DANISH-CRT – Protocol Version 1, 25012017

Does targeted positioning of the LV pacing lead towards the latest local electrical activation when implanting CRT devices reduce the incidence of the combined endpoint "death or non-planned hospitalisation for heart failure" in patients with heart failure and prolonged QRS?
A Danish national randomised study

ClinicalTrials.gov NCT 03280862

DANISH-CRT

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A Danish national randomised study

Protocol by Jens Cosedis Nielsen, Aarhus University Hospital on behalf of the DANISH study group

Background:

Cardiac resynchronization therapy (CRT) is a well-established treatment for patients with clinical heart failure, NYHA class II, III and IV (outpatient) in spite of optimised medical treatment (OMT), reduced left ventricular function with LVEF ≤ 35% and left bundle branch block (LBBB). CRT is established by implanting an advanced pacemaker system with three leads in the right atrium, right ventricle, and in the coronary sinus (CS) for pacing the left ventricle (LV), and often is combined with an implantable defibrillator (ICD) function. On average, CRT treatment improves longevity, quality of life and functional class, and reduces heart failure symptoms (1-5). Thus, at present, CRT is offered to heart failure patients in OMT with LBBB and QRS≥130 ms (milliseconds) (5), QRS>150 ms regardless of QRS morphology or chronic right ventricular (RV) pacing (6). However, it is a significant problem that 30-40% of CRT patients do not benefit measurably – showing symptomatic improvement or improved cardiac pump function – from this therapy (so-called non-responders). LV lead placement is one of the major determinants of beneficial effect from CRT.

The latest ESC guidelines from 2013 recommend to consider targeting the LV lead to an area of late activation in the left ventricle (***IIb, level B***) (6). This is based on the TARGET study including 220 patients (7). In this study, the site of latest mechanical activation was identified by echocardiography. Both the primary endpoint (reduction in left ventricular end systolic volume (LVESV) after 6 months) and the secondary endpoint, clinical response rate, turned out in favour of LV lead positioning corresponding to the latest activation. However, it is a major limitation in the TARGET study that in 15% of the patients in the control group the LV lead was positioned in scar tissue and in 14% the LV lead was in an anterior, anteroseptal, or inferoseptal position. Such LV lead positions are associated with a poorer effect of CRT and a poorer patient outcome. Thus, the control group was not treated according to daily standard in Danish CRT-implanting centres. This may play a substantial role in explaining the study result.

Furthermore, it is recommended that the LV lead is not positioned apically as this is associated with a poorer outcome (***IIa, level B***) (6, 8, 9). The randomised STARTER study of 187 patients showed a lower incidence of the endpoint "*HF hospitalisation or death*" with placement of the LV lead in a position corresponding to the latest mechanical LV activation as guided by echocardiography (10). Also in this study the LV lead position in the control group was far from optimal, 33% were placed apically and 15% anterolaterally. Thus, suboptimal treatment of the control group may also have influenced these study results substantially.

In a double-blind, randomised trial conducted at Aarhus University Hospital we studied targeted positioning of the LV lead to the coronary sinus (CS) branch closest to the latest mechanically activated area of the left ventricle. (11). We included 182 patients with heart failure (HF) and LBBB. Responders were defined as patients reaching the composite endpoint: alive ***and*** no heart failure admissions ***and*** increase in either

NYHA class (≥class 1) or ≥10% increase in 6MWT (6-minute walk test) after 6 months. We found a higher clinical response rate (74% vs 58%, p=0.02) in the intervention group, but no difference in HF hospitalisation or death, nor after 1.8 years. Measured by the change in LVEF and LV dimension the effect of CRT was marked (LVEF increase from 25% to 37% in mean), and equal in the two treatment arms. In our control group, the LV lead was positioned in the first priority CS branch in 65% of the patients versus 83% in the intervention group, and only 3% were positioned apically or in scar tissue. With a more optimally treated control group the effect of LV lead positioning guided by echocardiography seems less pronounced.

Several observational studies, including post-hoc analysis of data from the above mentioned trial, suggest that a very late local electrical activation coinciding with LV lead position is associated with a better clinical and echocardiographic outcome (12, 13) (Europace abstract 002132, 2016, appendix 1). In daily clinical practice in Denmark the LV lead is typically placed in a posterolateral position with a relatively late local electrical activation in LBBB. The LV lead is not positioned to pace in an apical or anterior site unless this is where the very late activation is found after abandoning other potential target branches (due to high pacing threshold, phrenic nerve pacing or unstable lead position). Based on the existing literature, some physicians already search for late activation when positioning the LV lead, even though this strategy has not been tested in a controlled design.

Detailed mapping for a late activation may give rise to extended operating times, increased risk of infection, use of more electrodes and more hardware, which increases the costs, and increases radiation exposure for patient and staff. Furthermore, one may have to accept a higher threshold in a very late activated area which will reduce battery longevity of the device. It has not been settled, whether targeting towards the latest activation that may in some patients be close to scar tissue can be pro-arrhythmic.

At present, it is completely 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 non-apical posterolateral position with regard to improving patient prognosis (death or hospitalisation for heart failure).

Hypothesis:

Targeted positioning of the LV lead to the CS branch with the latest local electrical LV activation reduces the incidence of the combined endpoint "death or hospitalisation for heart failure" compared to standard CRT implantation in patients with heart failure and prolonged QRS.

Aim:

To investigate, whether targeted positioning of the LV lead to the CS branch with the latest local electrical LV activation reduces the incidence of the combined endpoint "death or hospitalisation for heart failure" compared to standard CRT implantation in patients with heart failure and prolonged QRS.

Inclusion:

Patient must meet all the following criteria:

- Age >40 years
- Heart failure, NYHA II, III, outpatient IV
- LVEF ≤35% measured by echocardiography
- In optimised medical treatment for heart failure*
- Branch block, defined as one of the following:
    - [1]"true LBBB" ≥130ms (Definition of LBBB according to AHA/ACC/HRS Scientific Statement from 2009: 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 leads V5 and V6*")
    - [2]LBBB-similar, 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)
    - [4]RV pacing indicated by bradycardia (primary implantation) and indication for CRT (heart failure, reduced LVEF≤35% prior to RV pacing and 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.
- Ischaemic heart disease (IHD) or non-IHD

- Sinus rhythm or atrial fibrillation
- Life expectancy >2 years
- Signed informed consent

*: optimised medical treatment for heart failure means: treatment with target dose betablocker, ACE inhibitor/angiotensin receptor blocker/combination of ACE inhibitor - neprilysin inhibitor, and aldosterone receptor antagonist as indicated according to guidelines. If impossible to uptitrate one ore more of the drugs to target dose, then treatment with maximum tolerated dose.

Exclusion criteria:

- NYHA class I
- AMI within the latest 3 months
- CABG within the latest 3 months
- Life expectancy <2 years
- Participation in another clinical trial of experimental treatment (does *not* include studies e.g. randomising patients to one of more stent types for PCI and following patients registry-based). Patients included in the national trial of hydralazine and metformin for heart failure may also be included
- Contraindication for establishing implantable device treatment
- Previously implanted CRT system
- Does not wish to participate

Endpoints:

Primary:

- Death or non-planned hospitalisation for heart failure
    - Death
    - Non-planned hospitalisation for heart failure (non-planned hospitalisation >24 hours due to heart failure requiring intensified heart failure therapy)

Secondary:

- Sudden death
- Cardiac death
- Clinical response defined as "*increase in NYHA class (≥1 class from baseline)* ***or*** *improved walking distance by 6MWT (≥10% from baseline)*" after 6 and 24 months
- 6MWT, changes from baseline to follow-up after 6 and 24 months
- NYHA class, changes from baseline to follow-up after 6, and 24 months
- Quality of Life (QoL) and patient reported outcomes (PROs), changes from baseline to follow-up after 6, 12, 24 and 48 months
- Echocardiographic endpoints (re-modelling of LV: LVESV, LVEDV, LVEF). See supplementary protocol on imaging
- ICD therapy (time to first and number of appropriate and inappropriate ICD therapy, respectively, in addition as ATP and shock therapy, respectively)
- Time to first episode of VT/VF
- Persistent atrial fibrillation
- Recently diagnosed atrial fibrillation (>30 seconds recorded by the implanted device)
- Procedure time at implantation, fluoroscopy time and dose
- Number of LV leads used at implantation
- Device-related complications (periprocedural: lead re-operation, pneumothorax, hemothorax, pericardial bleeding/tamponade and later (30 days post implantation): LV lead re-operation, device replacement due to battery depletion, and infection requiring extraction)
- Battery longevity (measured by [1]number of device replacements during the study period due to battery depletion and [2] device battery longevity + estimated remaining device battery longevity as reported by the device at last study follow-up)

Study design:

Double-blind randomised controlled trial. Patients are included and randomised 1:1 into two groups for implantation of 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, non-apical position (***control group***).

Pre-operative examinations to be carried out **in all patients in both treatment arms**:

- Echocardiography for identification of large areas of scar tissue (defined as areas of aneurysme or depleated and akinetic areas) and of the latest activated LV segment
- CT scan for visualisation of the CS branches. No CT-based scar tissue determination is done prior to implantation

In both groups the implanting physician is provided with information on large areas of scar tissue, and in which LV segments. The implanting physician may access the echocardiography to assess scar tissue localisation. The purpose of the echocardiography is to avoid placing the LV lead directly in scar tissue at implantation.

Moreover, determination of the latest LV activation by echocardiography will be used ***post-operatively*** to compare the findings from the electrical activation used during implantation with the pre-operative echocardiography findings. The implanting physician will have no knowledge of the latest activated LV segment as determined by echocardiography prior to implantation. No advanced scar-tissue-analysis will be done by echocardiography before implantation.

At implantation the implanting physician will be able to see the CT scan with visualisation of CS branches from all patients in both groups.

Cardiac MRI may be done for substudy purpose. The implanting physician will have no knowledge of the results of the MRI scan prior to implantation.

Device implantation

In all patients in both treatment arms the RV electrode is placed in a right ventricular septal position, preferentially. Based upon the implanting physician's discretion, an apical position can be chosen taking into consideration the stability of the electrode, electrical values and defibrillator vector. Atrial electrodes are positioned according to the implanting physician's preference.

In all patients in both groups a multipolar (quadripolar) LV lead is used as first choice. However, the implanting physician may change to a bipolar LV lead if a multipolar lead cannot be implanted.

The intervention group: In all patients, a balloon occlusion venography of the coronary sinus will be done during the procedure. Supplementary, selective venography may be used to visualise all the CS branches from the CT scan. The local electrical activation is measured and recorded in ***all potentially accessible branches of the coronary sinus*** (all CS branches, where a LV lead may be positioned), basal, mid-ventricular and apical, and the LV lead is positioned in the CS branch according to the latest local electrical activation, considering acceptable stability, pace threshold and threshold for phrenic nerve stimulation. Guided by the echocardiography, positioning of the LV lead directly in scar tissue is avoided, if possible (see figure 1-3). Mapping is done using the LV lead or/and a guidewire (e.g. Vision wire, Biotronik). Number of mapped CS branches, LV lead target branch, and position in the branch (apical, mid-ventricular or basal) is recorded. The implanting physician will judge, whether mapping can be done using the LV lead, or a supplementary guide wire must be used. Likewise, in each case, the implanting physician will judge the limit for additional operation time and fluoroscopy used for mapping and LV lead placement in each patient.

- In patients with true LBBB mapping is done under the patient's native ventricle activation (LBBB).
- In all other patients the electrical activation in the CS branches is mapped under RV pacing.

In rare cases a very long latency from pacing at the LV lead to start of the generated QRS can be observed. In these cases, where latency exceeds 60-70 ms, and correction for this by programming the VV interval is deemed impossible (and the desired resynchronisation of the contraction therefore not possible), the LV lead is placed according to latest LV activation where this phenomenon is not found.

The control group: In all patients, balloon occlusion venography in the coronary sinus is done during the procedure. Subsequently 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, non-apical position, and taking into consideration stability, pace threshold and threshold for phrenic nerve stimulation. Here too, positioning directly in scar tissue is avoided, if possible. Mapping for late activation is not done in this group. See figure 4.

In both treatment arms: In all patients, fluoroscopic images/film of the position in two planes (LAO 40-60^{o} and RAO 30-40^{o}) of the three leads is recorded and saved by the end of the procedure. Operation time (first

incision - last suture) and fluoroscopy time and dose are recorded. Time used for mapping of CS and positioning of the LV lead is recorded.

After implantation, the VV interval (the interval from pacing in the right ventricle until pacing in the left ventricle) is set for the narrowest possible QRS. The AV interval is set short enough to avoid fusion between the biventricular pacing and the intrinsic ventricular activation.

The day after the implantation, the delay of activation of LV where the LV lead is positioned is measured in all patients (at that time, the lead is expected to be in a stable position that might be a little different from immediately after the implantation). In LBBB patients the interval from RV sensing to LV sensing is measured, in all other patients RV pacing to LV sensing is measured (use device-programmer).

CT scan: In all patients, a contrast-enhanced CT scan for visualisation of the CS branches and later definition of LV scar tissue is done prior to implantation. Moreover, a flash CT scan without contrast is done in all patients after implantation, prior to discharge for a precise determination of the lead positions (14). In patients with significantly reduced renal function (estimated GFR <30ml/min/1.73 m^2) the pre-operative contrast-enhanced CT is omitted, but the post-operative CT without contrast is done.

Randomisation 1:1, stratified for [a]true LBBB, [b]other BBB and [c]RV pacing (identification of the latest activated LV segment may be especially important in patients without true LBBB). Randomisation is done web-based in the case-record form used for data collection. Block-randomisation is used to ensure that each centre includes a similar number of patients in each treatment group (blocks of 10+10 for LBBB and RV pacing, 5+5 for other BBB). Randomisation takes place after informed consent has been obtained and before device implantation.

Blinding: The implanting physician knows the randomisation arm in order to provide the correct treatment. The patients will not know the randomisation arm. Follow-up is done equally in the two treatment groups, by other health personnel than the implanting physician, and blinded for randomisation and treatment (intervention or control). The primary endpoint and cause of death is adjudicated by an endpoint committee blinded for randomisation and treatment (intervention or control).

Recruitment/obtaining informed consent:

Eligible study candidates are found among patients who are admitted for CRT implantation and meet the inclusion criteria. Typically, the first contact will be made in the department the day before the procedure. A short oral introduction will be given by a doctor or nurse related to the study. If the potential candidate is interested, an informative interview is scheduled. The patient is advised about the right to have an observer present at this interview (a family member, a friend, or a member of the staff with no relation to the study). The written information is handed over to ensure that the patient has sufficient time for reading prior to the interview. The informative interview takes place in the patient's ward and is carried out by a doctor or nurse related to the study. If the interview can not be undisturbed in the ward, it is done in another quiet place. During the interview the patient will have sufficient time to listen to the oral information and ask questions. It will be possible to have at least 24 hours for reflection before giving informed consent. A copy of the written consent is handed over to the patient.

Follow-up:

Patients are followed prospectively and primary and secondary endpoints recorded. Clinical follow-up is scheduled after 3, 6 and 12 months, subsequently annual appearance. Moreover, all patients are followed by remote monitoring of their CRT device. This ensures early detection of technical issues and some clinical problems and is current standard for CRT-D devices.

Echocardiographic follow-up plus 6MWT and NYHA classification is scheduled after 6 and 24 months. See supplementary protocol on study imaging.

Post implantation, prior to discharge, and in the set device mode (DDD or VVI) ECG-12 with CRT, ECG-12 with pure RV pacing, and ECG-12 with pure LV pacing are recorded. At each follow-up ECG-12 is recorded when the patient arrives, with the existing device settings. The interval from RV pacing to activating the LV lead is measured at each follow-up visit. ECG's are recorded and stored digitally.

At each visit, the patient's current medication is recorded.

Patient-reported outcomes (PRO's):

At baseline and again after 6, 12, 24 and 48 months the following questionnaires will be used:

Kansas City Cardiomyopathy Questionnaire (KCCQ-12), 12 items

Patient Health Questionnaire (PHQ-9), 9 items

Generalized Anxiety Disorder (GAD-7), 7 items

At baseline in addition:

Expectations towards ICD therapy (EXPECT-ICD), 10 items

Brief Illness Perception Questionnaire (BIPQ), 9 items

Resulting in 47 items at baseline and 28 items after 6, 12, 24 and 48 months.

Details regarding PRO's shown in the PRO-appendix.

All patients are followed until the last included patient has been followed for at least 2 years.

If, at 3 months after implantation, there is no clinical response (defined as "*no improvement in NYHA class **and** <10% improvement of the 6MWT walking distance*") AV and VV optimisation guided by echocardiography is done in both groups. A separate protocol will be prepared for this optimisation.

In patients, who develop or have persistent atrial fibrillation, where sinus rhythm is not immediately obtained by medication and/or by DC cardioversion, there is a risk of a large frequency of intrinsic conducted ventricular activations without effective CRT. If effective CRT drops to <95% the patients are offered ablation of the AV node (His-ablation) or pulmonary vein isolation at the follow-up physician's discretion for the purpose of re-establishing effective CRT close to 100% of the time. If patients develop frequent ventricular extrasystoles that compromise effective CRT (to <95%), ablation for ventricular extrasystoles or medical antiarrhythmic treatment is offered at the follow-up physician's discretion. Atrial fibrillation and ventricular extrasystoles are handled equally in the two treatment arms.

Sample size:

Power calculation:

Based on previous studies as well as data from the CRT population at Aarhus University Hospital, Skejby (n=1600) it is assumed that 35% of the population will reach the primary endpoint "death or non-planned hospitalisation for heart failure" within a period of 4 years. Based also on the above mentioned randomised controlled trial of 182 patients and up to 3 years of follow-up, and on the result of the DANISH study, this seems realistic (15). Half of these endpoints are expected to be deaths and the other half of non-planned hospitalisation for heart failure. To show a relative reduction of 25% in the incidence of this endpoint (to an absolute 26%) with $\alpha=0.05$ and $1-\beta=0.80$, n=432 patients must be included in each group. Given these

assumptions, 264 primary endpoints will occur during the study period. Assuming that no more than 10% of the patients withdraw during the study period, it will be sufficient to **include n=500 patients in each group**. Thus, a total of n=1000 patients need to be included in the study. The study is not designed to detect a significant reduction in mortality.

If, alternatively, one wanted to show a 20% reduction (from 35% to 28%), 719 patients should be included in each group (453 primary endpoints), 1500 patients in total. If one wanted to show a 30% reduction (from 35% to 24.5%) 315 patients should be included in each group, 700 in total.

Data analysis:

The primary analysis is carried out as an intention-to-treat analysis (patients randomised to the intervention group are compared with patients randomised to the control group without regard for their actual treatment). The primary data analysis will present time to the primary endpoint in Kaplan-Meier curves for each treatment group and if relevant stratification variable. Hazard ratio for reaching the primary endpoint in the intervention group relative to the control group is calculated by use of Cox regression model. Supplementary, restricted mean survival time is calculated.

Besides a non-adjusted analysis, also an analysis adjusted for age, gender, QRS morphology (LBBB/non-LBBB/RV paced), QRS width (≥150 ms /<150 ms), NYHA class (II/III or outpatient IV), underlying disease (IHD/non-IHD determined heart failure), as well as including centre is done.

Subgroup analyses of the primary endpoint are planned for patients

- with different gender
- with higher and lower age (around the median)
- with QLV (time from QRS start to local LV activation where the LV lead is positioned) above/below the median value, respectively
- in NYHA class II and III/outpatient IV, respectively, at baseline
- with baseline LVEF above/below the median value, respectively
- with ischaemic and non-ischaemic background for heart failure, respectively
- with LBBB and non-LBBB, respectively
- with upgrade from RV pacing to CRT and primary implantation of CRT, respectively
- with the RV lead in a septal and non-septal position, respectively (RV lead position determined by flash CT after implantation)

- with the RV lead in an apical and non-apical position, respectively (RV lead position determined by flash CT after implantation)
- with and without echocardiography detected dyssynchrony, respectively (radial time-to-peak, cross-correlation and pattern-analysis) of LV
- scar tissue/perfusion evaluation by CT scan. Total percentage of scar tissue (higher/lower than median) as well as impact of scar tissue localisation with regard to the site of LV lead position (LV lead close to scar (in or in neighbour-segment in a 17-segment model of LV) or remote to scar.

Analysis for statistical interaction is done with respect to the subgroup-analysis above and presented graphically in a Forest plot.

Secondary endpoints are compared in a similar way using Cox regression or multipel linear or logistical regression analysis. In datasets with repeated measures, ANOVA is used. Whether data are normally distributed or not and whether single or repeated data determinations exist are taken into consideration. If relevant, competing risk is adjusted for in the analyses.

A p-value <0.05 is considered significant in two-sided test.

Adjudication of endpoints:

Monthly during the study/follow-up, the study secretariat will verify vital status for all included patients through the Civil Registration System (CPR). In case of death, the centre following the patient will gather information on the death from the patient's GP and from other hospitals/departments, if relevant. This information will be forwarded to the study secretariat coordinating the adjudication of endpoints. A copy of the death certificate is obtained, unless the cause of death is known (e.g. during hospital admission).

The endpoint committee consists of the members of the steering committee.

All hospitalisations are adjudicated by the endpoint committee, blinded for randomisation and actual treatment for the purpose of determining, whether it is a non-planned hospitalisation for heart failure. In practice, all required information (hospital records, description of echocardiography, x-ray images etc.) will be forwarded to two members of the endpoint committee, both from other centres than the one where the patient is followed or was admitted. These two will judge, whether the patient has reached the endpoint "non-planned hospitalisation for heart failure" (and thus the primary study endpoint) and will record this in the CRF. In case of disagreement among the two adjudicators a third member of the endpoint committee will be involved, also from another centre than the one following the patient. The adjudication

will then be based on the majority among the three members of the endpoint committee. The same procedure applies to adjudication of cause of death by the endpoint committee.

Data collection and processing:

The study is notified to the Danish Data Protection Agency the Region's common notification system, and the Danish Act on Processing of Personal Data will be observed during the study.

Clinical data with no personal identifiers will be disclosed to the study in anonymised form. All data collected in relation to the study will be used solely for research purposes. In case of hospitalisation for heart failure or recording of deaths possibly related to the study treatment, this information will be disclosed from the patient files to the study. Likewise, information from the patients' regular pacemaker or ICD follow-up will be disclosed to the study investigators during the study period for the purpose of recording incidences of therapy from the implanted device as well as detection of arrhythmia (atrial fibrillation) by the device. Furthermore, information on the electrical function of the device will be disclosed.

Ethical considerations, including side effects, risks and inconveniences

The study is conducted in accordance with the latest version of the Declaration of Helsinki (2013). The study will be approved by the Ethics Committee of Central Denmark Region. The study will be reported to ClinicalTrials.gov prior to initiation.

A standard implantation of a CRT system is associated with a non-negligible risk of complications (16). It is unknown, whether this risk will be higher in the intervention group, where mapping of the activation in CS is done. This 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 the complication risk with respect to CS dissections/perforations, bleedings or infections. In a pilot study at Aarhus University Hospital, we recorded no more complications at procedures including mapping of activation in the CS branches. In the present planned study, all implantation related complications are recorded in both treatment groups. Only patients with indication for CRT according to the current guidelines are offered participation in the study. Based on the existing literature, it is expected that the intervention including positioning of the LV lead after mapping of the CS branches will potentially increase the percentage of patients that benefit from CRT and improve the prognosis in the patient cohort treated with CRT. A positive

study result confirming the study hypothesis will lead to a changed implantation strategy in patients with indication for CRT, nationally and internationally.

Fluoroscopy dose: At the pre-operative CT scan the patients are exposed to a fluoroscopy dose of 6-24 milliSievert (mSv) dependent of weight, height and heart rhythm. At the post-operative flash CT they are exposed to another 2 mSv, approximately. Thus, the total effective fluoroscopy dose at these CT scans constitutes 8-26 mSv. Such fluoroscopy dose is not deterministically injurious but subjects the patients to a stochastic radiation exposure injury. In a healthy younger than 50-year-old, a fluoroscopy dose of 20 mSv will increase the risk of dying from cancer from 25% to 25.1%. The mean age for CRT patients is approx. 65 years, 90% are older than 50 years, and patients younger than 41 years are excluded. In comparison, the mortality rate in patients with severe heart failure and CRT indication is approx. 20-25% after five years, and more effective CRT treatment bears the potential to significantly increase lifetime and improve the patients' Quality of Life considerably. According to the guidelines for the use of ionising radiation in health research projects >90% of the patients (the >50-year-old) are in risk category IIb, and the younger than 50-year-olds (<10%) in risk category III. In the light of the potential benefit from improved CRT treatment the described radiation risk is considered justifiable.

Participating centres:

All Danish CRT-implanting centres (Gentofte Hospital, Odense University Hospital, Rigshospitalet, Aalborg University Hospital, Aarhus University Hospital (coordinating centre)).

A collaboration between CRT-implanting physicians, heart failure specialists, and specialist in cardiac imaging (echo, CT).

Rigshospitalet is core lab for echocardiography and CT-derived data.

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Is the DANISH-CRT study feasible?

At present 950 CRT P/D implantations per year are performed in Denmark. It is estimated that at least half of these are eligible for a study as described here. Thus, we should be able to include 1000 patients within a maximum of 3½-4 years. At Aarhus University Hospital, mapping of the CS branches at CRT implantation is currently being investigated in a pilot study and provided the willingness to spend additional time on the implantations such a study set-up is feasible. Echocardiography and CT may be done in a clinical context in the departments.

We aim at financing a research nurse 20 hours/week at each CRT centre throughout the 6-year study period.

Information, inclusion and follow-up may be performed primarily by research nurses. Echocardiography will be performed by technicians/doctors. No need for PhD students for inclusion and coordination of pre-implantation imaging and analysis.

Aarhus University Hospital holds an internet-based CRF that can easily be extended and used for this study.

Is the study interesting?

The study will answer the question, whether mapping of LV activation in CS and positioning of the LV lead according to the latest local electrical activation is beneficial for the patient. Based on small studies in the literature, some physicians already search for late activation when implanting CRT systems, but the effect of this strategy has not yet been tested in a randomised controlled trial. The endpoint is clinically relevant and has been previously defined in correlation with heart failure and CRT. Dimensioning of the study is realistic.

The study can be conducted in a national collaboration. Recently, the study group completed the DANISH study in a national collaboration (15). In Denmark, CRT treatment is centralised to few high-volume centres, relatively high-volume physicians, and with a well-organised follow-up, feasible to complete including home monitoring in 95% of the enrolled CRT patients. Something that is quite extraordinary in an international perspective.

Data (imaging, electrical data, and clinical data) collected during the study period and the prospective clinical follow-up in a large randomised controlled trial will create the basis for a series of studies and PhD courses for young physicians in all participating centres nationally.

Searching Clinical Trials gives no indication that a similar study is in the pipeline.

Publication:

The study is expected to result in a series of publications in international recognised peer-reviewed journals. The results will be published whether positive, negative, neutral or inconclusive. The main publications will include co-authors from the steering committee representing all participating centres. Primary investigator in the study will prepare the draft manuscript and will be first author. All other authors will be involved in data analysis and interpretation as well as manuscript revision and approval. In subsequent work the author group will consist of investigators actively contributing to data collection, analysis and preparation of the manuscript. As a rule, co-authors from each actively contributing centre will be included.

Economics:

DANISH-CRT is an investigator-initiated study based on a scientific collaboration between physicians from all CRT-implanting hospitals in Denmark.

Budget (6 years):

Secretariat (AUH):	200.000 DKK/year for 6 years	1.200.000 DKK
Research nurses:	20h/w (200.000 DKK/year) in each centre for 6 years	6.000.000 DKK
CRF construction and support:		50.000 DKK
Meetings:	10.000 DKK/year	60.000 DKK
Echo and CT analyses (technician salary): 1.000 DKK/patient (3 hours/patient)		1.000.000 DKK
Transfer of images:	100 DKK/patient	100.000 DKK
Storage capacity for images created in the study, server etc.		59.000 DKK
Total		**8.469.000 DKK**

Raising such a budget is realistic. The study organisation will apply the Danish Heart Foundation, the Danish Council for Independent Research and private foundations for financial support. Moreover, the device industry will be asked to support the study financially.

It is not realistic to raise funds for reimbursement to the centres for each enrolled patient (apart from financing the research nurse).

The investigators do not benefit financially from the study and are not associated with the expected funders, except for membership of the Danish Heart Foundation and the Danish Heart Foundation Research Council (Lars Køber and Jacob Møller).

The patients will receive no remuneration for their participation in the DANISH-CRT study.

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Implantation in the intervention group:

The RV lead is implanted.

In case of true LBBB mapping is done under native activation. In all other patients, mapping of the local electrical activation in the CS branches (Figure 1) is done under RV pacing at a frequency of at least 80/min (must always exceed the patient's native rhythm by at least 10/min). The LV lead or/and an electrically active guidewire (e.g. Vision wire, Biotronik) may be used at the discretion of the implanting physician. The interval in milliseconds from RV sensing (at LBBB and native activation) or pacing to sensing locally in the CS branches is measured using Prucka system or similar ECG recording equipment or device programmer. Measurement proceeds until a vertical, sharp deflection in the electrocardiogram (Figure 2). Measurement is done throughout the course of the vein (basal, mid-ventricular and apical, if possible). The implanting physician will judge the reasonable additional operation time and fluoroscopy used in each patient.

The LV lead is placed with the poles used for pacing corresponding to the latest local activation in the CS branches (Figure 3).

Figure 1

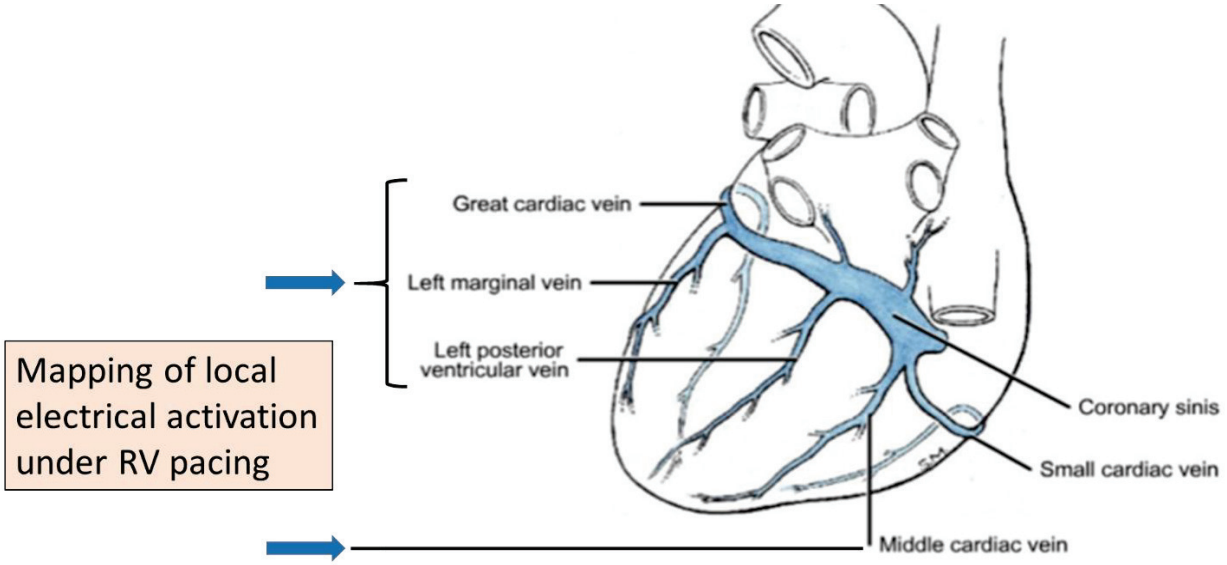


Figure 2:

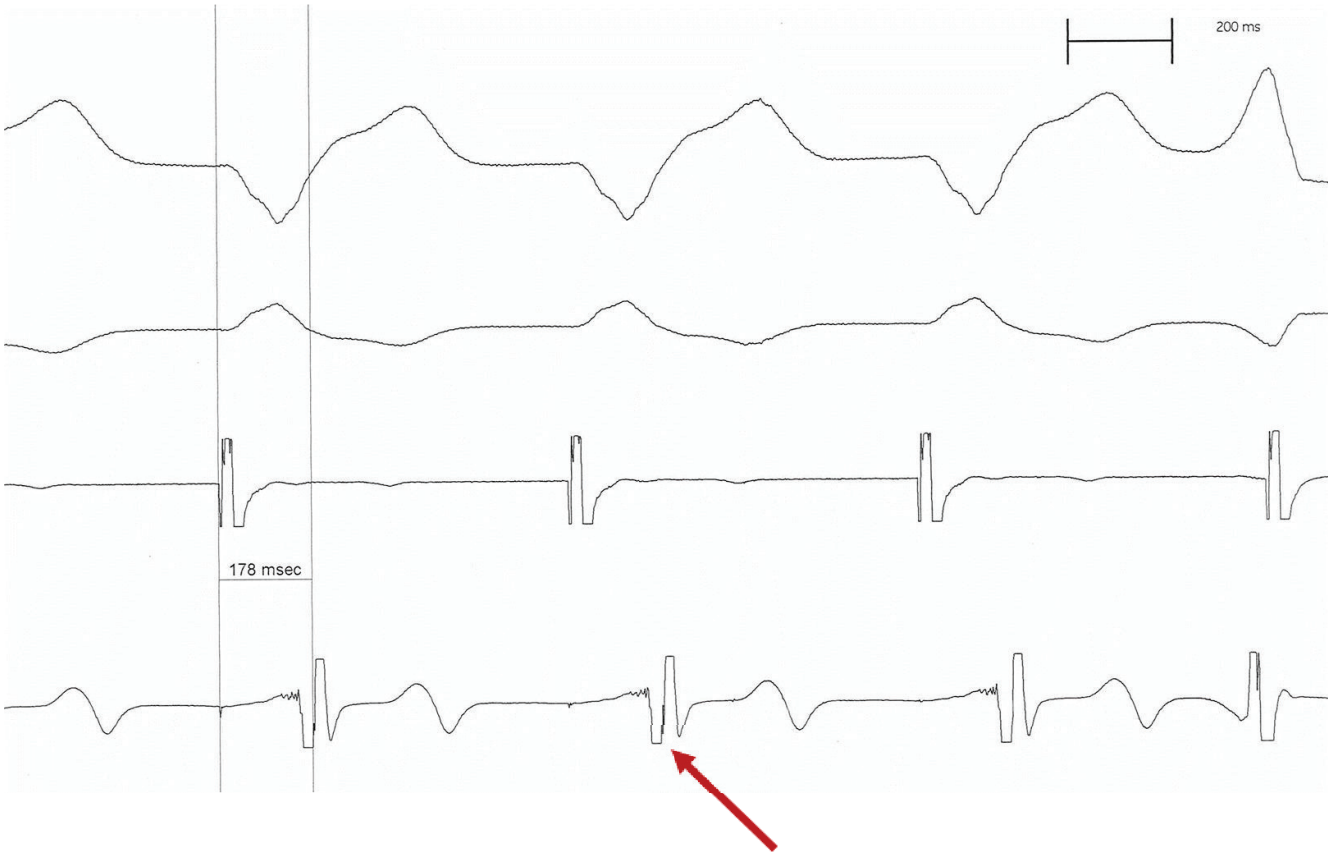
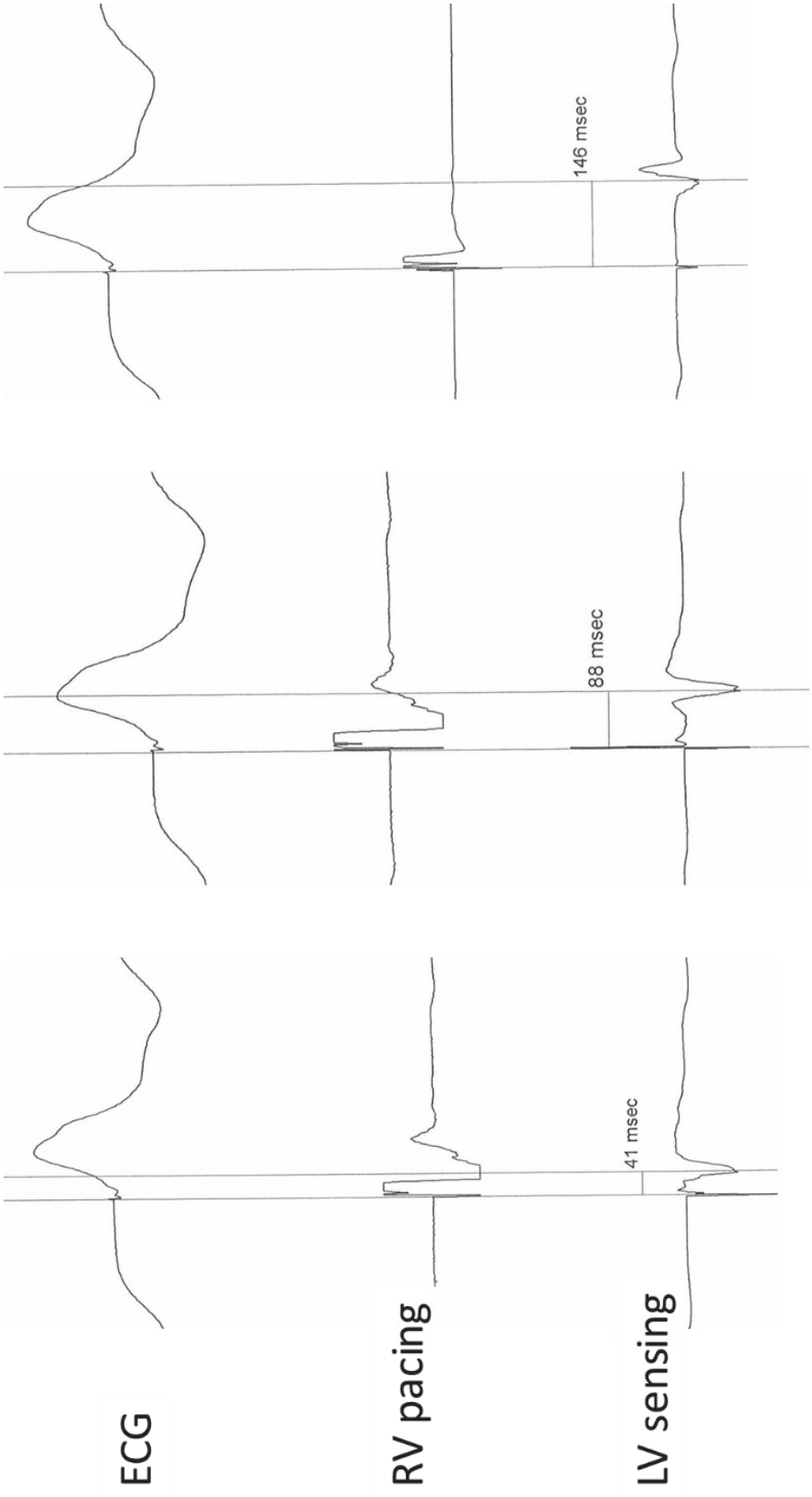


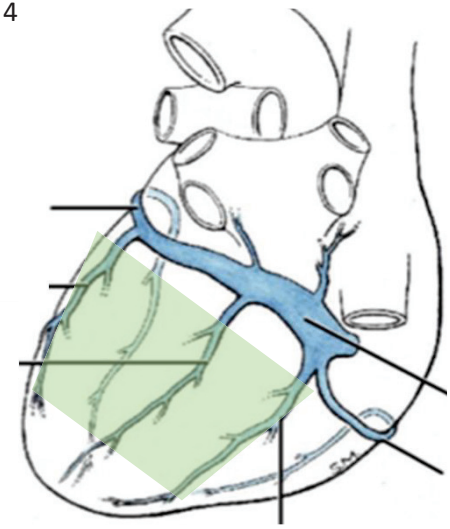
Figure 3

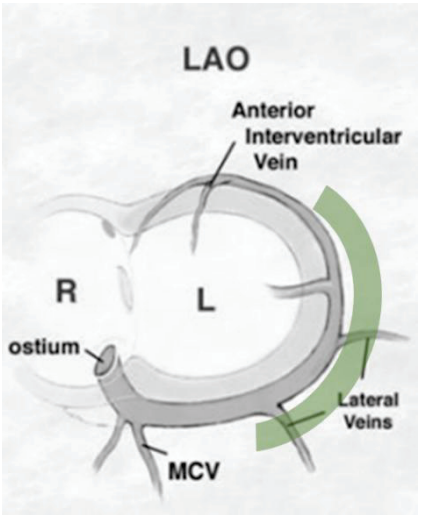


Implantation in the control group:

Preferentially, the LV lead is positioned basal or mid-ventricular (green area in figure 4, left), non-apical, and posterolateral 2-5 o'clock in mitral annulus (indicated in green in figure 4, right).

Figure 4





Example of pre-implantation CT scan showing the CS branches: