093/eurheartisupp/suad119
- Joza J, Burri H, Andrade JG, Linz D, Ellenbogen KA, Vernooy K. Atrioventricular node ablation for atrial fibrillation in the era of conduction system pacing. Eur Heart J 2024;45:4887–4901. https://doi.org/10.1093/eurhearti/ehae656
- 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 1983;106:284–291. https://doi.org/10.1016 /0002-8703(83)90194-1
- 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 2012;5:786-793. https://doi.org/10.1161/CIRCHEARTFAILURE.112.968321
- 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 1996;78:1433–1436. https://doi.org/10.1016/s0002-9149(97)89297-1
- Sohns C, Fox H, Marrouche NF, Crijns HJGM, Costard-Jaeckle A, Bergau L, et al.; CASTLE HTx Investigators. Catheter ablation in end-stage heart failure with atrial fibrillation. N Engl J Med 2023;389:1380–1389. https://doi.org/10.1056/ /NEIMoa2306037
- Brachmann J, Sohns C, Andresen D, Siebels J, Sehner S, Boersma L, et al. Atrial fibrillation burden and clinical outcomes in heart failure: The CASTLE-AF trial. JACC Clin Electrophysiol 2021;7:594–603. https://doi.org/10.1016/j.jacep.2020.11 021
- Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al.; CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: The CABANA randomized clinical trial. JAMA 2019;321:1261–1274. https://doi.org/10.1001/jama.2019.0693
- Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2024;45:3314–3414. https://doi .org/10.1093/eurhearti/ehae176
- Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024;149:e1-e156. https://doi.org/10.1161/CIR.00000000000001193
- Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: Two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2009;2:349–361. https://doi.org/10.1161/CIRCEP.108.824789
- Tan ES, Rienstra M, Wiesfeld AC, Schoonderwoerd BA, Hobbel HH, Van Gelder IC. Long-term outcome of the atrioventricular node ablation and pacemaker implantation for symptomatic refractory atrial fibrillation. *Europace* 2008;10:412–418. https://doi.org/10.1093/europace/eun020
- Wang T, Fang T, Cheng Z. Comparison of the efficacy and safety endpoints of five therapies for atrial fibrillation: A network meta-analysis. Front Cardiovasc Med 2022;9:853149. https://doi.org/10.3389/fcvm.2022.853149
- Chatterjee NA, Upadhyay GA, Ellenbogen KA, McAlister FA, Choudhry NK, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: A meta-analysis and systematic review. Circ Arrhythm Electrophysiol 2012;5:68–76. https://doi.org/10 .1161/CIRCEP.111.967810
- Vernooy K, Dijkman B, Cheriex EC, Prinzen FW, Crijns HJ. Ventricular remodeling during long-term right ventricular pacing following His bundle ablation. Am J Cardiol 2006;97:1223–1227. https://doi.org/10.1016/j.amjcard.2005.11.044

- Brignole M, Pokushalov E, Pentimalli F, Palmisano P, Chieffo E, Occhetta E, et al.;
 APAF-CRT Investigators. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. Eur Heart J 2018;39:3999–4008. https://doi.org/10.1093/eurhearti/ehy555
- Brignole M, Pentimalli F, Palmisano P, Landolina M, Quartieri F, Occhetta E, et al.; APAF-CRT Trial Investigators. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: The APAF-CRT mortality trial. Eur Heart J 2021;42:4731–4739. https://doi.org/10.1093/eurhearti/ehab569
- Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al.; EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013;369:1395–1405. https://doi.org/10.1056 /NEJMoa1306687
- 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 2017;6:e005309. https://doi.org/10.1161 //AHA.116.005309
- 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. Heart Rhythm 2022;19:1116–1123. https://doi.org/10.1016/j.hrthm.2022 03 1222
- Herbert J, Kovacsovics A, Brito R, Masson N, Burri H. Mid-term performance of His bundle pacing and usefulness of backup leads. *Europace* 2024;26:euae168. https://doi.org/10.1093/europace/euae168
- Žižek D, Antolič B, Mežnar AZ, Zavrl-Džananović D, Jan M, Štublar J, et al. Biventricular versus His bundle pacing after atrioventricular node ablation in heart failure patients with narrow QRS. Acta Cardiol 2022;77:222–230. https://doi. .org/10.1080/00015385.2021.1903196
- Ivanovski M, Mrak M, Mežnar AZ, Žižek D. Biventricular versus conduction system pacing after atrioventricular node ablation in heart failure patients with atrial fibrillation. J Cardiovasc Dev Dis 2022;9:209. https://doi.org/10.3390 /icdd9070209
- Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, et al.; ESC Scientific Document Group. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J 2021;42:3427–3520. https://doi. org/10.1093/eurheartj/ehab364
- Burri H, Jastrzebski M, Cano Ó, Čurila K, de Pooter J, Huang W, et al. EHRA clinical consensus statement on conduction system pacing implantation: Endorsed by the Asia Pacific Heart Rhythm Society (APHRS), Canadian Heart Rhythm Society (CHRS), and Latin American Heart Rhythm Society (LAHRS). Europace 2023;25:1208–1236. https://doi.org/10.1093/europace/euad043
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–270. https://doi.org/10.1093/ehjci/jev014
- 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. Heart Rhythm 2022;19:1948–1955. https://doi.org/10.1016/j.hrthm.2022.07.009
- Chen M, Shi J, Zhang Y, Ge X, Zhang X, Fan W, et al. Comparative cost analysis of implanting devices in different cardiac resynchronization therapeutic strategies. Clin Cardiol 2023;46:1227–1233. https://doi.org/10.1002/clc.24107
- Tay JCK, Lim ETS, Wong TJ, Feng JJ, Ching CK, Tan BY. Right bundle branch activation during left bundle branch pacing: Marginal gains in left bundle branch pacing-optimized cardiac resynchronization therapy and the effects of atrioventricular delay dynamic optimization. Heart Rhythm Case Rep 2023;10:191–197. https://doi.org/10.1016/j.hrcr.2023.12.005
- Cai M, Wu S, Wang S, Zheng R, Jiang L, Lian L, et al. Left bundle branch pacing postatrioventricular junction ablation for atrial fibrillation: Propensity score matching with His bundle pacing. Circ Arrhythm Electrophysiol 2022;15:e010926. https://doi.org/10.1161/CIRCEP.122.010926