Does Targeted Positioning of the Left Ventricular Pacing Lead Towards the Latest Local Electrical Activation in Cardiac Resynchronization Therapy Reduce the Incidence of Death or Hospitalization for Heart Failure?

Kronborg, Mads Brix; Frausing, Maria Hee Jung Park; Svendsen, Jesper Hastrup; Johansen, Jens Brock; Riahi, Sam; Haarbo, Jens; Poulsen, Steen Hvitfeldt; Eiskjær, Hans; Køber, Lars; Øvrehus, Kristian; Sommer, Anders Munck; Schou, Morten; Nørgaard, Bjarne Linde; Risum, Niels; Poulsen, Mikael Kjær; Søgaard, Peter; Sandgaard, Niels; Kofoed, Klaus F.; Hansen, Thomas Fritz; Graff, Claus; Pedersen, Susanne S; Skals, Regitze Gyldenholm; Nielsen, Jens Cosedis

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Does targeted positioning of the left ventricular pacing lead towards the latest local electrical activation in cardiac resynchronization therapy reduce the incidence of death or hospitalization for heart failure?

Mads Brix Kronborg, MD, PhD, DMSc [a,b], Maria Hee Jung Park Frausing, MD, PhD [a,b], Jesper Hastrup Svendsen, MD, DMSc [c,d], Jens Brock Johansen, MD, PhD [e], Sam Riahi, MD, PhD [f,g], Jens Haarbo, MD, DMSc [h], Steen Hvitfeldt Poulsen, MD, DMSc [a,b], Hans Eiskjær, MD, DMSc [a,b], Lars Køber, MD, DMSc [c], Kristian Øvrehus, MD, PhD [e], Anders Munck Sommer, MD, PhD [f], Morten Schou, MD, PhD [h], Bjarne Linde Nørgaard, MD, PhD, DMSc [a,b], Niels Risum, MD, PhD [c], Mikael Kjær Poulsen, MD, PhD [e], Peter Søgaard, MD, DMSc [f], Niels Sandgaard, MD, PhD [e], Klaus F. Kofoed, MD, PhD, DMSc [c,i,d], Thomas Fritz Hansen, MD [h], Claus Graff, MSc, PhD [j], Susanne S Pedersen, MSc, PhD [e,k], Regitze Gyldenholm Skals, MSc [l], and Jens Cosedis Nielsen, MD, PhD, DMSc [a,b] ***Aarhus, Denmark; Copenhagen, Denmark; Odense, Denmark; Aalborg, Denmark; Odense, Denmark***

Background Cardiac resynchronization therapy (CRT) improves symptoms, health-related quality of life and long-term survival in patients with systolic heart failure (HF) and shortens QRS duration. However, up to one third of patients attain no measurable clinical benefit from CRT. An important determinant of clinical response is optimal choice in left ventricular (LV) pacing site. Observational data have shown that achieving an LV lead position at a site of late electrical activation is associated with better clinical and echocardiographic outcomes compared to standard placement, but mapping-guided LV lead placement towards the site of latest electrical activation has never been investigated in a randomized controlled trial (RCT). The purpose of this study was to evaluate the effect of targeted positioning of the LV lead towards the latest electrically activated area. We hypothesize that this strategy is superior to standard LV lead placement.

Methods The DANISH-CRT trial is a national, double-blinded RCT (ClinicalTrials.gov NCT03280862). A total of 1,000 patients referred for a de novo CRT implantation or an upgrade to CRT from right ventricular pacing will be randomized 1:1 to receive conventional LV lead positioning preferably in a nonapical posterolateral branch of the coronary sinus (CS) (control group) or targeted positioning of the LV lead to the CS branch with the latest local electrical LV activation (intervention group). In the intervention group, late activation will be determined using electrical mapping of the CS. The primary endpoint is a composite of death and nonplanned HF hospitalization. Patients are followed for a minimum of 2 years and until 264 primary endpoints occurred. Analyses will be conducted according to the intention-to-treat principle. Enrollment for this trial began in March 2018, and per April 2023, a total of 823 patients have been included. Enrollment is expected to be complete by mid-2024.

Conclusions The DANISH-CRT trial will clarify whether mapping-guided positioning of the LV lead according to the latest local electrical activation in the CS is beneficial for patients in terms of reducing the composite endpoint of

From the [a]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark, [b]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, [c]Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark, [d]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [e]Department of Cardiology, Odense University Hospital, Odense, Denmark, [f]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark, [g]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark, [h]Department of Cardiology, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark, [i]Department of Radiology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark, [j]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark, [k]Department of Psychology, University of Southern Denmark, Odense, Denmark, [l]Unit of Biostatistics, Aalborg University Hospital, Aalborg, Denmark

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Reprint requests: Mads Brix Kronborg, Department of Cardiology, Aarhus University Hospital, Palle-Juul Jensens Bvld. 99, Aarhus N, Denmark, 8200.
E-mail address: mads.brix.kronborg@clin.au.dk.
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death or nonplanned hospitalization for heart failure. Results from this trial are expected to impact future guidelines on CRT.

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Background

Cardiac resynchronization therapy (CRT) is a well-established treatment for patients with heart failure (HF), reduced left ventricular ejection fraction (LVEF), and prolonged ventricular activation. It is established by implanting an advanced pacemaker system with leads positioned in the right atrium, right ventricle, and in the coronary sinus (CS) to provide biventricular pacing. In patients at risk of sustained ventricular arrhythmias, it can be combined with a cardiac defibrillator (CRT-D). CRT is currently offered to patients with symptomatic HF despite optimal medical treatment (OMT), LVEF ≤35%, and left bundle branch block (LBBB) with QRS≥130 milliseconds (ms)[1,2] or QRS>150 ms regardless of morphology or chronic right ventricular (RV) pacing. Consistent evidence has demonstrated that CRT improves survival, symptoms, and health-related quality of life (HRQoL).[3-6] However, approximately one third of patients do not derive a measurable clinical benefit from this treatment[7]. The causes are not completely understood but left ventricular (LV) lead position has been identified as an important determinant of clinical response to CRT.

It is common clinical practice to (preferably) position the LV lead in a nonapical section of a posterolateral branch of the CS. Based on observational data,[8,9] this position is favorable because the left ventricle is paced where LV activation is late in patients with LBBB and during right ventricular pacing. It has been proposed that targeted LV pacing in an area with late mechanical activation of the left ventricle can further improve patient outcomes. Two moderately sized trials investigated the effect of echocardiography-guided targeting of the LV lead towards the site of latest mechanical activation. The TARGET trial included 220 patients to examine the influence of targeted LV lead placement on CRT outcome. The primary endpoint was a ≥15% reduction in left ventricular end systolic volume (LVESV) after 6 months, and clinical response rate was included as a secondary endpoint.[10] Both endpoints were in favor of targeted LV lead positioning. The STARTER trial included 187 patients and observed a lower incidence of the primary composite endpoint of HF hospitalization or death when the LV lead was positioned at the site of latest mechanical activation.[11] A caveat of both trials, however, was the high proportion of suboptimal LV lead positions in controls.

In a double-blinded RCT conducted at Aarhus University Hospital, we investigated the influence of a multimodality imaging-guided strategy for targeting the LV lead towards the CS branch closest to the latest mechanically activated area of the left ventricle.[12] The trial included 182 patients with HF and LBBB. We found a higher clinical response rate (defined by a composite of being alive without HF hospitalization and with symptomatic improvement after six months) in the intervention group (74% vs 58%, P=0.02), but observed no difference in HF hospitalization or death - even after extended follow-up.[13] The effect of CRT on ventricular remodeling was marked (mean LVEF increase from 25% to 37%), but similar across treatment groups. In this trial, the LV lead was successfully positioned in nonapical positions without scar tissue in 97% of patients. Thus, these results may indicate that the effect of imaging-guided lead placement is less pronounced when controls are more optimally treated.

Several observational studies suggest that an LV lead position in an area with very late local *electrical* activation is associated with better clinical and echocardiographic outcomes,[14-16] and some physicians already search for late activation when they position the LV lead. However, this strategy has not been tested in a controlled setting. A moderately sized single-center cohort study has shown that detailed mapping for late activation in the CS is feasible and not associated with excess complications,[17] but such strategy may have additional costs. Mapping of the CS can cause extended operating times, increased risk of infection, and excessive use of hardware; this will increase costs and radiation exposure for patients and staff. Furthermore, it may be necessary to accept a higher pacing threshold in a very late activated area, which will reduce battery longevity of the device. Finally, the site of latest activation may in some patients be near scar tissue, and it has not been clarified whether targeting the latest activated area can be pro-arrhythmic.

In terms of patient outcomes, it is currently unsettled whether targeted positioning of the LV lead to the latest electrically activated area of LV is superior to current standard CRT with the LV lead preferentially in a nonapical posterolateral position. The DANISH-CRT trial was designed to answer this question.

Methods

Trial design, aim and hypotheses

The DANISH-CRT trial is an investigator-initiated, double-blinded, national RCT (ClinicalTrials.gov NCT03280862) aimed to evaluate whether targeted

Table I. Inclusion and exclusion criteria in the DANISH-CRT trial.

Inclusion Criteria

- Age >40 years
- Heart failure, NYHA II or III, or outpatient IV
- LVEF ≤35% measured by echocardiography
- Optimal medical treatment for heart failure*
- Bundle branch block, defined as one of the following:
  - True LBBB according to AHA/ACC/HRS Scientific Statement from 2009[18] † and ≥130ms
  - [2]LBBB-like, intraventricular conduction delay (IVCD), right bundle branch block (RBBB), all >150ms or
  - [3]RV paced QRS and indication for upgrade to CRT (>50% RV pacing) or
  - [4]RV pacing indicated by bradycardia with expected large percentage of RV pacing
- Indication for primary CRT-D or CRT-P implantation or upgrade from RV pacing (pacemaker or ICD) to CRT-D or CRT-P.
- Heart failure due to ischemic heart disease (IHD) or non-IHD
- Sinus rhythm or atrial fibrillation
- Life expectancy >2 years
- Signed informed consent

Exclusion criteria:

- AMI within the latest 3 months
- CABG within the latest 3 months
- Life expectancy <2 years
- Participation in another clinical trial of experimental treatment‡
- Contraindication for establishing CIED treatment

[2]ACE inhibitor, angiotensin receptor blocker or combined ACE- and neprilysin inhibitor, and [3]aldosterone receptor antagonist as indicated according to guidelines. From 2021, addition of a sodium-glucose cotransporter 2 (SGLT2) inhibitor was recommended.

*Optimal medical treatment for heart failure includes treatment with maximum tolerated doses of [1]betablocker

† QRS≥130 ms, 'broad notched or slurred R-wave in leads I, aVL, V5, and V6 (an occasional RS pattern *in V5 and V6 may occur because of displaced transition of the QRS complex), absent Q-waves in leads I, V5, and V6, normal R peak time in leads V1, V2, and V3 (if R-waves are present) and >60ms leads V5 and V6*'.

‡ Patients included in the national trial of hydralazine and metformin for heart failure may be included. AMI: acute myocardial infarction. CABG: coronary artery bypass graft. CRT: cardiac resynchronization therapy pacemaker (P) or defibrillator (D). IHD: Ischemic heart disease. LVEF: left ventricular ejection fraction. NYHA: New York Heart Association.

positioning of the LV lead to the CS branch with the latest local electrical LV activation reduces the incidence of the composite endpoint of death and nonplanned HF hospitalization. We hypothesize that such targeted positioning of the LV lead will reduce the incidence of the composite endpoint compared to conventional CRT implantation in patients with HF and prolonged QRS. The trial will enroll 1,000 patients and follow them for a minimum of two years and until 264 primary endpoints occurred.

Patient population

Eligible candidates are identified among patients referred for CRT implantation who meet the inclusion criteria. Criteria for inclusion and exclusion are shown in Table I. Patients ≥40 years of age with an indication for primary implantation of a CRT pacemaker (CRT-P) or CRT defibrillator (CRT-D) according to current guidelines or for an upgrade from RV pacing to CRT-P or CRT-D are eligible for inclusion. Patients are excluded in case of recent acute myocardial infarction (AMI) or coronary artery bypass graft (CABG) (<3 months), life expectancy <2 years, participation in another experimental trial or if treatment with a cardiac implantable electronic device (CIED) is contraindicated. LBBB is defined according to the 2009 AHA/ACC/HRS Scientific Statement[18]: QRS≥130 ms, broad notched or slurred R wave in leads I, aVL, V5, and V6 (an occasional RS pattern in V5 and V6 may occur because of displaced transition of the QRS complex), absent Q-waves in leads I, V5, and V6, normal R peak time in leads V1, V2, and V3 (if R waves are present) and >60 ms in leads V5 and V6. Patients are required to be in OMT for HF. This includes treatment in target doses of (1) a betablocker, (2) an angiotensin converting-enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB) or a combined ACE- and neprilysin inhibitor, and (3) an aldosterone receptor antagonist, as suggested by societal guidelines. In case titration to target dose is not possible, treatment with the maximum tolerated dose is accepted. After release of the 2021 ESC Guidelines for treatment of heart failure,[2] a sodium-glucose cotransporter 2 (SGLT2) inhibitor is recommended either at time of inclusion for new patients, or at first follow-up in patients already included. All patients must submit a written, informed consent before participation is possible.

Study endpoints

The primary endpoint is a composite of time to death or first nonplanned HF hospitalization. Nonplanned HF hospitalization is defined as a nonplanned hospitalization lasting >24 hours due to HF with requirement for intensified HF therapy. Secondary endpoints include the 2 components of the primary endpoint and a series of

Table II. Endpoints in the DANISH-CRT trial.

Primary endpoint

- Death or nonplanned hospitalization for heart failure (nonplanned hospitalization >24 hours due to heart failure requiring intensified heart failure therapy)

Secondary end points:

- Death
- Nonplanned hospitalization for heart failure
- Sudden death
- Cardiovascular death
- Echocardiographic endpoints (measures of LV function and dimensions/volumes)*
- Clinical response defined as *increase in NYHA class (≥1 class)* ***or*** *improved walking distance by 6MWT (≥10%)**
- 6MWT*
- NYHA class*
- Quality of Life (QoL) and patient reported outcomes: Kansas City Cardiomyopathy Questionnaire (KCCQ-12),[19] Patient Health Questionnaire (PHQ-9), and Generalized Anxiety Disorder (GAD-7), Brief Illness Perception Questionnaire (BIPQ), and for ICD carriers: The Implantable Cardioverter Defibrillator Patient Concerns Questionnaire (ICDC) and at baseline Expectations towards ICD Therapy (EXPECT-ICD)*
- Atrial fibrillation, persistent and as first diagnosed atrial fibrillation (>30 seconds recorded by the implanted device)
- Number of LV leads used for implantation

Safety endpoints:

- Device-related complications
- Procedure time at implantation, fluoroscopy time and dose
- ICD therapy
- CIED Battery longevity

*Change from baseline to follow-up after 6-, 12-, 24- and 48 months. 6MWT: six-minute walking test. CIED: Cardiac implanted electronic device.ICD: Implantable cardioverter defibrillator. LV: left ventricular. NYHA: New York Heart Association.

endpoints related to HRQoL, functional level and wellbeing,[19] left ventricular performance, cardiac implantable electronic device (CIED) function, and complications (Table II).

Every 4 to 6 months, the study coordinating center verifies vital status for all included patients using data obtained from the Danish National Personal Civil Registration System (CPR). In case of death, the center responsible for follow-up collects information about cause of death from the general practitioner and from other hospitals/departments when relevant. This information and relevant data for all hospitalizations is uploaded electronically to the study case report form (CRF) to be used for endpoint adjudication. The endpoint committee consists of three experienced cardiologists and trialists who are not otherwise involved in the trial. All hospitalizations are adjudicated to determine whether criteria for nonplanned HF hospitalization are fulfilled, and deaths are adjudicated with respect to cardiac deaths including whether they can be classified as sudden deaths. Personnel involved in data collection and endpoint adjudication are blinded to group allocation.

Randomization

Patients are randomized in a 1:1 fashion to receive either (1) a CRT-D/P device with the LV lead positioned according to the latest electrical activation in the CS (*intervention group*) or (2) a CRT-D/P device with the LV lead positioned preferentially in a posterolateral, nonapical position (*control group*). Randomization is stratified by the presence of (a) true LBBB, (b) other bundle branch block (BBB) and (c) RV pacing. Block-randomization is used to ensure that each center includes a similar number of patients for each treatment group. Patients with LBBB and RV pacing will be randomized at each center in blocks of 10 (intervention) + 10 (control) and for patients with other BBB in blocks of 5 (intervention) + 5 (control). Randomization is conducted electronically using the CRF. This system is also used for data collection in the trial. LVEF ≤35% verified by echocardiography and signed informed consent must be provided prior to randomization.

The implanting physician is aware of group allocation to provide the correct treatment; only the implanting physician can access this information and the implanting physician is not involved in the follow-up of the patients. With omission of the allocated LV lead implantation strategy, CIED procedure descriptions are recorded in the electronic patient chart for all patients. Follow-up is identical in the 2 treatment groups, and patients and other healthcare personnel are blinded to randomization and treatment (intervention or control).

Device implantation

All patients undergo a preoperative echocardiography to determine ventricular function and -dimensions, and to identify akinetic, depleted or aneurysmatic myocardial areas that might represent scar tissue. A preprocedural contrast-enhanced cardiac CT scan is performed to visualize the CS branches.[16,20] The preoperative cardiac CT is omitted in the event of known allergy to contrast media or an estimated GFR <30 ml/min/1.73 m^2. The implanting physician can access imaging data to identify scar tissue (to avoid lead placement in this area) and CS anatomy but is not aware of the latest activated LV segment as determined by echocardiography.

The RV electrode is preferentially placed in an RV septal position unless factors related to lead stability, electrical values, and defibrillation vector favor an apical position (at the discretion of the implanting physician). The atrial electrode is positioned at the preference of the implanting physician. Conventional or targeted LV lead placement is determined by randomization (see below). In general, multipolar (quadripolar) LV leads are used as first choice. However, the implanting physician may use a bipolar LV lead if a multipolar lead cannot be implanted. Balloon occlusion venography to visualize the CS is performed in all patients. Supplementary selective venography may be used to visualize CS branches. Guided by the preoperative echocardiography, positioning of the LV lead directly into scar tissue is avoided in both intervention and control group, if possible.

In *the intervention group*, local electrical activation is measured and recorded in all CS branches where a LV lead may potentially be positioned. All measurements are completed for basal, mid-ventricular and apical lead positions (Fig. 1). Mapping is performed using the LV lead or/and an electrically active guidewire (e.g., VisionWire, Biotronik, Germany) as decided by the implanting physician. The LV lead is positioned in the CS branch with the latest local electrical activation if lead stability, pacing threshold and threshold for phrenic nerve stimulation are acceptable. If it is not possible to implant the lead in that area, the implanter aims for the next position with latest activation according to the measurements obtained during mapping of the CS branches. Number of mapped CS branches, LV lead target branch, and LV lead position in the branch (apical, mid-ventricular or basal) are recorded.

In patients with true LBBB, CS mapping is performed during native ventricular activation (LBBB). In all other patients, electrical activation in the CS branches is mapped during RV pacing. In rare cases, a very long latency from pacing at the LV lead to start of the generated QRS-complex is observed. In cases where this latency exceeds 60-70 ms and correction by programming the VV interval to obtain resynchronization is not possible, the LV lead is placed according to latest LV activation where this phenomenon is not observed.

In *the control group*, the LV lead is placed in the branch judged to be most suitable, preferentially in a posterolateral (2-5 o'clock in the mitral annulus), and mid-ventricular or basal, nonapical position (Fig. 2), and taking into consideration lead stability, pacing threshold and threshold for phrenic nerve stimulation. Mapping for late activation is not performed.

In all patients, fluoroscopic images of the lead positions in two planes (LAO 40-60° and RAO 30-40°) are recorded at the end of procedure. Operation time from first incision to last suture set and fluoroscopy time and -dose are recorded, as is time used for mapping of CS and positioning of the LV lead. After implantation, the VV interval (the interval from pacing in the RV until pacing in the LV) is adjusted to obtain the narrowest possible QRS. The AV delay is programmed to be short enough to avoid fusion between biventricular pacing and intrinsic ventricular activation. The day after implantation, LV activation delay relative to the sensed RV signal - or to RV-pacing in patients without intrinsic rhythm - is measured.

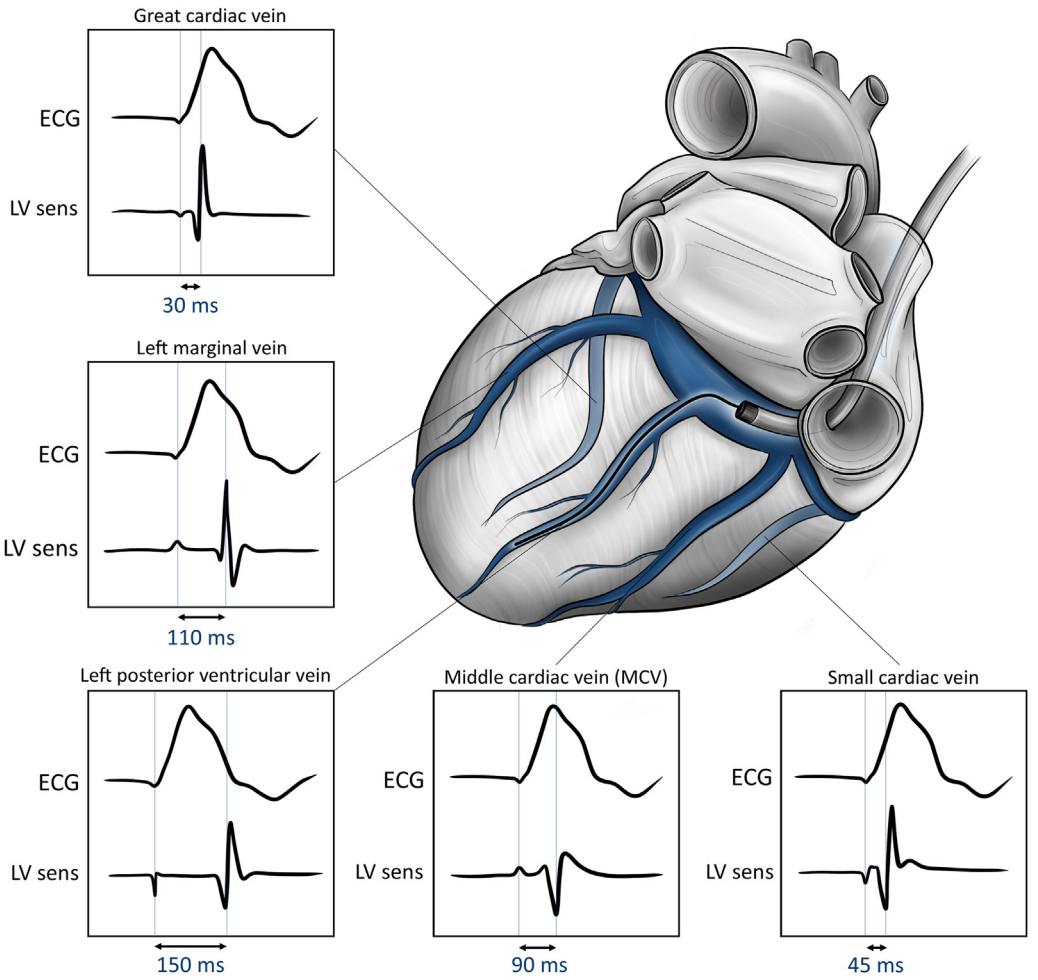
Prior to discharge or no later than 3 months after implantation, all patients undergo a prospectively electrocardiogram-triggered high-pitch spiral CT scan for precise determination of the lead positions.[16] After implantation and prior to discharge, an ECG-12 with the device programmed to CRT, RV-only pacing, and LV-only pacing will be recorded.

Follow-up visits

An overview of baseline- and follow-up examinations is provided in Table III. Clinical- and device check-ups are scheduled after 3, 6 and 12 months, and annually thereafter. Remote monitoring is established for all patients. Echocardiographic follow-up, New York Heart Association (NYHA) classification and patient-reported outcome (PRO) questionnaires are scheduled after 6 and 24 months. Following questionnaires are used: Brief Illness Perception Questionnaire (BIPQ), Kansas City Cardiomyopathy Questionnaire (KCCQ), Patient Health Questionnaire (PHQ), Generalized Anxiety Disorder (GAD), and for ICD carriers: The Implantable Cardioverter Defibrillator Patient Concerns Questionnaire (ICDC) and at baseline Expectations towards ICD Therapy (EXPECT-ICD). A six-minute walking test (6MWT) is performed at 6 and 24 months. At each follow-up visit, medication is recorded, an ECG-12 is obtained upon patient arrival, and the interval from RV pacing to LV lead activation is measured. If, at 3 months after implantation, there is no clinical response (defined as no improvement in NYHA class), AV and VV optimization guided by a standard echocardiographic protocol is performed.

In patients who develop or have persistent atrial fibrillation and where sinus rhythm cannot immediately be obtained by medication and/or direct current (DC) cardioversion, there is risk of compromised CRT due to frequent intrinsic ventricular activation. If effective CRT

Fig. 1



Placement of the LV lead in the intervention group. Timing of local electrical activation measuring form RV activation to the first large deflection on the LV EGM is recorded in all CS branches where an LV lead may potentially be positioned using the LV lead or an electrically active guidewire. The LV lead is positioned in the CS branch with the latest local electrical activation if lead stability, pacing threshold and threshold for phrenic nerve stimulation are acceptable.

drops <95%, patients are offered pulmonary vein isolation or AV node ablation (His-ablation) to re-establish effective CRT close to 100% of the time. Likewise, if a patient develops frequent ventricular premature beats that compromise effective CRT (<95%), they are offered either medical antiarrhythmic treatment or catheter ablation for ventricular premature beats. Choices in treatment strategy will be based upon shared decision making between patient and physician. Atrial fibrillation and ventricular premature beats are handled equally in the 2 treatment arms. At all follow-up visits the device is interrogated and episodes with VT/VF are registered and adjudicated as appropriate or inappropriate therapy by experienced device specialist. All follow-up personnel are blinded to treatment assignment.

Sample size calculation

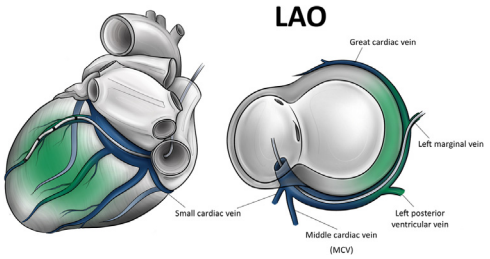
Based on previous studies[12,13,21] as well as data from the CRT population at Aarhus University Hospital (n=1600),[22] we assume that 35% of the population will reach the primary composite endpoint of death or nonplanned HF hospitalization within 4 years. Half are expected to be deaths. To show a relative reduction of 25% of the primary endpoint to an absolute incidence of 26% with α=0.05 and 1-β=0.80, 409 patients must be included in each group. Assuming this is accurate, we would expect 264 primary endpoints to occur during the study period. If the attrition rate is <10%, inclusion of 500 patients in each group will be sufficient. Thus, this trial will include a total of 1000 patients. This study was

Table III. Data collection in the DANISH-CRT trial.

	Baseline	Implant Procedure	Before discharge	3 months	6 months	12 months	24 months	36 months	48 months	Annual
Medication	•			•	•	•	•	•	•	•
Echocardiography	•				•		•			
Electrical parameters		•								
CS measurements*		•								
Fluoroscopy		•								
AV-VV optimization			•	(•)‡						
Cardiac CT scan†	•		•							
Clinical assessment	•			•	•	•	•	•	•	•
CIED check-up			•	•	•	•	•	•	•	•
NYHA class	•			•	•		•		•	
PRO questionnaires§	•				•		•		•	
ECG-12	•		•	•	•	•	•	•	•	•
RVP-LV interval			•	•	•	•	•	•	•	•
6MWT					•		•			
Remote monitoring			•							

* Only in intervention group. CS activation is measured in all accessible CS branches in a basal-, mid- and apical position.
† Contrast-enhanced CT scan before implantation, and flash CT scan (without contrast) before discharge and after implantation.
‡ Only performed in patients without clinical response to CRT at the 3-month follow-up.
§ Includes BIPQ (Brief Illness Perception Questionnaire), KCCQ (Kansas City Cardiomyopathy Questionnaire), PHQ (Patient Health Questionnaire), GAD (Generalized Anxiety Disorder), and for ICD carriers, ICDC (The Implantable Cardioverter Defibrillator Patient Concerns Questionnaire) and at baseline, EXPECT-ICD (Expectations towards ICD Therapy).6MWT: six-minute walking test. CIED: cardiac implantable electronic device. CS: coronary sinus. CT: computerized tomography. ECG-12: 12-lead electrocardiogram. NYHA: New York Heart Association. PRO: patient-reported outcome. RVP-LV interval: interval from right ventricular pacing to left ventricular lead activation.

Fig. 2



Placement of LV lead in the control group. The LV lead is placed in the branch judged to be most suitable, preferentially in a posterolateral (2-5 o'clock in the mitral annulus), and mid-ventricular or basal, nonapical position, and taking into consideration lead stability, pacing threshold and threshold for phrenic nerve stimulation.

not designed to detect a significant reduction in mortality.

Statistical analyses

Baseline characteristics in each treatment group will be presented in means with standard deviations or medians with interquartile ranges, as appropriate. The primary analysis will be conducted according to the intention-to-treat principle. Time to the primary composite endpoint of death or nonplanned HF hospitalization for each treatment group will be assessed using the Kaplan-Meier. Hazard ratios will be computed using a Cox regression model. Restricted mean survival time difference for the primary composite endpoint will be estimated as a supplementary analysis. An additional analysis will be adjusted for age, sex, QRS morphology (LBBB/non-LBBB/RV paced), QRS width (≥150ms/<150ms), NYHA class (II/III or outpatient IV), underlying disease (ischemic heart disease (IHD)/non-IHD etiology) and center. Statistical interaction is assessed for all subgroup analyses (Table IV) and presented graphically in a forest plot. A multiple Cox-, multiple linear- or modified Poisson regression model will be used to analyze between-group differences in secondary endpoints, as appropriate. Repeated measures analysis of variance or a linear mixed model will be used as most appropriate for data with repeated measures. When relevant, analyses will be adjusted for competing risks and multiple comparison. A *P*-value <0.05 is considered significant in 2-sided tests. No or very few missing data are expected for the primary endpoint. In case of missing data in secondary analyses sufficiently extensive to raise questions about the robustness of the results, sensitivity analyses using multiple imputation will be performed and assumptions about the missing data mechanism will be reported.

Ethical statement

A standard CRT implantation is associated with a non-negligible risk of complications.[23] It is not known whether this risk will be higher or lower in the interven-

Table IV. Planned subgroup analyses in the DANISH-CRT trial for baseline.

- Sex difference
- Higher and lower age (above versus below the median)
- Q-LV time above/below the median value
- IED above/below the median value for patients with intrinsic rhythm at implantation
- NYHA class II or NYHA class III/outpatient IV
- LVEF above/below the median value
- Ischemic or nonischemic heart failure etiology
- LBBB, non-LBBB or RV-pacing
- Upgrade from RV pacing to CRT or primary implantation of CRT
- RV lead in a septal or a nonseptal position*
- RV lead in an apical or a nonapical position*
- Presence or absence of LV dyssynchrony at echocardiography (radial time-to-peak, cross-correlation, and pattern-analysis)
- Scar tissue/perfusion evaluation by CT scan. Total percentage of scar tissue (higher/lower than median) as well as scar tissue localization relative to LV lead position (LV lead close to scar (in or in neighbor-segment in a 17-segment model of LV) or remote to scar
- Permanent/persistent AF, paroxysmal AF or sinus rhythm at baseline

* As determined by an electrocardiogram-triggered high-pitch spiral CT after implantation.AF: atrial fibrillation. CRT: cardiac resynchronization therapy. CT: computerized tomography. IED: difference in time between sensed signals on RV and LV pacing leads. LBBB: left bundle branch block. LVEF: left ventricular ejection fraction. NYHA: New York Heart Association. Q-LV: time from start of QRS to local LV activation. RV: right ventricular.

tion group, where CS mapping is performed. CS mapping is expected to prolong the implantation procedure, and it is uncertain whether the more extensive handling of guiding sheaths, guide wires and leads will increase complication risk with respect to CS dissection or perforation, bleeding, and infection. In a pilot study at Aarhus University Hospital, CS mapping was not associated with excess complications.[17] In the present trial, all implantation-related complications are recorded.

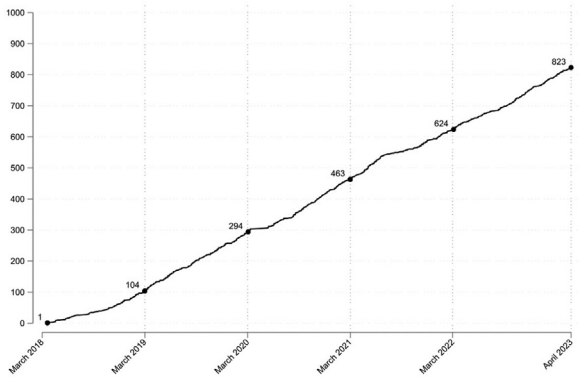
Only patients with an indication for CRT according to current guidelines are included in the study. Based on the existing literature, we hypothesized that mapping-guided LV lead positioning will increase the proportion of patients who benefit from CRT and improve patient prognosis. This trial will clarify whether such a strategy is justified.

At the preoperative CT scan, patients are exposed to a radiation dose of 15 millisievert (mSv) depending on weight, height, and heart rhythm. At the postoperative electrocardiogram-triggered high-pitch spiral CT, they are exposed to another approximate 2 mSv. Thus, the total effective radiation dose of these CT scans constitutes 8-26 mSv. Such radiation dose is not deterministically injurious but subjects the patients to a stochastic radiation exposure injury. In a healthy person younger than 50 years of age, a radiation dose of 20 mSv will increase risk of dying from cancer from 25% to 25.1%. The mean age for CRT patients is approximately 65 years, 90% are older than 50 years, and only patients older than 40 years are included. In comparison, the mortality rate in patients with severe HF and CRT indication is approximately 20%-25% after 5 years, and more effective CRT treatment can increase longevity and considerably improve QoL. According to guidelines for the use of ionizing radiation in health research projects, >90% of the patients (the >50-years old) are in risk category IIb, and those younger than 50 years (<10%) in risk category III.[24,25] Considering the potential benefits to patients from improved CRT treatment, the higher radiation risk is justified.

Study conduct

In Denmark, CRT implantations are centralized to 5 high-volume centers. This study is planned and conducted in a close collaboration between device specialists, heart failure specialists, and specialists in cardiac imaging from all 5 centers: Copenhagen University Hospital - Herlev and Gentofte, Odense University Hospital, Copenhagen University Hospital - Rigshospitalet, Aalborg University Hospital, and Aarhus University Hospital (coordinating center). Recently, this study group completed the DANISH trial on the effect of prophylactic ICDs in patients with nonischemic HF.[21] Follow-up is well-organized and based on experiences from daily clinical practice. Remote monitoring can be established successfully in >95% of the enrolled CRT patients. Imaging core lab is located at Copenhagen University Hospital - Rigshospitalet, statistical core lab and core lab for ECG analysis at Aalborg University, and core lab for patient-reported outcomes (PROs) and QoL analyses at Odense University Hospital. Positive, negative, neutral, or inconclusive results will be published. This trial is conducted in accordance with the latest version of the Declaration of Helsinki (2013) and approved by the Ethics Committee of Central Denmark Region. The study is registered under the common notification system of the Danish Data Protection Agency and will adhere to the Danish Act on Processing of Personal Data. The study is supported by funding form Novo Nordisk Foundation (NNF17OC0029148), Danish Heart Foundation (17-R116-A7405-22046, and 21-R151-A9920-22199) and Danish Pacemaker and ICD Register. Information about the

Fig. 3



Patient inclusion in the DANISH-CRT trial per April 26, 2023 (n=823 patients). Enrollment is expected to complete by mid-2024, and follow-up 2 years later.

work and composition of Data and Safety Monitoring Board is provided in the appendix.

Inclusion status

A stable number of around 700 CRT-P/-D implantations are performed each year in Denmark as de novo implantations (70-75%) or upgrades (25-30%) from cardiac pacing or ICD treatment. During planning, it was estimated that at least half of these patients would be eligible for inclusion into this study. Hence, an inclusion period of no more than 4 to 5 years was estimated to be sufficient for enrollment of 1,000 patients. Enrollment for the DANISH-CRT trial commenced during the period between March 20, 2018, and March 6, 2019, in the 5 centers. A total of 823 patients have been enrolled and randomized as of April 26, 2023 (Fig. 3). Patient accrual is expected to complete by mid-2024. Follow-up will complete after a minimum of 2 years and when 264 primary end points have occurred. Thus far, included patients have a mean age of 70±9 years, mean LVEF 27±6%, 24% are women, 57% have HF of nonischemic etiology, 35% are upgrades from existing pacemaker or ICD-systems and 65% are de-novo implantations; 69% with true LBBB and 23% with paced QRS.

Discussion

While the landmark clinical trials performed 15 to 20 years ago established CRT as a therapy that saves lives,[3-5] reduces hospitalizations and improves QoL in patients with HF and LBBB, there has been a lack of large, well-powered RCTs to investigate the effect of different implant strategies on hard endpoints. Lead designs and delivery sheaths have improved during the last decades, thus increasing the number of possible target veins and overall success of rate of LV lead implantation. The DANISH-CRT trial will determine whether mapping of LV activation in the CS and LV lead positioning according to the latest local electrical activation is beneficial for patients in reducing the composite endpoint of death or nonplanned HF hospitalization. Furthermore, secondary endpoints will allow for evaluation of whether this strategy is beneficial in terms of LV remodeling, risk of arrhythmia, patient reported outcomes and device-related complications.

The primary endpoint for this trial is clinically relevant and has been used previously in HF trials, and for investigating the effect of CRT.[6] In Denmark, all deaths are registered in central registries, and this information can be obtained for all included patients. Hence, information about mortality in the study population will be both accurate and complete. All hospitalizations will be adjudicated by an independent endpoint committee, and it is realistic to obtain a true estimate of this endpoint component as well. Additional data is collected on LV function and -remodeling, patient reported outcomes, and QoL, as well as device-related information on occurrence of arrhythmias and complications.

This is a double-blinded trial where neither patients nor health care personnel responsible for patient follow-up are aware of randomization assignment or whether the allocated strategy for LV lead implantation was successful. Because this study is conducted over several years in high-volume centers, it is realistic that blinding can be maintained, and cross-over between treatment arms is highly unlikely.

Former studies have predominantly investigated use of targeted LV lead placement according to the latest mechanical activation.[10,11,26] The site of latest mechanical and electrical activation differs according to some studies,[27,28] but not in others.[29,30] In one study, we compared targeting mechanical against electrical late activation, and targeting the latest electrical activation was similar or better than targeting the latest mechanical activation based on change in LVEF.[17] We previously documented the reproducibility and repeatability of identifying the latest electrical activation by mapping the CS.[31] Using mechanical latest activation requires advanced imaging by one or more imaging modalities, and often also image integration prior to implantation.[12,20] These are time-consuming and expensive procedures. Still, LV lead placement is restricted by CS anatomy. With electrical activation, CS mapping and the LV lead implantation can be performed in a single procedure without need for prior imaging and image integration.

Most patients included in this trial show LBBB QRS morphology. Another large patient group comprises patients undergoing upgrades from cardiac pacing with a pacemaker or an ICD. Relatively few patients with nonspecific intraventricular conduction disease or right bundle branch block (RBBB) have been included. There-

fore, findings from this study will likely be most relevant to patients with LBBB or upgrade from RV pacing. In prior CRT studies, the number of patients with nonspecific intraventricular conduction disease or RBBB was also low.[5,6] Based on current patient inclusion, these patients comprise a small proportion of patients referred for CRT implantation in Denmark and are rarely approached for inclusion in the DANISH-CRT trial.

Within recent years, conduction-system pacing (CSP) has been introduced as an alternative to CRT. Observational data on CSP in HF are promising,[32,33] and small RCTs with short follow-up indicate similar effects of CSP and CRT on LV remodeling.[34] In contrast to CRT, CSP for HF with BBB is not supported by large or even moderately sized RCTs. Long-term effects of CSP in this setting is largely unknown, as is long-term safety. This is reflected in the most recent guidelines on pacing and CRT, where no recommendation for CSP in patients with HF and BBB was provided.[1] CRT is a well-documented and life-saving therapy for this patient group and will have to remain a first choice until large RCTs indicate that CSP is a better or as good as CRT for patients with HF with BBB on the long-term. Even if this is the case, it will most likely not be possible to establish resynchronization by CSP in certain patients[32] who will therefore need CRT as we know today.

Conclusions

The DANISH-CRT trial will clarify whether mapping-guided positioning of the LV lead according to the latest local electrical activation in the CS is beneficial for patient in terms of reducing the composite endpoint of all-cause death or nonplanned hospitalization for heart failure. Results from this trial are expected to impact future guidelines on CRT implementation.

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Conflict of interests

JCN is supported by grants from the Novo Nordisk Foundation (NNF16OC0018658, NNF17OC0029148), JHS reports membership of advisory committee in Medtronic, research grant outside this work from Medtronic and speakers' honorarium from Medtronic. LK report speakers' honorarium from AstraZeneca, Bayer, Boehringer, Novartis and Novo, not related to this manuscript. MHJPF reports speakers' honorarium from Medtronic outside submitted work. Remaining authors report no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.05.011.

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