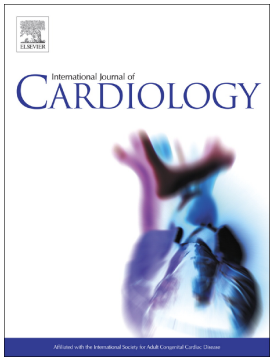
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Importance of structural heart disease and diastolic dysfunction in heart failure with preserved ejection fraction assessed according to the ESC Guidelines - a substudy in the Ka (Karolinska) Ren (Rennes) Study

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Abstract

Aims: To study prevalence and prognostic importance of diagnostic echocardiographic variables in patients with suspected heart failure with preserved ejection fraction (HFpEF) in the prospective KaRen register study.

Methods and results: KaRen patients were included following an acute HF-presentation, using Framingham criteria, B-type natriuretic peptide (BNP) >100 ng/L or N-terminal pro-BNP (NT-pro-BNP) >300 ng/L, and left ventricular (LV) ejection fraction ≥45%. Echocardiography was performed after 4-8 weeks and analysed at a core laboratory. In this substudy HFpEF was diagnosed according to the ESC guidelines for heart failure 2016.

A total of 539 patients were included with a follow-up after 4-8 weeks in 438 patients. Complete echocardiography and ECG were available in 356 patients. At least two abnormal echocardiographic criteria for HFpEF were found in 94% (n=333). Echocardiographic signs of structural heart disease and diastolic dysfunction according to 4 criteria by ESC were found in 76% (n=270). Diastolic dysfunction was graded as mild in 30% (n=107), moderate in 27% (n=97) or severe in 35% (n=124). After multivariate analyses with adjustment for age, gender, EF and natriuretic peptides we found two independent predictors of worse prognosis: presence of moderate and severe diastolic dysfunction (HR 1.8, CI 1.2-2.7, p=0.0037) and presence of a high number (≥4) of abnormal diastolic parameters (HR 2.0, CI 1.3-3.1, p=0.0033).

Conclusion: The majority of KaRen patients with suspected HFpEF had diagnostic echocardiographic criteria for HFpEF according to ESC Guidelines. Our findings support using 2016 ESC HF guidelines for risk prediction in HFpEF.

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Key words: Heart failure with preserved ejection fraction, echocardiography, prognosis, diagnosis, diastolic dysfunction.

Introduction

Heart failure (HF) is an increasing health problem in the world, especially in the developed countries (1). HF is one of the most frequent causes of hospital admission (2, 3), and is also associated with high mortality (4). About 40-50% of the patients with HF have preserved left ventricular (LV) ejection fraction (EF), named HFpEF, and this percentage is growing (5). Both morbidity and mortality in HFpEF are similar to those in HF with reduced EF (HFrEF), and a recent study from the KaRen group showed that non-cardiovascular co-morbidities have a great impact on prognosis in HFpEF (6). There is no established treatment for HFpEF (7). In 2007 the European Society of Cardiology (ESC) adopted a consensus statement (8) that recommended that the diagnosis of HFpEF should be based on a combination of biochemical (values of natriuretic peptides) and echocardiographical (such as mitral inflow and tissue Doppler variables, volume of the left atrium or mass of the left ventricle) parameters.

Methods

Study design

The Karolinska-Rennes (KaRen) study has been previously described (9). It is a prospective multicentre observational cohort study that aims to characterize clinical and echocardiographic characteristics in HFpEF and their prognostic importance (10). Patients were included in the KaRen study between 1 May 2007 and 1 December 2011; the inclusion took place in 10 French and 3 Swedish University hospitals. In short patients were included

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following an acute presentation of HF according to all of the following: the Framingham criteria (11), left ventricular ejection fraction (LVEF) ≥45% and elevated levels of natriuretic peptides: B-type natriuretic peptide (BNP) >100 ng/L or N-terminal pro-BNP (NT-pro-BNP) ≥300 ng/L within 72 hours of presentation. The study was approved by local ethic committees.

Study purpose

Our aim in this substudy was to investigate to what extent patients with clinical signs of HF and preserved EF fulfil the diagnostic criteria of HFpEF set by most recent ESC HF guidelines (12). These selected patients with assumed HFpEF underwent an extensive Doppler echocardiographic investigation in stable phase 4-8 weeks after admission to assess if the initial HFpEF diagnosis could be verified. Additionally, severity of diastolic dysfunction was evaluated. Finally, our aim was to investigate if these diagnostic parameters had an influence on the primary outcome of the KaRen study - mortality and hospitalizations for HF**.**

Patients

A total of 539 consecutive patients were enrolled in the KaRen study. Of these, 438 patients had a follow-up visit after 4-8 weeks. An electrocardiogram (ECG) was available in 393 patients and a complete echocardiography in 356 patients of them (9), so there were totally 413 patients with either analysable ECG or echocardiogram. Our analysis is restricted to the 356 patients with analysable echocardiogram.

Follow up

The quantitative analysis was performed in a 'Core laboratory' (CIC-IT 1414, CHU Rennes, France) (13). A 12-lead ECG was also performed at the follow-up visit and analyzed by

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another core laboratory (Karolinska University Hospital, Stockholm, Sweden). The primary study endpoint was time to death from all causes or first hospitalisation for HF.

Echocardiography

The examinations were performed according to a checklist on the same type of machine (ViVid 7, manufactured by GE Healthcare, Horten, Norway). In this paper our findings were put in relation to the eight criteria defined by the ESC HF guidelines (12). Cardiac structure was characterized by left ventricular mass index (LVMI) and left atrial volume index (LAVI). The diastolic LV function was characterized by isovolumetric relaxation time (IVRT), deceleration time (DT), ratio of mitral E to A velocity (E/A), average mitral tissue Doppler e' velocity, ratio of mitral Doppler E velocity to average mitral tissue Doppler e'-velocity (E/e') and peak flow velocity of tricuspid regurgitation (TR). Systolic LV function was characterized by LVEF. Right-sided cardiac catheterisation was not part of the protocol.

Diagnosis of HFPEF in a model according to present ESC guidelines

The ESC HF Guidelines list both clinical and the aforementioned echocardiographic criteria for diagnosing HFpEF (12). First, the patient should have symptoms and signs typical of HF. Second, echocardiography should show normal or only slightly reduced LVEF (reduced LVEF is defined as <50%). Finally, structural heart disease, such as LV hypertrophy and enlargement of the left atrium (LA) or direct and indirect measures of diastolic LV dysfunction, such as elevated E/e' or low e' or tricuspid regurgitation velocity should be used (9).

Previous definitions of HFpEF Consensus statement by ESC

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According to a more detailed earlier ESC Consensus statement (8) patients should have symptoms or signs of HF, normal or mildly reduced left ventricular systolic function (normal LVEF defined as >50%) and non-enlarged LV (LVDVI <97 mL/m^2). Then there are several pathways leading to the HFpEF diagnosis. They include elevated filling pressures, such as measured invasively by mean pulmonary capillary wedge pressure >12 mmHg or signs of abnormal LV relaxation, filling, or diastolic stiffness. Secondly, the diagnosis can be based on echocardiography showing increased E/e' ratio (>15). If E/e' is only moderately increased, the diagnosis should be made with either measuring of biomarkers (NT-pro-BNP >220 ng/L or BNP >200 ng/L is sufficient for diagnosing HFpEF) or other echocardiographic investigations regarding LV mass, LA volume or diastolic LV dysfunction.

Additional Echo guidelines (ASE and EACVI)

Echocardiographic guidelines for evaluation of left ventricular diastolic function are recently presented from the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACV) (14). They recommend evaluation of following variables when assessing the diastolic function of the LV: e', average E/e', LAVI and peak flow velocity of tricuspid regurgitation (TR). These guidelines advocate the use of numerous variables to add diagnostic value.

Definitions and cut-offs for the present analysis

Based on the aforementioned criteria in the ESC Guidelines, the Consensus statement and the ASE/EACV Guidelines we have chosen the echocardiographic cut-off

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values for this KaRen substudy. The cut-off values for the eight echocardiographic parameters are defined in Appendix 1. For HF biomarkers we used following cut-off values in the KaRen study: BNP >100 ng/L and NT-pro-BNP>300 ng/L.

Grading of diastolic function

The classification of diastolic function was based on the ESC algorithm and its cut-offs (8, 12) and also on a semi-quantitative grading of diastolic function (9, 14). A similar classification method has previously been used by the Mayo Clinic group (15). Classification was as follows: 0) normal, 1) relaxation abnormality (mild dysfunction), 2) pseudo-normalisation (moderate dysfunction), and 3) restrictive filling abnormality (severe dysfunction). A relaxation abnormality was based on presence of at least one abnormal mitral inflow parameter (E/A<0.5, IVRT >110 ms or DT>280 ms) or dilatation of the left atrium (increased LAVI).

To distinguish pseudo-normal from normal diastolic function, E/e' and TR were used and, for the diastolic function to be classified as pseudo-normal, one of these parameters had to be elevated (≥13 or ≥2.8 respectively). Besides that, at least one of the following three mitral inflow parameters had to be within the normal range: E/A (0.5-2), IVRT (55-110 ms) or DT (150-280ms). For diagnosis of the restrictive pattern, the cut-offs for E/e' and TR were the same as for pseudo-normalisation, but a value for at least one of the mitral inflow parameters had to be pathological: E/A >2, IVRT <55 ms or DT <150 ms. Our diagnostic criteria are summarized in Appendix 2**.** The patients not fulfilling the abovementioned diagnostic criteria were assessed to have normal diastolic LV function.

In patients with atrial fibrillation where E/A could not be measured, the diastolic function was assessed using following parameters: LAVI, DT, IVRT and E/e' according to the

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abovementioned algorithm. This is the method recommended by the current EACVI/EHRA Consensus Document (16).

Statistical analysis

The categorical variables were expressed as n (%) and the continuous variables were expressed as mean ± standard deviation. The data were split according to the definitions of cut-offs above. For prognostic assessment of the outcome predictors, univariate and multivariate Cox regressions were used. The multivariate analysis was performed to assess if there was additive prognostic value of adding echo variables and diastolic grading or structural disease classifications adjusted for age, gender, ejection fraction and level of natriuretic peptides.

The data sets were analysed using the standard SAS procedures (PHREG Procedure and LIFETEST Procedure). Considering the limited available number of patients and that some missing data were found in the echo parameters, we did multiple imputations (PROC MI) using a fully conditional specification method that performed a regression method to impute missing values for continuous variables. After 25 complete data sets were analyzed using standard SAS procedures (PROC PHREG), we used the MIANALYZE procedure that combined the results of theses 25 analyses and generates valid statistical inferences. Hazard ratios (95% CI) estimated through Cox regression (PROC PHREG) were used as measure of association with the primary study endpoint.

Ethics

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This study is performed in accordance to the Declaration of Helsinki and is approved by French and Swedish ethics committees and by the CNIL (Comité National Informatique et Libertés) in France.

Results

Patients´characteristics

Demographic and clinical characterics of the KaRen study population has been published (9, 10) – they are summarized in Appendix 3. The patients were elderly and many of them had a previous history of cardiac or other diseases. A clear majority of the patients had symptoms of heart failure.

The patients were followed up by telephone calls and reviews of chart or death registry every 6 month for 18 months after closure of enrolment, so each patient had a follow-up time of at least 18 months. With a mean follow-up of 28 months 156 patients (43.8%) reached the combined primary endpoint (10). Thirty-nine per cent of the patients (n=171) were diagnosed with atrial arrhythmia after the examination of their ECGs (9), mainly atrial fibrillation.

In Table 1 the baseline clinical characteristics are presented, both overall and stratified by number of echo abnormalities.

Echocardiography after 4-8 weeks

Prevalence of abnormal echocardiographic variables was high, as summarized in Appendix 3. For most of the included patients the echocardiographic parameters were pathological. Signs of structural dysfunction (LAVI≥34 ml/m^2or LVMI ≥95/115 g/m^2) were found in 92% (n=328). Signs of diastolic dysfunction (E/e' ≥13, or e'<9 cm/s, or TR ≥2.8 m/s) were found

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in 82% (n=290). Signs of both structural and diastolic dysfunction were found in 76% (n=270).

In Table 2 the key echo variables are presented.

At least one abnormal echocardiographic criterion for HFpEF was found in 98% (n=351) and 94% (n=333) had at least two pathological criteria. One to three abnormal criteria were found in 38% (n=134), four criteria in 24% (n=84), 5-8 abnormal criteria in 39% (n=138) of the patients.

According to the above-mentioned classification method, grading of the diastolic function was performed by D. Matan and H. Persson. Out of the total of 356 patients examined with echocardiography, 107 patients (30%) had mild diastolic dysfunction (relaxation abnormality), 97 patients (27%) had moderate diastolic dysfunction (pseudo-normalisation) and 124 patients (35%) had severe diastolic dysfunction (restrictive pattern). Twenty-four patients (7%) were assessed to have normal diastolic LV function. Four patients (1%) were assessed as non-classifiable due to diverging/conflicting data; they were excluded from further analysis. Thus, 352 (99%) of the 356 patients were possible to classify based on available parameters.

Influence of parameters on outcome

After univariate analysis, it was shown that abnormal values of the following diastolic parameters have significant ($p<0.05$) impact on the outcome: E/A, E/e', TR and LVMI. The outcome was also dependent on the number of abnormal diastolic parameters as defined by separation of number of abnormal variables into tertiles (with significant impact when four or more parameters were pathological). Thirdly, diastolic dysfunction showed a graded

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association to outcome, where patients with severe diastolic dysfunction had significantly worse outcome compared to those with normal diastolic function.

A multivariable analysis with adjustment for age, gender and EF was performed showing that the outcome was significantly worse for the patients with moderate and severe diastolic dysfunction compared to normal and mild dysfunction. The outcome was also significantly worse for the patients with echocardiographic signs of both structural and diastolic dysfunction compared to those without such signs. Finally, the outcome was significantly worse when the number of the pathological diastolic parameters was four or more. The results of the multivariate analysis are summarized in Table 3 and in Figure 1. These results remained unchanged for number of abnormal variables and grading of diastolic after further adjustment for BNP/ NT-pro-BNP values.

Discussion

Short summary of study and results

Our findings suggest that clinical diagnosis of HF based on Framingham criteria with the addition of a modest increase in natriuretic peptides can be used for finding a cohort of patients with objective echocardiographic and diagnostic criteria for HFpEF according to the most recent guidelines from the ESC and verified by extensive echocardiography in a core lab centre. Our prognostic results strengthen the use of parameters and cut-offs recommended by ESC, as we could show that both the number of pathological diastolic parameters, and moderate and severe diastolic dysfunction are independent predictors of prognosis, respectively. Our finding support previous studies, such as I-PRESERVE (17), TOPCAT (18) and CHARM (18), clinical trials that showed the prognostic importance of echocardiographic signs of HFpEF.

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Patients

Out of totally 539 patients included in the KaRen study, 183 were not examined with echocardiography and ECG and thus excluded from this substudy. However, as the vast majority of the patients in the substudy had pathological echocardiographic criteria, there is a high probability that also the patients lost to follow-up would be diagnosed with HFpEF if a full diagnostic echocardiographic study had been performed. Apart from higher mean age (80 ± 9 vs 76 ± 9 years; p=0.006), there were no statistically significant differences between the patients who returned for the follow-up visit and those who did not (9).

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Echocardiography and diagnostic algorithms for HFpEF

The inclusion criteria in the KaRen study – to use both clinical and echocardiographic data together with natriuretic peptides – are in accordance with the recommendations in the ESC Guidelines (12). The echocardiographic cut-off values we used are consistent with those suggested in the Guidelines and in previous studies (14, 19). Some of the parameters, particularly for diastolic function, are relatively difficult to achieve in every patient, which makes diagnostic algorithms of several alternative parameters or biomarker data attractive for clinical use (14). As can be seen in the present study, using 8 variables as suggested by ESC makes a diagnosis possible in most HFpEF patients with a preliminary diagnosis based only on clinical data, preserved EF and a modest increase in natriuretic peptide level. By using several diagnostic parameters we were able to classify most of the patients, a similar finding compared to a previous study performed on a similar clinical population with echoes interpreted by a core lab (19). If we only used clinical diagnosis of HF and preserved EF, we would have included a large proportion of patients with normal LV function and a subsequent very low mortality and low risk of future heart failure (19-21). Further, the prognostic value of most of these parameters strengthens the case for using them. However, in a recent paper from the KaRen study only E/e' showed an independent prognostic value (10) when creating a full predictive model including all available variables in the study. However, the present analysis is more adapted to what is generally available in the clinical situation.

Many patients in KaRen showed an enlarged LV, and also other measures of depressed LV longitudinal function (9). Therefore, by only including preserved EF in the primary diagnosis a relatively large population of patients with enlarged LV volume would be diagnosed as HFpEF, which is not in accordance with the ESC guidelines.

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The patients with suspected HFpEF can be selected by clinical signs and the levels of natriuretic peptides, but echocardiography is necessary to confirm the diagnosis by verifying cardiac dysfunction, in this case with evidence of LV dysfunction. Several recent studies have confirmed the necessity of echocardiography in diagnosing HFpEF (22-24). However, many clinicians still diagnose HF clinically without echocardiography, and using natriuretic peptides for screening is thus important (25). Echocardiographic access is a strong limitation due to poor availability in most countries. Selection of patients to echocardiography by using increase in natriuretic peptides is important, because of their strong negative predictive value when under ESCs threshold levels.

We also examined whether only LAVI by itself could be used for prognosing of the outcome in HFpEF, and concluded that it was not the case, although LAVI was related to diastolic dysfunction (Appendix 4). This is consistent with the findings in the CHARMES study.

Natriuretic peptides

Recent studies have shown that analysis of biomarkers, both BNP and NT-pro-BNP, can be used for diagnosing of HFpEF (19, 20, 26, 27), often in conjunction with use of conventional echocardiographic parameters as suggested in the ESC Guidelines and in the Consensus Statement. Further, both these biomarkers can be used as predictors of prognosis in HFpEF, as elevated values in BNP and NT-pro-BNP are associated with increased frequency of adverse cardiovascular events (28, 29). In the I-PRESERVE study NT-pro-BNP was the strongest outcome predictor for all cardiovascular events (30). In the present study we show additive prognostic role of using echocardiography on top of using natriuretic peptides.

Clinical diagnosis and Framingham criteria

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In the KaRen study the presence of clinical signs of HF according to the Framingham criteria was mandatory for inclusion. Clinical signs of HF are still important for correct diagnosis and prognosis in heart failure (31, 32), as has been shown in numerous studies from 1970s and onwards (26, 33). Whether a less formal clinical diagnosis than the Framingham criteria are useful to the same degree is not certain, but a recent HF hospitalization and time from this event was a very strong predictor for future events in patients with chronic heart failure with reduced and preserved EF (34).

Outcome

After multivariate analyses with adjustment for age, gender and EF and natriuretic peptides we found two factors that were independent predictors of worse prognosis: presence of moderate and severe diastolic dysfunction and presence of a high number (four or more) of pathological diastolic parameters. Presence of structural heart disease and presence of diastolic dysfunction using only 4 criteria (LAVI, LVMI, E/e' and TR) did not show independent prognostic value when adjusted for natriuretic peptides. Further studies are required for better understanding of the predictive value of different echocardiographic parameters in HFpEF.

Study limitations

Several limitations can be identified in this study. First, there is no comparator, non-HFpEF, group in the KaRen study, which may diminish the strength of showing prognostic utility for the diagnostic strategy. However, in our opinion, the KaRen study uses real world data interpreted in accordance with the ESC diagnostic algorithm, which provides an insight in diagnosis and prognosis of HFpEF, which adds to insights from clinical trials with more selected HFpEF patients (16-18).

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Secondly, in our study we do not account for age-related variation in the parameters of diastolic dysfunction, although such variation has been previously described (35). However, the results from the CHARM echocardiographic study carried out by this group (19) have shown that using age-adjusted and non age-adjusted normal values of diastolic dysfunction does not make a significant difference to prognostic utility and proportion of patients in the respective subgroups of diastolic dysfunction in the same HFpEF population (36).

Thirdly, KaRen patients were included based on EF ≥45% and not >50% as is now the present recommendation by ESC. However, we kept the few (n=9) patients with EF ≤50% in the present analysis because they belong to the new category introduced by ESC with heart failure and midrange ejection fraction (HFmrEF). According to the ESC Guidelines the same objective diagnostic criteria should be used for HFmrEF as the ones used in this analysis.

Fourthly, this study does not include an age-matched control group without heart failure diagnosis, which is a weakness as to possibility to compare the echocardiographic findings in HFpEF population and in healthy individuals. However, our findings can be compared to the normal reference ranges of echocardiographic parameters that have been gathered in the NORRE study (37), the largest European registry study carried out by the the European Association of Cardiovascular Imaging (EACVI).

Finally, it should be noticed that the generalizability of the study findings is limited to HFpEF, as one of the inclusion criteria of the study was EF ≥45%.

Conclusions

In summary, we conclude that almost all patients with suspected HF based on Framingham criteria, modest increase of natriuretic peptides and EF ≥45% met objective diagnostic

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echocardiographic criteria for HFpEF as defined by the ESC guidelines. Our findings support the use of the ESC guidelines for risk prediction in HFpEF.

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Conflict of interest: The authors report no relationships that could be construed as a conflict of interest.

* The list of the KaRen investigators is provided in Appendix 5.

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Figure legends

Figure 1. Probability of adverse event according to number of abnormal diastolic parameters (Kaplan-Meier Curve with univariate analysis). Tertile 1 (0-3 abnormal variables) versus Tertile 2 and 3 (4-8 abnormal variables).

Abbreviations: HF = heart failure, HR = hazard ratio, CI = confidence interval.

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Table 1. Baseline clinical characteristics, both overall and stratified by number of echo abnormalities

Characteristic	Missing	Overall	Number of echo abnormalities		
	N	N = 356	< 4	4	5 to 8
			N = 106	N = 94	N = 156
Age, years	0	76 (9)	73 (10)	76 (9)	78 (8)
Gender, female	0	201 (56.5)	54 (50.9)	53 (56.4)	94 (60.3)
BMI, kg/m²	17	29.5 (6.5)	30.7 (7.2)	29.9 (6.6)	28.5 (5.8)
AF or flutter	34	118 (36.6)	31 (34.8)	35 (40.7)	52 (35.4)
Hypertension	1	282 (79.4)	73 (69.9)	82 (88.2)	127 (81.4)
Prior HF	4	136 (38.6)	28 (26.4)	43 (46.2)	65 (42.5)
CAD	9	118 (34.0)	37 (35.6)	36 (39.1)	45 (29.8)
Diabetes	0	115 (32.3)	27 (25.5)	33 (35.1)	55 (32.3)
Renal failure	1	157 (44.1)	41 (38.7)	38 (40.4)	78 (50.0)
NYHA II-IV	55	237 (78.7)	59 (68.6)	67 (80.7)	111 (84.1)
NT-pro-BNP	66	1409 [2112]	1070 [1584]	1071 [1486]	1751 [2466]

Values are mean (SD), median [IQR] or number (percentage);

Abbreviations: BMI = body mass index, AF = atrial fibrillation (on EKG), HF = heart failure, CAD = coronary artery disease NYHA = New York Heart Association heart failure classification, NT-pro-BNP = N-terminal pro-B-type natriuretic peptide.

The diagnosis renal failure is based on either chronic renal insufficiency or creatinine serum level greater than 100 µmol/L on admission.

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Table 2. Key echo measures (and measures of,) as both continuous variables and percent abnormal, along with the N for each measure (to indicate the extent of missing data for each measure) in the study sample overall and stratified by the number of echo abnormalities.

Characteristic	Missing N	Overall N = 356	Number of echo abnormalities		
			< 4 N = 106	4 N = 94	5 to 8 N = 156
LVEF, %	14	62.4 (7.0)	62.9 (6.4)	62.1 (6.7)	62.1 (7.5)
IVRT, ms	20	91.8 (31.2)	93.8 (20.7)	93.2 (30.3)	89.5 (37.3)
< 55 or > 110 ms, %		118 (33.1)	18 (17.0)	27 (28.7)	73 (46.8)
DT, ms	7	194 (75)	199 (54)	198 (70)	189 (90)
< 150 or > 280 ms, %		141 (39.6)	18 (17.0)	30 (31.9)	93 (59.6)
E/A	92	2.1 (1.4)	1.8 (1.1)	1.9 (1.2)	2.4 (1.5)
< 0.5 or > 2, %		168 (47.2)	32 (30.2)	40 (42.5)	96 (61.5)
E', cm/s	8	8.0 (2.6)	9.2 (2.6)	8.2 (2.6)	7.0 (2.2)
< 9 cm/s, %		227 (63.8)	44 (41.5)	56 (59.6)	127 (81.4)
E/E'	24	12.8 (6.1)	9.1 (3.5)	11.8 (5.8)	16.0 (6.1)
≥ 13, %		138 (38.8)	7 (6.60)	27 (28.7)	104 (66.7)
LAVI, mL/m^2	18	47.6 (16.1)	40.2 (14.3)	46.6 (15.8)	52.8 (15.4)
>34 mL/m^2, %		280 (78.6)	60 (56.6)	78 (83.0)	142 (91.0)
LVMI, g/m² VG6	104	125 (37)	106 (36)	127 (32)	137 (35)
LVH, %		255 (71.6)	43 (40.6)	72 (76.6)	140 (89.7)
TR	49	2.8 (0.7)	2.4 (0.6)	2.8 (0.5)	3.1 (0.6)
≥ 2.8 m/s		179 (50.3)	17 (16.0)	46 (48.9)	116 (74.4)

Values are mean (SD) or number (percentage);

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Abbreviations: É = mitral tissue Doppler É velocity, E/É = ratio of mitral Doppler E velocity to mitral tissue Doppler É velocity, DT = deceleration time, E/A = ratio of mitral E to A velocity, IVRT = isovolumetric relaxation time, LAVI = left atrial volume index, LVEF = left ventricle ejection fraction, LVMI = left ventricular mass index, LVH if LVMI>95 g/m^2 in women or >115 g/m^2 in men, TR = tricuspid regurgitation.

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Table 3. Rates (per 100 person-years) and hazard ratio (HR) for death from all causes or first hospitalization for heart failure according to diastolic parameters, with adjustment for age, gender and EF (first row) and further adjustment for BNP/pro-BNP quintiles (*second row*).

Parameters	Value	N	No events	Event rates	HR (95% CL)	p-value
Number	< 4	106	56	25.5	1.00	
	4	94	58	32.9	1.5 (0.8 - 2.7)	0.1594
					1.4 (0.7 – 2.6)	0.3116
	5 to 8	156	147	58.4	2.3 (1.5 - 3.6)	0.0002
					2.0 (1.3 - 3.3)	0.0032
	4 to 8	250	205	47.9	2.0 (1.3 - 3.2)	0.0020
					1. 8 (1.1 – 2.8)	0.0189
Structural abnormality and diastolic dysfunction	No	81	39	21.2	1.00	
	Yes	275	222	47.8	2.1 (1.3 – 3.2)	0.0020
					1. 7 (1.0 - 2.7)	0.0380
Diastolic dysfunction	0	24	10	18.5	1.00	
	1	107	59	27.9	1.5 (0.6 - 4.2)	0.4154
					1.3 (0.4 - 3.9)	0.6875
	2	97	70	37.3	2.1 (0.8 - 5.8)	0.1403
					1.9 (0.6 - 6.1)	0.2505
	3	124	120	64.4	3.0 (1.1 - 8.0)	0.0278
					2.5 (0.8 - 7.5)	0.1146

Diastolic dysfunction: grade 1 = relaxation abnormality, grade 2 = pseudo-normalisation, grade3 = restrictivity.

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Highlights

- A model for grading the diastolic dysfunction of the heart is proposed.
- Most of the patients with suspected heart failure based on the Framingham criteria, increase of natriuretic peptides and normal ejection fraction met objective diagnostic echocardiographic criteria for heart failure with preserved ejection fraction according to the ESC guidelines.
- The ESC heart failure guidelines can be used for risk prediction in heart failure with preserved ejection fraction.

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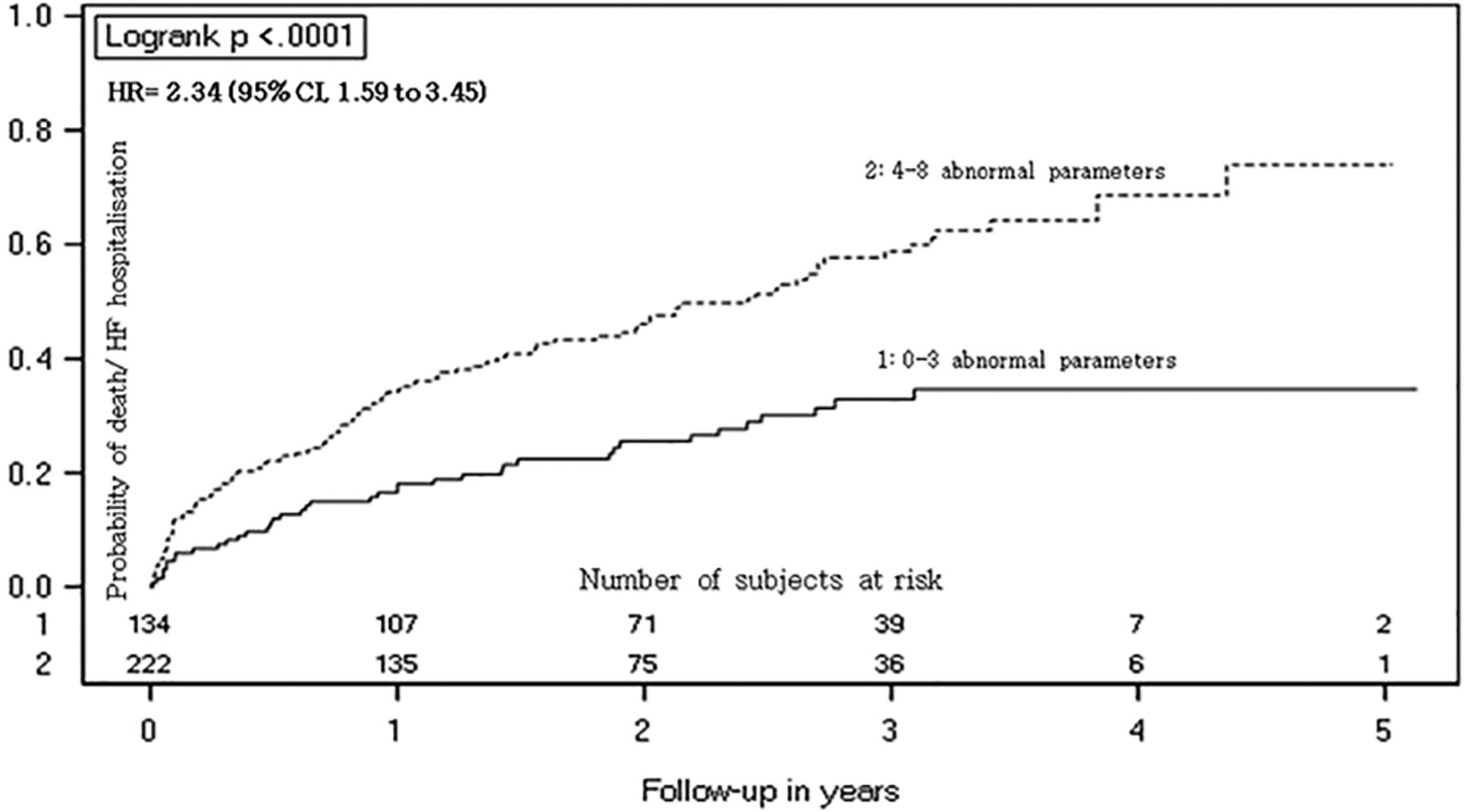

Logrank p <.0001
HR= 2.34 (95% CI, 1.59 to 3.45)
Probability of death/ HF hospitalisation
2: 4-8 abnormal parameters
1: 0-3 abnormal parameters
Number of subjects at risk
1 134 107 71 39 7 2
2 222 135 75 36 6 1
0 1 2 3 4 5
Follow-up in years

Figure 1