Rationale and design of the Karolinska-Rennes (KaRen) prospective study of dyssynchrony in heart failure with preserved ejection fraction

Erwan Donal[1]*, Lars H. Lund[2], Cecilia Linde[2], Magnus Edner[3], Stéphane Lafitte[4], Hans Persson[3], Fabrice Bauer[5], John Öhrvik[2], Pierre-Vladimir Ennezat[6], Camilla Hage[2], Ida Löfman[2], Yves Juilliere[7], Damien Logeart[8], Geneviève Derumeaux[9], Pascal Gueret[10], and Jean-Claude Daubert[1]

[1]Cardiology, CHU Pontchaillou, 35033 Rennes, France; [2]Cardiology, Karolinska University Hospital, Stockholm, Sweden; [3]Cardiology, Danderyd University Hospital, Stockholm, Sweden; [4]Cardiology, Haut-Lévêque University Hospital, Pessac, France; [5]Cardiology, Charles Nicolle University Hospital, Rouen, France; [6]Cardiology, Hôpital Cardiologique, CHU Lille, France; [7]Cardiology, CHU Nancy, France; [8]Cardiology, Hôpital Lariboisière, Paris, France; [9]Cardiology, Hôpital Louis Pradel, Lyon, France; and [10]Cardiology, CHU Henri-Mondor, Créteil, France

Aims	Heart failure with preserved ejection fraction (HFPEF) is common but not well understood. Electrical dyssynchrony in systolic heart failure is harmful. Little is known about the prevalence and the prognostic impact of dyssynchrony in HFPEF.
Methods and results	We have designed a prospective, multicenter, international, observational study to characterize HFPEF and to determine whether electrical or mechanical dyssynchrony affects prognosis. Patients presenting with acute heart failure (HF) will be screened so as to identify 400 patients with HFPEF. Inclusion criteria will be: acute presentation with Framingham criteria for HF, left ventricular ejection fraction $\geq$ 45%, brain natriuretic peptide (BNP) > 100 pg/mL or NT–proBNP > 300 pg/mL. Once stabilized, 4–8 weeks after the index presentation, patients will return and undergo questionnaires, serology, ECG, and Doppler echocardiography. Thereafter, patients will be followed for mortality and HF hospitalization every 6 months for at least 18 months. Sub-studies will focus on echocardiographic changes from the acute presentation to the stable condition and on exercise echocardiography, cardiopulmonary exercise testing, and serological markers.
Conclusion	KaRen aims to characterize electrical and mechanical dyssynchrony and to assess its prognostic impact in HFPEF. The results might improve our understanding of HFPEF and generate answers to the question whether dyssynchrony could be a target for therapy in HFPEF.
Keywords	Heart failure • Preserved ejection fraction • Diastolic dysfunction • Dyssynchrony • Echocardiography

Introduction

Congestive heart failure (CHF) affects about 2% of the western population, with prevalence increasing sharply from 1% in 40-year-olds to 10% above age 75, and it is the most common cause of hospitalization in patients over 65 years of age. CHF is defined as a syndrome characterized by impaired ability of the heart to fill with and/or to eject blood, resulting in a classical constellation of signs and symptoms.[1]

Heart failure with preserved ejection fraction (HFPEF) is increasingly being recognized as a pathophysiological entity.[2] The proportion of patients with HFPEF is about 50% in the general heart failure (HF) population.[3,4] These patients were previously classified as having diastolic heart failure (DHF) or HFPEF. However, DHF has its own definition[1–3] and may not be strictly identical to HFPEF. HFPEF can be defined as an ejection fraction (EF) $\geq$ 45%, $\geq$ 50%, or $\geq$ 55%.[2] The prognosis of HPPEF in epidemiological surveys is nearly as poor as for systolic heart failure (SHF), but

in clinical trials of HFPEF (PEP-CHF, CHARM-preserved), the prognosis is much better than in clinical trials of SHF.[5,6]

Ventricular dyssynchrony in SHF is frequent and portends a worse outcome.[7] Electrical dyssynchrony as indicated by prolonged QRS duration ($\geq$120 ms) and/or left bundle branch block (LBBB) is present in approximately 30% of patients.[7] In HFPEF, the prevalence of electrical and/or mechanical dyssynchrony during systole and/or diastole ranges from 10% to 60%.[7–11] The prognostic significance of QRS-prolongation and of parameters of mechanical dyssynchrony has, to the best of our knowledge, not yet been evaluated in patients with HFPEF. In one of the few prospective studies including HFPEF patients, notably the CHARM-preserved population, the simple finding of a LBBB had a modest, or possibly no predictive impact on cardiovascular death or hospitalization for HF after a mean follow-up of 38 months.[12]

Methods

Study purpose

The main purpose is to test the independent prognostic (mortality and hospitalization for HF) value of electrical and/or mechanical dyssynchrony after a follow-up of 18 months.

Study design

KaRen is a prospective, European, multicenter study of consecutive patients presenting with acute signs and symptoms of HF and a preserved EF. Over a 2-year period, patients presenting acutely with HF will be screened, and patients will be included based on symptoms, brain natriuretic peptide (BNP) or NT-proBNP, and EF in the acute state. Patients will return to a stable state 4–8 weeks later for detailed echocardiography and assessment of dyssynchrony, clinical examination, ECG, quality-of-life questionnaires, and serology. Sub-studies will include a detailed echocardiography also during the acute presentation, cardiopulmonary exercise (CPX) testing, as well as serology markers for myocardial fibrosis. Follow-up will be performed through phone call every 6 months until the end of the study (Figure 1). KaRen involves no intervention. Patients will be managed routinely by their own physician. The study conforms to the Declaration of Helsinki and has been approved by French and Swedish ethics committees and by the CNIL (Comité National Informatique et Libertés) in France.
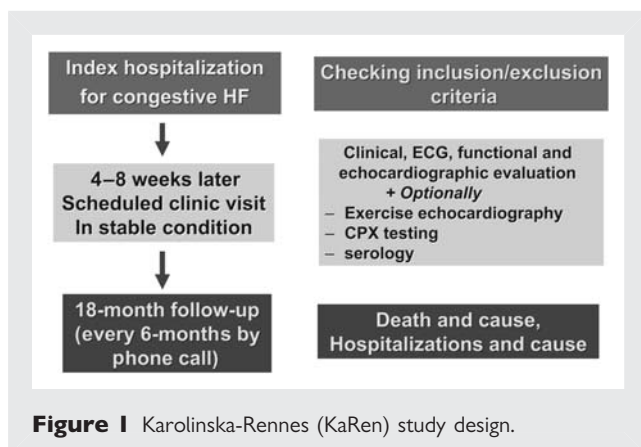
Figure 1 Karolinska-Rennes (KaRen) study design.

Inclusion/exclusion criteria

The study protocol was designed to enrol a patient population with HF symptoms similar to those observed in epidemiological and community-based studies. In practice, inclusion criteria are similar to those used in major recent or ongoing studies in HFPEF, principally the I-PRESERVE study[13,14] with NT-proBNP (BNP) threshold values being defined from the CHARM data.[5,6,13,15–18]

Detailed exclusion criteria are given in Table 1.

The inclusion criteria are as follows:

(1) Acute presentation to the hospital with clinical signs and symptoms of HF, according to the Framingham criteria.[19]
(2) BNP > 100 pg/mL or NT-proBNP > 300 pg/mL.
(3) LVEF $\geq$ 45% by echocardiography within the first 72 h. The measurement will be carried out according to guidelines.[20]

All inclusion criteria (clinical HF, EF, and peptide criteria) must be established within 72 h of presentation. Enrolment will occur during this time or shortly thereafter, after the presence of any of the exclusion criteria has been ruled out.

Key assessments performed 4–8 weeks after index event

All events including length of hospitalization and potential re-hospitalization will be recorded. Any re-admission prior to the 4–8-week follow-up will delay the follow-up to 4–8 weeks from that admission.

Clinical parameters

Physical exam, history since the index presentation, and serology including peptides will be collected.

Functional assessment

Patients will be evaluated by the 'Minnesota Living with Heart Failure questionnaire', a 21-item disease-specific instrument with scores ranging from 0 to 5 and with a summary score ranging from 0 to 105, the highest score representing the worst health-related quality-of-life. There are two specific health-related quality-of-life domains: physical limitations (maximal score = 40) and emotional limitations (maximal

Table 1 Key exclusion criteria for patients in the Karolinska-Rennes (KaRen) study

(1) Evidence of primary hypertrophic or restrictive cardiomyopathy or systemic illness known to be associated with infiltrative heart disease
(2) Known cause of right heart failure (HF) not related to left ventricular (LV) dysfunction
(3) Pericardial constriction
(4) Clinically significant pulmonary disease as evidenced by requirement of current home oxygen
(5) End-stage renal disease currently requiring dialysis
(6) Bi-ventricular pacemaker (cardiac resynchronization therapy) (patients who have a conventional pacemaker may be included)
(7) Anticipated or indication for cardiac surgery (patients who have indication for surgery but may not undergo surgery because of some contraindication, for example age, may not be included)
(8) Anticipated percutaneous intervention on aortic stenosis (patients who undergo other percutaneous intervention, for example percutaneous coronary intervention, may be included)

score = 25). Validity, reliability, and reproducibility of the Minnesota questionnaire have been established and both a French and a Swedish version exists.[21] The questionnaire will be filled in by each subject at the inclusion visit prior to other assessments, the subject being alone in a quiet environment.

This functional assessment will be complemented using the EuroQOL.[22]

Electrocardiogram

A 12-lead surface ECG will be recorded at 50 mm/s speed. The following parameters will be analysed centrally (Karolinska University Hospital, Stockholm, Sweden): rate, rhythm, intervals (P-wave duration, PR, QRS, QT, QTc), axis (QRS), and morphology [P-wave, QRS: (LBBB, right bundle branch block, intraventricular conduction delay), abnormal Q wave, ST-T changes]. QRS duration is defined as the duration of the widest QRS complex.

At least 10 beats will be requested in patients with atrial fibrillation and 5 in patients with sinus rhythm. Dyssynchrony will be defined as QRS ≥ 120 ms, but patients will be analysed according to QRS width as a continuous variable and in 10 ms increments.

The definition of electrical dyssynchrony is a QRS > 120 ms in accordance with the current ESC guidelines.[23]

Echocardiography

Technical requirements

Each echocardiographic examination will be performed according to a checklist using the same machine (ViVid Seven, GE Healthcare, Horten, Norway). The quantitative analysis will be conducted in a 'Core Lab' (Rennes University Hospital, France). Specific attention will be given to the quality of echocardiographic images and of the ECG traces. In patients with atrial fibrillation, at least 10 beats are required for each recording.

The recent PROSPECT trial drew attention to the difficulty of assessing mechanical dyssynchrony with sufficient reliability.[24] As requested in the recent ESC guidelines for cardiac pacing and resynchronization therapy,[23] all examinations for dyssynchrony assessment will be performed by experienced echocardiographers (at least 50 exams per year investigating dyssynchrony). In addition, a pre-study validation of each echocardiographer will be performed.

Table 2 Diastolic dysfunction characterization according to echo-Doppler information

	Mitral inflow	Pulmonary venous inflow	E/Ea
Normal	0.75 < E/A < 1.5 DT > 160 ms	S > D MV A-dur > PV A-dur	<10
Mild LV diastolic dysfunction	E/A < 0.75 DT > 240 ms	S > D MV A-dur > PV A-dur	<10
Moderate LV diastolic dysfunction	0.75 < E/A < 1.5 DT > 160 ms	S < D MV A-dur + 30 < PV A-dur	≥10
Severe LV diastolic dysfunction	E/A > 5 DT < 160 ms	S < D MV A-dur + 30 < PV A-dur	≥10

DT, deceleration time; MV A-dur, mitral valve A-wave duration; PV A-dur, pulmonary vein A-wave duration.

In addition to the study of dyssynchrony, assessment of LV diastolic function will be performed based on the variables reported in *Table 2*. Left ventricular mass, dimensions, volumes, and function will be assessed.[23] Right ventricular (RV) function will also be explored by tricuspid annulus excursion (TAPSE), pulse Doppler tissue imaging (DTI), estimated pulmonary pressures, inferior vena cava dimensions, and pulmonary pre-ejection time delay, which are also used for the calculation of interventricular mechanical delays.[25]

Dyssynchrony analysis

In addition to conventional echo Doppler data, two-dimensional (2D) loops (parasternal short axis and apical four-, two-, and long-axis views) of the LV and the RV will be recorded successively in colour-mode (frame rate > 140/s) and in conventional grey scale mode (frame rate about 75/s).

For the same purpose, a three-dimensional (3D) matrix for further 3D volumetric dyssynchrony analysis will be recorded so as to measure the systolic dyssynchrony index (SDI) according to Image Arena (TomTec Imaging Systems, Unterschleissheim, Germany).

The following measurements will be carried out:

Atrioventricular, interventricular (difference between aortic and pulmonary pre-ejection time delays), and intra-LV dyssynchrony will be first assessed by conventional Doppler echo. In 2D, left ventricular filling duration (mitral inflow), aortic, and pulmonary pre-ejection time delays will be measured.

Temporal dyssynchrony will be assessed by M-mode in parasternal and apical four-chamber view, so as to measure the time delay between the ECG Q-wave and the maximal excursion of the posterior and lateral part of the mitral annulus in systole.

Intra-LV spatial dyssynchrony will be assessed by: (i) M-mode in parasternal long- and short-axis (*Table 3*); (ii) myocardial velocity and strain curves (colour-coded DTI loops being post-processed on ECHOPAC, GE-Healthcare, Horten, Norway) in three apical views will be used to measure the time-to-peak difference within each LV wall (*Table 3*); (iii) a radial, circumferential, and longitudinal time to peak of deformation in the basal, and mid-segments of each LV wall will also be studied using the 2D-strain application; (iv) using 3D-volume information, significant intra-LV dyssynchrony will be defined by an SDI > 14%.

Systolic and diastolic intraventricular dyssynchrony will also be measured by tissue synchronization imaging analysis (TSI): TSI is a parametric imaging tool derived from the 2D tissue Doppler images. It will automatically calculate Ts (time from the beginning of the QRS complex to peak systolic velocity) in every position in the image with reference to the QRS. The operator can also manually adjust the start and end times of the TSI in order to analyse the ejection and/or diastolic phase. We will extend into early diastole (MVO + 250 ms) in order to detect dyssynchrony during this phase as well as during the ejection phase (AVO–AVC).

For the purpose of this study, mechanical dyssynchrony will be classified according to whether one, two, or three levels of dyssynchrony (inter- and/or atrioventricular and/or intra-LV) are found.

We do not have any predetermined idea of the parameters that are the most relevant in HFPEF. Different combinations of intra-LV parameters of mechanical dyssynchrony will be tested to find the best way to assess their prognostic value. We will distinguish parameters describing: radial dyssynchrony, longitudinal dyssynchrony, and 3D volumic assessment of LV dyssynchrony.

Data collection

Each investigator will enter clinical data into a web-based electronic case report form (Clinsource, Brussels, Belgium). The

Table 3 Review of the criteria currently used to characterize and quantify mechanical dyssynchrony by Doppler-echocardiography[25]

Methods	Measures	Cut-off values for dyssynchrony
Atrioventricular dyssynchrony		
Conventional Doppler	Mitral inflow duration	<40% of the cycle length
Interventricular dyssynchrony		
Conventional Doppler	Difference between aortic and pulmonary pre-ejection times	≥40 ms
Intra-LV dyssynchrony		
Conventional Doppler	Aortic pre-ejection interval during spontaneous rhythm	≥140 ms
M-Mode	Time to peak LV posterior and/or lateral wall maximal excursion > time to mitral valve opening	Overlap systole−diastole
TVI	Maximal delay between peak systolic velocities of any two of 12 LV segments	>100 ms
TVI	Maximal delay between peak systolic velocities in four LV segments	≥65 ms
TVI	Standard deviation of time to peak systolic velocity of 12 LV segments	≥33 ms
TSI	Time to peak velocities of opposing ventricular walls	≥65 ms
Longitudinal strain	Temporal difference in septal-lateral peak systolic strain	≥50 ms
Radial strain	Time difference of peak radial strain in the septum vs. the posterior wall	≥130 ms
Real-time 3D	SDI	≥14.7%

LV, left ventricular; SDI, systolic dyssynchrony index; TSI, tissue synchronization imaging analysis; DT, deceleration time.

echocardiographic analysis will be performed by the Core Laboratory. The follow-up data will be obtained and entered onto the web-based electronic case reports by dedicated research staff.

Long-term follow-up

Patients will be followed by phone call and/or chart and death registry review every 6-months for 18-months after closure of enrolment, such that all patients will have a minimal of 18-month follow-up period.

Study endpoints

The primary outcome will be all-cause death and/or hospitalization for HF. Hospitalization for HF is defined as admission to hospital for any length of time, including day-care, with either treatment of HF or for HF being the main component of the admission. Acute presentation to an outpatient clinical or emergency room that does not result in admission will be registered but not counted as a primary endpoint. Evidence of worsening HF must include at least one of the following items: increasing dyspnoea on exertion, orthopnoea, nocturnal dyspnoea, pulmonary oedema, increasing peripheral oedema, increasing fatigue or decreasing exercise tolerance, renal hypoperfusion (i.e. worsening renal function), raised jugular venous pressure, and radiological signs of CHF.

The secondary outcome will be overall mortality. This is of particular interest as one possible explanation for the high mortality observed in epidemiological surveys[15,16] is mortality from non-cardiovascular causes.

Analysis will be performed according to pre-specified subgroups as defined by parameters measured at inclusion (see Supplementary material).

Sample sizes

In unselected populations with HF, approximately 50% have HFPEF. Prognosis ranges from 8−9% annual cardiovascular mortality or hospitalization for HF over 3 years as observed in the CHARM-Preserved trial, to 22−29% overall mortality over 1 year in unselected HF populations. The prevalence of dyssynchrony in HFPEF is not well known. In the Swedish Heart Failure Registry (S-HFR), approximately 20% of patients had a QRS > 120 ms (Uppsala Clinical Research Centre) while another study reported a figure of 40%. The prognosis of dyssynchrony in HFPEF is not well-determined. In the aforementioned study, 6-month mortality or hospitalization for HF amounted to 66% in patients with dyssynchrony and to 40% in patients without dyssynchrony.[6]

Based on the above data, we estimate that in our unselected population, 50% of HF patients will have HFPEF, 20−40% of those will have dyssynchrony; we further estimate that the combined endpoint of all-cause mortality or HF hospitalization over 18 months will occur in 35−40% of patients without dyssynchrony and in 50−55% of patients with dyssynchrony. Taking these estimations as a base along with an 80% statistical power and a two-sided significance level of 5%, to detect a significant difference in the endpoint at 18 months, we would need to screen approximately 800 patients with HF so as to enrol 400 patients with HFPEF.

Statistical analysis

Patients will be analysed according to the study endpoints. Kaplan-Meier curves of event-free survival for the predefined subpopulation (no dyssynchrony, electrical dyssynchrony, mechanical dyssynchrony) will be plotted and they will be compared using the log-rank test. Any patient who is lost to follow-up will be censored from the Kaplan-Meier analysis, that is, removed from the population 'at risk' without being counted as an event. Baseline characteristics will be presented as median and quartiles for continuous variables and as number and percentage for categorical variables. Comparisons between groups for baseline variables will be made using independent sample t-tests and analysis of variance (ANOVA) for normally distributed continuous variables and Mann−Whitney U test and Kruskal-Wallis ANOVA for non-normal distributions. Partial correlation coefficients will be

calculated to assess relationships between markers and other parameters, such as echocardiography parameters. Non-normally distributed variables will be log-transformed. To determine if dyssynchrony is a significant predictor of mortality or cardiovascular hospitalization, we will first screen for univariate predictors. Secondly, a multiple Cox proportional hazards regression will be used for the best subset selection with Mallow's Cox proportional being performed, adjusting for age, gender, and other known risk factors for mortality or hospitalization. In parallel to this selection, we will focus on dyssynchrony and assess the minimal predicting combination of predictors. Age, BNP, and/or NT-proBNP (values obtained at the time of decompensation and at the scheduled hospitalization will be considered separately in the analysis) will be used in the prognostic models as important control variables. The results of the logistic regression models will be reported as odds ratios (OR) and 95% confidence intervals (CI). The discriminatory ability of the models will be compared using computed areas under the receiver-operating curve (ROC). The relationship between continuous predictors will be examined using Spearman correlation coefficients as appropriate, whereas the relationship between a categorical and a continuous predictor will be assessed using t-test analysis. Significant differences will be defined as a P-value < 0.05.

The reproducibility of echocardiographic and ECG measurements will be analysed using the intra-class correlations searching for indices ranging from 0.8 to 0.9 for the intra-observer variability, and from 0.7 to 0.9 for the inter-observer variability. The agreement between measurements performed by different observers will be analysed using the Bland–Altman method. The bias and 95% CIs will be calculated as described by Bland–Altman.

Substudies

Patients will be entered into the main trial and subsequently, after giving separate informed consent, will be entered into substudies depending on their own free choice and also on local participation in the substudies.

Extended Doppler echocardiography performed at the index event

To assess whether cardiac functions and mechanical dyssynchrony alter from the acute to the stable phase, an extended echocardiography protocol similar to that requested at the 4–8-week visit will be performed in the acute setting (first 72 h following admission or visit).

Exercise echocardiography

Patients with HFPEF may be symptomatic only during exercise. Although they may have normal diastolic parameters on echocardiography at rest, exercise can unmask signs of diastolic dysfunction and increased filling pressures.[8,26] Relaxation and/or compliance abnormalities associated with a rapid increase in LV end-diastolic pressure when exercising may explain symptoms. Furthermore, exercise echocardiography will provide a complementary assessment of electrical and mechanical dyssynchrony as evaluated in systolic HF.[27] Except for the real time 3D assessment of dyssynchrony, we intend to perform the same measurements during exercise as we do at rest. Women will not exceed 45 W and men 60 W.

Cardiopulmonary exercise testing

CPX testing with calculation of peak VO_2 consumption (peak VO_2) closely correlates with severity of HF and is the best single prognostic predictor in SHF. The HF survival score (HFSS) and the Seattle Heart Failure Model (SHFM) are the best multivariable prognostic predictors in SHF.[28] In SHF, exercise intolerance is thought to reflect both increased filling pressures (certainly a feature of HFPEF as well) and reduced cardiac output, resulting in impaired skeletal muscle function and metabolic disturbances. Little is known about these aspects in HFPEF. CPX parameters and their prognostic significance have not been studied thoroughly in HFPEF and results are conflicting.[29] Therefore, in this substudy we will look for the prognostic value of conventional parameters currently used for patients with systolic heart failure (peak VO_2, slope VE/VCO$_2$ slope).[30]

Serology

This substudy aims to characterize serum markers in order to assess HF severity and its pathophysiology. SHF is known to be associated with neuroendocrine activation, inflammation, and anabolic–catabolic imbalance.[31–33] We intend to assess the prevalence and importance of these factors in HFPEF. We will also examine collagen turn-over and determine whether an increase in collagen turn-over is correlated with markers of dyssynchrony, systolic, and diastolic function, neurohormonal activation, inflammation and anabolic–catabolic imbalance. These substudies will further improve our understanding of HFPEF, its determinants, and its prognosis.

Discussion

To our knowledge, this is the first study to describe the prevalence and prognostic impact of electrical and mechanical dyssynchrony in HFPEF. The prospective multicenter design will allow detailed assessment of many potentially important parameters in a broad population.

How to define HFPEF is still a matter of debate.[2,26] Since patients with acute decompensated HF along with HFPEF and patients with SHF share clinical similarities,[34] the clinical syndrome of acute HF will be defined by the Framingham criteria and by BNP or NT-proBNP measurement. To date, no clear BNP cut-off value has been proposed for patients with HFPEF. Among patients in the I-PRESERVE study, the median value of NT-proBNP at baseline was 339 pg/mL.[14] We have chosen relatively low cut-offs of 100 pg/mL for BNP and of 300 pg/mL for NT-proBNP so as to achieve a high sensitivity. However, this cut-off value may be adjusted depending on an intermediate analysis after 6 months.

ACC/AHA and ESC guidelines state that echocardiography is the single most useful test in the diagnosis of HF.[30] The definition of HFPEF varies and the knowledge of patient characteristics in this population is evolving. In the EuroHeart Survey, which included 6806 patients, a LVEF $> 40\%$ was considered to define HFPEF.[4] Patients with HFPEF were 4 years older on average, were more often female, had more hypertension or atrial fibrillation, and received less cardiovascular medication when compared to those with SHF. In the European Study Group on Diastolic Heart

Failure,[2] a normal LVEF was defined as LVEF > 50%. The cut-off value in defining systolic and non-systolic HF was 40% in the CHARM-preserved trial,[6] and 45% in I-PRESERVE trial.[13] In the recent OPTIMIZE-HF registry on 20,118 patients, no real difference in characteristics of HFPEF patients was observed regardless of whether the cut-off value for LVEF was >40% or >50%.[34] For these reasons, in KaRen, HFPEF will be defined as LVEF > 45%, the same as in the I-PRESERVE trial.[13]

The prognostic importance and prevalence of HFPEF has recently been recognized. The prevalence of HFPEF increased between 1987 and 2001 and mortality was similar in patients with either SHF or HFPEF. In subsequent large studies, patients with preserved/reduced EF had a 1-year mortality ratio ranging from 22/26% to 27/36%.[15,16] The 5-year survival was also similar regardless of whether the EF was reduced or not: 43/46%.[18] None of these studies provided the precise cause of death. In contrast, clinical trials of HFPEF suggest a much better prognosis. In CHARM-preserved,[6] 3-year cardiovascular mortality of HF hospitalization was only 8–9%; in PEP-CHF, 1 year all-cause mortality, or HF hospitalization was 11–15%.[5] The cause of death was unknown in most recently published registries.[15,16] Thus, it remains unclear whether HFPEF has an equally poor cardiovascular prognosis compared with SHF. Since KaRen will collect detailed data on prognosis, including causes of death and hospitalization, the principal aim of KaRen is to settle this issue.

In SHF, an inverse correlation exists between QRS duration and LVEF. As QRS duration increases, LV systolic function decreases, thereby worsening prognosis.[3,34] Large multicenter trials including patients with moderate to severe SHF have established the value of electrical dyssynchrony (QRS $\geq$ 120 ms) as an outcome marker and in selecting candidates for cardiac resynchronization therapy (CRT).[23] The presence and prognostic implications of electrical dyssynchrony in HFPEF are less clear. The baseline characteristics of the I-PRESERVE study showed that LBBB (QRS > 120 ms) was present in 9.1% of the 4133 patients.[14] Our study aims to prospectively investigate the prognosis of HFPEF patients by examining mortality and cardiovascular events. It should be possible to determine whether electrical and/or mechanical dyssynchrony have a significant and an independent impact on prognosis.

Cardiac dyssynchrony will not only be defined on the basis of QRS width. Mechanical dyssynchrony will also be analysed by means of echocardiography. We have designed the protocol by taking into account the results of recent multicentre studies using echocardiography.[24] Several Doppler echocardiography techniques have been used to explore cardiac dyssynchrony.[25] However, despite numerous studies, no single echocardiographic criterion has been validated and proven clinically useful for predicting individual patient response to CRT.[25] Our study may be able to demonstrate that dyssynchrony can be reliably assessed by echocardiography. The HFPEF population might prove easier to explore than the SHF population, as contractility is only weakly depressed and LV non-enlarged. Consequently, Doppler echocardiography criteria could prove easier to collect. Furthermore, mechanical dyssynchrony will be defined by a multi-parametric approach. Patients will be classified according to the presence of interventricular and/or atrioventricular and/or intra-LV criteria of

mechanical dyssynchrony and correlations with outcome will be examined according to the degree of dyssynchrony.[25]

Limitations of the study

The inclusion of patients with many co-morbidities along with HFPEF in a prospective registry is a difficult challenge that we will have to take up.[5,6,13]

Characterizing mechanical dyssynchrony using Doppler echocardiography has been very challenging in most multicenter trials. This has been a learning experience. Therefore, the reproducibility and feasibility of the assessment of mechanical dyssynchrony will obviously be a major task. To minimize these difficulties, each echocardiographic examination will be recorded digitally by trained investigators and analysed in a Core Laboratory.

Conclusion

This study is being conducted to provide answers to the following questions:

(1) What is the prevalence of electrical and/or mechanical dyssynchrony in the HFPEF population?
(2) How do electrical and mechanical dyssynchrony correlate with outcome as assessed by a combined endpoint of either all-cause death or HF hospitalization?

This prospective observational study also aims to assess the potential usefulness of conducting clinical trials on CRT in patients with HFPEF.

Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

Acknowledgements

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