DESIGN PAPER

Cardiac resynchronization therapy and AV node ablation in heart failure with reduced ejection fraction and atrial fibrillation: Rationale and design of the CAAN-AF trial

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BACKGROUND Cardiac resynchronization therapy (CRT) is an important treatment modality for patients with symptomatic heart failure (HF) with reduced ejection fraction (HFrEF) and QRS prolongation on electrocardiogram. However, patients with atrial fibrillation (AF) appear to benefit less from CRT compared to patients in sinus rhythm. Atrioventricular (AV) node ablation has been shown in observational studies to improve the efficacy of CRT in patients with AF.

OBJECTIVE We aimed to evaluate the effect of AV node ablation on CRT efficacy in patients with permanent AF.

METHODS Participants with permanent AF and a reduced left ventricular ejection fraction (≤35%) who receive a CRT-defibrillator are randomized in a 1:1 fashion to AV node ablation or medical rate control for treatment of AF. A sample size of 590 participants allows a detection of a 25% reduction in the primary end point at 80% power.

RESULTS The primary end point is a composite of all-cause mortality and non-fatal HF events after 2 years of follow-up. The secondary end points include all-cause mortality, cardiovascular mortality, non-fatal HF events, 6-minute walking distance, quality-of-life, unscheduled hospitalizations, ventricular arrhythmias requiring device therapies, and biventricular pacing percentage.

CONCLUSION The CRT And AV Node ablation trial in AF (CAAN-AF) will be the first randomized controlled trial to investigate the effect of AV node ablation on CRT efficacy in patients with AF and HFrEF. The results will guide physicians regarding the use of AV node ablation for patients with CRT and AF.

KEYWORDS Cardiac resynchronization therapy; Atrioventricular node ablation; Atrial fibrillation; Heart failure; Trial

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Introduction

Heart failure (HF) is a global public health burden affecting up to 26 million people worldwide.[1] Approximately half of patients with HF with reduced ejection fraction (HFrEF).[2] Cardiac conduction system disease is frequent in patients with HFrEF, with 25%–36% of patients with HFrEF exhibiting left bundle branch block (LBBB).[3] LBBB causes inter- and intra-ventricular dyssynchrony, impairing cardiovascular (CV) hemodynamics, reducing cardiac output, and significantly worsening long-term outcomes associated with HFrEF.[4] Cardiac resynchronization therapy (CRT) has

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KEY FINDINGS

- Atrial fibrillation (AF) reduces the benefits of cardiac resynchronization therapy (CRT).
- Current guidelines recommend performing atrioventricular node ablation (AVNA) in the case of incomplete biventricular pacing (<90% to 95%).
- There is no evidence available from a dedicated randomized controlled trial (RCT) to support this current guideline recommendation.
- The Cardiac resynchronization therapy and AV node ablation in heart failure with reduced ejection fraction and atrial fibrillation (CAAN-AF) trial is an RCT comparing AVNA to pharmacological rate control in patients with AF who are treated with a CRT defibrillator.

revolutionized the management of these patients through precisely-timed electrical pacing of both the right and left ventricles. CRT improves left ventricular (LV) ejection fraction (LVEF), reduces diastolic mitral regurgitation, and reverses the harmful effects of LV remodeling.[5,6] A number of randomized controlled trials (RCTs) have shown that CRT significantly reduces all-cause and CV mortality, HF hospitalizations, and HF symptoms.[7–9] Today, CRT is a cornerstone treatment for patients with symptomatic HF (New York Heart Association [NYHA] class II–IV), LVEF ≤35%, and a QRS duration of ≥120 ms.[10]

However, the benefits of CRT do not seem to extend to those with concomitant atrial fibrillation (AF).[11] HFrEF and AF frequently co-exist, and the presence of AF has been shown to increase mortality associated with HFrEF.[12–14] Most RCTs investigating CRT specifically excluded patients with AF. Observational data show that patients with permanent AF do not obtain the same benefit as those in sinus rhythm, and suggest that CRT may not confer any significant mortality benefit beyond optimal medical therapy.[15,16] This observation is supported by a pre-specified sub-analysis from the Resynchronization for ambulatory heart failure trial. This analysis, performed in patients with permanent AF, found there was no difference in the primary outcome of death or HF hospitalization between those assigned to CRT-defibrillator (CRT-D) vs defibrillator only (implantable cardioverter defibrillator) (hazard ratio, 0.96; 95% confidence interval [CI]: 0.65–1.41; $P = .82$).[11]

The reasons for this lack of effectiveness in AF remain unclear. The presence of AF may be a marker of advanced HF, which has progressed beyond the threshold for CRT benefit. Additionally, the absence of atrial contraction and the irregular R-R intervals in AF may also impair CRT benefit. Alternatively, poorer outcomes may be a result of the reduced biventricular pacing percentage associated with AF due to increased intrinsic conduction through the atrioventricular (AV) node, resulting in higher rates of non-paced beats, fusion beats (in which intrinsically conducted and paced beats occur simultaneously), and pseudofusion beats (in which pacing occurs after intrinsic conduction through the AV node).

AV node ablation provides a potential solution to improve the effectiveness of CRT in patients with AF. After AV node ablation, the ventricular contraction becomes entirely reliant on biventricular pacing from the CRT device, maximizing biventricular pacing percentage and preventing fusion and pseudofusion beats. Observational data has suggested that AV node ablation can significantly reduce mortality associated with HFrEF in patients with CRT and coexistent AF.[15,16] One meta-analysis found that the relative risk for all-cause mortality in patients undergoing AV node ablation was 0.42 (95% CI: 0.26–0.68; $P < .001$) compared to medical rate control.[15] Despite this, acceptance of this strategy remains limited, as AV node ablation guarantees permanent pacemaker dependency. Clinical equipoise exists due to the lack of randomized trial data supporting systematic AV node ablation in this subset of patients. We are, therefore, carrying out an RCT comparing AV node ablation with optimal medical management for the treatment of persistent or permanent AF in patients with a CRT-D device. We hypothesize that in patients with a CRT-D and permanent AF, AV node ablation will result in a significant reduction in mortality and non-fatal HF events compared with pharmacotherapy for ventricular rate control alone.

Here, we report the rationale and design of this study entitled 'The **C**RT **A**nd **A**V **N**ode ablation trial in **AF** (CAAN-AF) study.'

Trial design

Structure and oversight

The CAAN-AF study is a phase IV, international, investigator-initiated multicenter, prospective RCT. Participants are randomized 1:1 to either pharmacotherapy for ventricular rate control (control arm) or AV node ablation (intervention arm). The trial is conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. Ethical and Governance Approval has been obtained from the relevant Ethical Committees for the respective recruiting sites. All participants must provide written informed consent before inclusion. The University of Adelaide acts as the sponsor. The trial is funded by a grant awarded from the National Health and Medical Research Council (1080920) of Australia. Additional support was received from Boston Scientific

Table 1 A list of participant inclusion and exclusion criteria

Inclusion criteria
• At least 18 years old
• Permanent* AF
• NYHA class II, III, or ambulatory class IV HF
• Documented evidence of LVEF ≤35% on echocardiogram or CMR
• QRS duration on 12-lead ECG ≥120 ms
• Able and willing to provide informed consent and comply with all pre-, post-, and follow-up testing requirements
Exclusion criteria
• <18 years
• Pregnancy
• Previous AV node ablation
• Second- or third-degree AV block
• Inability to provide consent
• Life expectancy less than 24 months due to comorbid illness other than heart failure, eg, cancer, end-stage renal disease, or liver failure
• Paroxysmal AF that self-terminates within 7 days

AF = atrial fibrillation; CMR = cardiac magnetic resonance imaging; ECG = electrocardiogram; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

*Permanent AF is defined as where obtaining and maintaining sinus rhythm is deemed either not worthwhile or to be ineffective in the long term, or where both the patient and the physician accept the presence of AF, where rhythm control intervention is, by definition, no longer pursued, or where sinus rhythm cannot be restored.

and Medtronic. The study was managed by the South Australian Health and Medical Research Institute, and Abbott Medical provided database management. Microport provided ambulatory 12-lead monitoring and software for sub-study use. All CRT-D devices are implanted as clinically determined based on current guideline recommendations. The trial is registered at ClinicalTrials.gov with trial identification NCT01522898.

The trial was conceptualized and designed by the Steering Committee, independent from industry support. The Steering Committee was responsible for the development of the clinical investigational plan and the recruitment of qualified centers. During the trial, the Steering Committee is responsible for providing academic leadership, ensuring proper study conduct and protocol adherence, and advising and recommending changes to the protocol based on emerging scientific and/or clinical advances. The statistical analysis plan was developed by a senior statistician (GT) from the Data Management and Analysis Centre at the University of Adelaide.

A Clinical End Point Committee (CEC) will adjudicate all clinical events (eg, mortality, hospital admission, and device therapies) according to pre-specified criteria in a manner blinded to treatment assignment. The CEC consists of specialists who have expertise in HF and arrhythmia management. An independent Data and Safety Monitoring Board (DSMB) contributed to the development of the clinical investigational plan and will continuously monitor the safety data to ensure patient safety. The DSMB may recommend early termination during the trial, guided by pre-specified stopping boundaries.

The members of the Committees and Boards are listed in the Appendix.

Trial patients

All participants in the CAAN-AF trial are patients aged 18 years or older, who can read and provide informed consent. Table 1 outlines the inclusion and exclusion criteria for the trial. Patients with symptomatic HF, LVEF <35%, QRS duration >120 ms, and permanent AF will be eligible for inclusion. Patients must be scheduled for a CRT-D device implantation (Pathway A) or must have a pre-existing CRT-D device (Pathway B) (Figure 1).

Pathway A relates to participants who do not have a CRT-D implant and agree to have one implanted, as well as participants who have an existing single- or dual-chamber device and agree to have an upgrade to a CRT-D device. These participants are enrolled and undergo a pre-implantation assessment within 30 days before CRT-D implantation/upgrade. Within 30–180 days following CRT-D implantation/upgrade, HF therapy and device programming should be optimized, after which the baseline assessments should be performed. Pathway B relates to participants with a pre-existing CRT-D device for more than 30 days. These participants can be enrolled on a rolling basis; however, HF and device therapy must be optimized before the baseline assessments are conducted.

HF therapy is managed by the dedicated HF teams from the participating sites and should be optimized according to the 2012 European Society of Cardiology (ESC) guidelines and should minimally include, if available and tolerated, an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, a beta-adrenoceptor blocker, and a mineralocorticoid-receptor antagonist.[17]

CRT-D devices should be programmed to optimize biventricular pacing. Device-specific algorithms to encourage biventricular pacing can be used, including conducted AF response and ventricular sensed response. In addition, optimization of ventricular synchrony is allowed using either the device algorithms or echocardiography, as clinically determined by the treating physician. Ultimately, device therapy and programming are at the discretion of the treating clinician at individual sites.

Randomization

Following consent and baseline assessments, participants are randomized to either pharmacotherapy for ventricular rate control (control arm) or AV node ablation (intervention arm). Randomization is carried out using a computer-generated web-based randomization schedule. Randomization is stratified using randomly permuted blocks of sizes 2

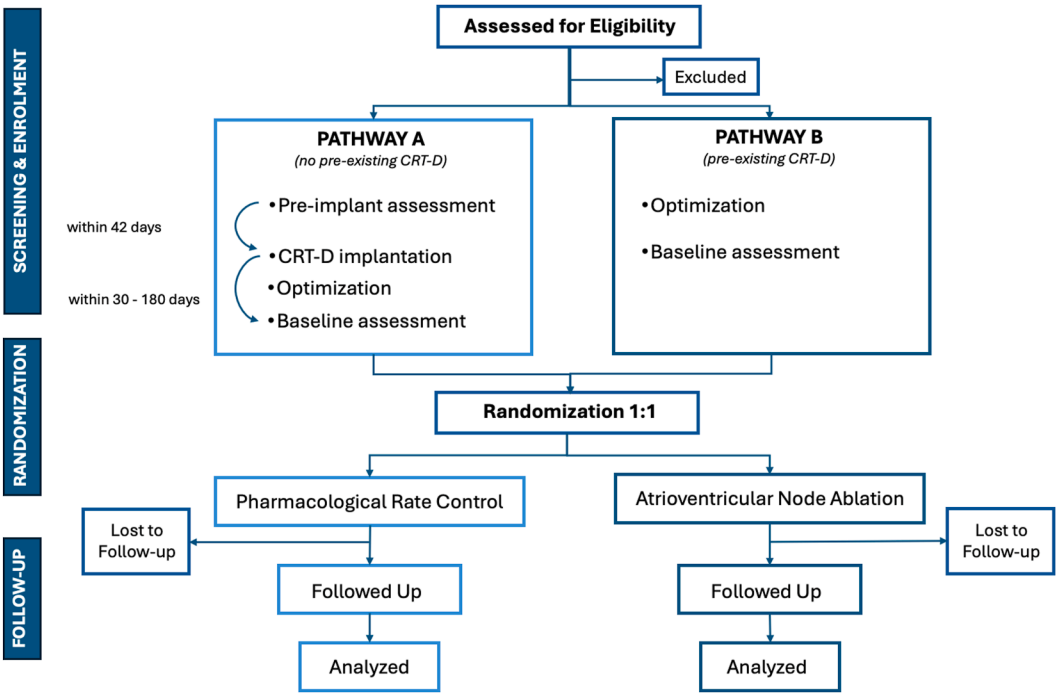

Figure 1 Participant pathway flowsheet. At enrollment, participants are assigned to either Pathway A or Pathway B depending on whether they have a pre-existing CRT-D device. Patients without a pre-existing CRT-D will first undergo pre-implant assessments, then have the CRT-D implant. If the implant fails, they will be excluded from the study at this stage. Following implant, the participant's device and HF therapy are optimized. Within 30 to 180 days, participants will undergo the baseline assessments followed by randomization. Participants in Pathway B will have device and HF therapy optimized before the baseline assessments and randomization. Patients are randomized 1:1 to either pharmacological rate control or atrioventricular node ablation. All patients are followed up for a duration of 24 months. CRT-D = Cardiac resynchronization therapy-defibrillator; HF = heart failure.

and 4. The randomization schedule is incorporated within the online data management software (Abbott Study Portal).

Control group

Participants randomized to the control arm receive pharmacotherapy for ventricular rate control in AF. The precise nature of this pharmacotherapy is at the discretion of individual treating physicians. Rate control medications for use in this arm include beta-blockers, calcium channel blockers, digoxin, or amiodarone, and can include combination pharmacotherapy. The RACE II trial identified lenient rate control strategy (<110 bpm) as non-inferior to a strict rate control strategy (<80 bpm). In this trial, we have set a target resting heart rate, in the absence of symptoms, of <90 beats per minute to facilitate optimization of CRT.[18] Further pharmacological rate control strategies are undertaken at the discretion of the treating physician.

Intervention group

Participants randomized to the intervention arm undergo AV node ablation. AV node ablation is performed in accordance with standard clinical practice. The procedure involves femoral vein puncture and passage of an ablation catheter to the region of the compact AV node where radio frequency ablation is performed. The end point of ablation is complete AV block after a wait period of at least 10 minutes immediately after ablation. The procedure is considered a minor procedure with relatively minimal risk, and is an established form of therapy to achieve "rate control" of AF. The ablation should occur as close to randomization as possible, but no later than 6 weeks post-randomization.

Study visits and follow-up

All enrolled participants are followed up for at least 24 months in total. Face-to-face follow-up visits are carried out at 6-monthly intervals. Specific assessments carried out at these follow-up visits are detailed in Table 2. All follow-up visits involve physical examination and assessment of height, weight, and blood pressure. HF symptoms are described according to the NYHA functional classification system.

At each visit, quality-of-life is assessed using the Minnesota Living with HF (MLHF) questionnaire, the Center for Epidemiologic Studies Depression (CES-D) scale, and the 36-item Short Form (SF-36) survey. The MLHF questionnaire is a validated disease-specific tool to assess health-related quality-of-life in patients with HF and has been previously used in HF-related clinical studies.[19,20] The SF-36 questionnaire is a generic quality-of-life measure

Table 2 Follow-up schedule

	Follow-up			
Assessment	6-month	12-month	18-month	24-month
Current drug therapy	✔	✔	✔	✔
Physical examination	✔	✔	✔	✔
Adverse events post-consent	✔	✔	✔	✔
Device interrogation	✔	✔	✔	✔
6MWT	✔	✔	✔	✔
NT-proBNP	✔	✔		✔
Blood samples (Hb, INR, sodium, creatinine, potassium, eGFR)	✔	✔	✔	✔
Questionnaires SF-36, CES-Depression Scale, MLHF	✔	✔	✔	✔
Echocardiogram (TTE)	✔	✔		✔
24-hour Holter	✔			

6MWT = 6-minute walking test; CES = Center for Epidemiological Studies; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; INR = international normalized ratio; MLHF = Minnesota Living with Heart Failure; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SF-36 = 36-item Short Form survey; TTE = trans-thoracic echocardiogram.

which has been used to assess general quality-of-life in patients with congestive HF.[21] The CES-D questionnaire is a depression-specific questionnaire which has been used previously to assess the presence and severity of depression in patients with HF.[22]

At each visit, participants' exercise capacity is assessed with the 6-minute walk test (6MWT). The 6MWT has been shown to be a reliable and valid assessment of functional capacity in patients with HF, and particularly in those with more advanced HF.[23] The distance the participant walks in 6 minutes is rounded to the nearest meter. Finally, a blood sample is collected, and a device interrogation is performed. This interrogation includes assessment of device measurements, device programming, tachycardia programming, inappropriate shocks, arrhythmias, and shocks since the last visit.

An echocardiogram is acquired at randomization and at 6-, 12-, and 24-month post-randomization. Key parameters to be measured include ventricular size, ejection fraction, ventricular dyssynchrony, and atrial size. A 24-hour 12-lead Holter monitoring is scheduled at randomization and at 6 months post-randomization. The 12-lead Holter monitoring is being used—as opposed to standard Holter monitoring—to ensure that true biventricular pacing percentage can be effectively assessed. An independent, trained core laboratory is used for the processing and analysis of Holter data and echocardiograms.

Outcomes

The primary end point is a composite of all-cause mortality and non-fatal HF events (Table 3).[9] All-cause mortality is assessed for the duration of the trial, with information on deaths obtained from death certificates and medical records, and cross-referenced with family contact when necessary. Non-fatal HF events are defined as in the Multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy, that is, signs and/or symptoms of congestive HF responsive to intravenous diuretics or inotropes on an outpatient or emergency department (whether admitted or not) basis or augmentation of oral/parenteral decongestion regimen in inpatients.[9] Non-fatal HF events are adjudicated using documentation from the medical records, as well as discharge summaries and clinic letters.

Key secondary end points (Table 3) include (1) CV mortality, defined as death due to any CV cause including death due to myocardial infarction, sudden cardiac death, HF, stroke, CV procedures, and CV hemorrhage; (2) unscheduled hospitalizations, defined as any admission to hospital resulting in overnight stay or death; day-care admissions, admissions for diagnostic procedures, and elective surgeries will be recorded, but are not considered as unscheduled hospitalizations; (3) ventricular arrhythmias requiring device therapies; (4) inappropriate high-voltage device therapy;

Table 3 A list of primary and secondary end points

Primary end points
- A composite of all-cause mortality and non-fatal heart failure events.

Secondary end points
- All-cause mortality
- Cardiovascular mortality
- Non-fatal HF events
- Unplanned hospitalization
- Ventricular arrhythmias needing device therapies
- Inappropriate ICD shocks
- 6-minute walk test
- Quality of life
- Left ventricular end-systolic diameter
- % pacing by device and response to therapy
- Ventricular reverse remodeling
- NT-proBNP

HF = heart failure; ICD = implantable cardioverter defibrillator; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

(5) biventricular pacing percentage; (6) quality-of-life; and (7) 6MWD. Other end points include procedure-related adverse events—cardiac perforation, valvular injury, groin hematoma, LV end-systolic function, LV reverse remodeling, and NT-proBNP.

Sample size calculation

This RCT is powered to test the potential superiority of AV node ablation over pharmacological ventricular rate control. Sample size calculation is based on the estimated incidence rate of the primary end point in the 2 groups. A meta-analysis of observational data suggests that AV node ablation in patients with AF undergoing CRT for symptomatic HF and LV dyssynchrony reduces all-cause mortality by 58%.[15] Taking a conservative stance, the current trial has been powered to identify a 25% relative reduction in a composite end point of all-cause mortality and non-fatal HF events. The event rate in the control arm is estimated at 50 events per 100 person-years, based on the results of the COMPANION trial.[7] To achieve 80% power to detect a 25% reduction in event rate at a two-sided alpha of 5%, assuming 1:1 randomization and a 10% participant withdrawal or cross-over, it is estimated that 295 participants will be required for each treatment arm, which translates to a total of 590 participants. Crossovers are only permissible if the participant has experienced a non-fatal HF event and thus has reached the primary end point, to minimize dilution of power for the primary analysis. Analyses will be conducted under the intention-to-treat principle.

Given that the 58% reduction in all-cause mortality reported in the meta-analysis is substantially larger than the 25% reduction in all-cause mortality or non-fatal HF events assumed for the sample size calculation, the trial could—under an O'Brien-Fleming design—meet its primary end point at an earlier interim analysis.[24] Three formal interim analyses of the primary outcome will be performed at the 25%, 50%, and 75% information fractions. Enrollment may be stopped at any of these pre-specified interim analyses for either efficacy or futility. For efficacy, the formal stopping criteria to reject the null hypothesis of no difference between treatment groups at these 3 interim analyses are, respectively, two-tailed P-values $<.000015$, .0031, and .014, with $P < .044$ for the final analysis of the primary outcome. Additionally, futility analyses will be performed at each pre-specified interim analysis to quantify the probability that the final analysis will cross the O'Brien-Fleming efficacy boundary based on the data collected to date (ie, the observed conditional power).

Statistical analysis

Continuous variable data will be assessed for normality assumptions and analyzed using appropriate statistical tests. Categorical variables will be summarized using counts and percentages. All analyses will be performed based on the "intention-to-treat" principle. The primary outcome is the total number of composite events (all-cause mortality and non-fatal HF) between Intervention and Control groups. The primary outcome will be analyzed using a negative binomial regression model, adjusted for basic demographic parameters, medical history, and other potential risk factors, and interpreted using the incident rate ratio with 95% CIs. Quality-of-life data from the SF-36 and MLHF questionnaire will be analyzed using the mixed-effects model for repeated measures, with the baseline score as a covariate. CV mortality between the Intervention vs Control groups will be analyzed using logistic regression, adjusting for basic demographic parameters, medical history, and other potential risk factors. Total all-cause unplanned hospitalizations between groups will be analyzed using negative binomial regression. Time-to-first event will be analyzed using the log-rank test and Kaplan-Meier curves. Statistical analysis will be performed using R version 4.2.1. P-value $<.05$ will be considered statistically significant.

Discussion

The CAAN-AF trial is designed to compare the efficacy of AV node ablation with pharmacotherapy alone in patients with CRT-D and persistent or permanent AF (Graphical Abstract). CRT is a highly effective treatment modality for patients with HFrEF with electrocardiographic evidence of ventricular dyssynchrony.[7–9] However, patients with AF do not obtain the same benefit as those in sinus rhythm.[15] This international, investigator-initiated, multicenter RCT will investigate whether AV node ablation is superior to medical rate control in improving HF outcomes in patients with CRT and concomitant AF over a 2-year follow-up period.

The various benefits of CRT have been shown to be closely associated with the percentage of biventricular pacing delivered by the CRT device.[25] Patients with AF are more likely to have a reduced percentage of biventricular pacing for a number of reasons. First, in the absence of effective rate control, ventricular rates in AF are more likely to be higher than the base rate of the CRT device. Second, the R-R irregularity associated with AF is more likely to result in fusion between intrinsic conduction through the AV node and biventricular pacing. This results in inefficient biventricular capture and renders the device-detected biventricular pacing counts inaccurate. Even in the presence of adequate rate control, a good response to CRT in patients with AF has been shown to be closely associated with increased true biventricular pacing and reduced fusion and pseudofusion beats.[26]

Overall, 25% of patients with CRT develop AF.[27] Despite this, all the major RCTs excluded patients with AF, and observational data suggest that patients in AF do not derive the same benefit as those in sinus rhythm. As a result, the

2021 ESC guidelines on cardiac pacing and CRT provide only a class IIa recommendation with a level C of evidence (expert opinion).[10]

AV node ablation has the potential to improve the percentage of true biventricular pacing by preventing intrinsic conduction through the AV node. As a result of AV node ablation, each heartbeat becomes entirely reliant on biventricular pacing, and the risk of high ventricular rates and fusion beats due to intrinsic conduction becomes minimal. Observational data suggest that AV node ablation can significantly improve outcomes for patients with CRT and AF.[15,28] Based on the currently available data, the 2021 ESC guidelines on cardiac pacing and CRT provide a class IIa recommendation with a level B of evidence to perform AV node ablation in the case of incomplete biventricular pacing (<90% to 95%).[10] However, conclusive evidence obtained from an RCT to recommend (class I) AV node ablation for patients with CRT and AF is lacking. The CAAN-AF trial aims to provide the evidence required to guide physicians regarding the efficacy of CRT and AV node ablation in these patients.

Summary

The CAAN-AF study is an international, investigator-initiated, prospective multicenter RCT assessing the efficacy of AV node ablation in patients with CRT and coexistent AF. The hypothesis is that AV node ablation will result in improved clinical outcomes for patients with CRT, as evidenced by reduced all-cause mortality and non-fatal HF events, in comparison with pharmacological rate control.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All participants must provide a written informed consent before inclusion.

Ethics Statement: The trial is conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. Approval has been obtained from the relevant Ethical Committees for the respective recruiting sites.

Appendix

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