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Clinical research

Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey

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KEYWORDS
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Aims Due to a lack of clinical trials, scientific evidence regarding the management of patients with chronic heart failure and preserved left ventricular function (PLVF) is scarce. The EuroHeart Failure Survey provided information on the characteristics, treatment and outcomes of patients with PLVF as compared to patients with a left ventricular systolic dysfunction (LVSD).

Methods and results We performed a secondary analysis using data from the EuroHeart Failure Survey, only including patients with a measurement of LV function ($n = 6806$). We selected two groups: patients with LVSD (54%) and patients with a PLVF (46%). Patients with a PLVF were, on average, 4 years older and more often women (55% vs. 29%, respectively, $p < 0.001$) as compared to LVSD patients, and were more likely to have hypertension (59% vs. 50%, $p < 0.001$) and atrial fibrillation (25% vs. 23%, $p = 0.01$). PLVF patients received less cardiovascular medication compared to PLVF patients, with the exception of calcium antagonists. Multivariate analysis revealed that LVSD was an independent predictor for mortality, while no differences in treatment effect on mortality between the two groups was observed. A sensitivity analysis, using different thresholds to separate patients with and without LVSD revealed comparable findings.

Conclusions In the EuroHeart Failure Survey, a high percentage of heart failure patients had PLVF. Although major clinical differences were seen between the groups, morbidity and mortality was high in both groups.
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Introduction

Chronic heart failure is a major health problem and is associated with high morbidity and mortality.[1,2] Advances in therapy over the last two decades have proved highly effective in reducing morbidity and mortality rates. As a result, several effective treatment strategies are now available, including β-blockers and ACE-inhibitors, which have contributed to improved outcome in the real world.[3,4] However, most clinical investigations in chronic heart failure focussed on patients with left ventricular systolic dysfunction (LVSD). Consequently, scientific evidence regarding the management of patients with preserved left ventricular function (PLVF) is scarce.

To support physicians in everyday clinical decision-making, the European Society of Cardiology (ESC) published guidelines for the investigation and treatment of heart failure patients.[5,6] Since guidelines are intended to be evidence-based, treatment recommendations for patients with PLVF remain mainly speculative.[5] Still, it should be realised that these patients constitute a sizeable group; it is estimated that 30% to 50% of all heart failure patients do not have LVSD.[7] The EuroHeart Failure Survey was designed to evaluate to what extent treatment guidelines are implemented in clinical practice. A total of 10 701 suspected or confirmed heart failure patients were enrolled, of whom 3148 had PLVF. The survey provided a wealth of information on patient characteristics, diagnosis and treatment.[8,9] We aimed to describe to what extent the presence or absence of LVSD influenced patient profile, management and outcome.

Methods

The EuroHeart Failure Survey was the second in a series of surveys that were conducted under the umbrella of the EuroHeart Survey Program, which aimed to investigate the implementation of treatment guidelines in clinical practice. The design details of the Heart Failure Survey, which was undertaken during March 2000 and May 2001, were published previously.[9,10] In short, all consecutive discharges and deaths in the departments of cardiology, cardiovascular surgery, general internal medicine and geriatrics were screened over a 6-week period. The design of the EuroHeart Failure survey included 115 hospitals from 24 ESC member countries on a voluntary basis, including general hospitals and university centres.

Patients were enrolled if they fulfilled at least one of the following criteria were enrolled:

(1) a clinical diagnosis of heart failure during the admission;
(2) a diagnosis of heart failure recorded at any time in the last three years;
(3) administration of a loop diuretic for any reason other than renal failure during 24 h of death or discharge;
(4) pharmacological treatment for heart failure or ventricular dysfunction within 24 h of death or discharge.

In all 10 701 enrolled patients, data were collected on comorbid conditions including hypertension, diabetes, chronic atrial fibrillation and renal insufficiency. A clinical follow-up was performed, and vital status (dead or alive) was determined at 12 weeks after discharge. We also collected data on re-admission(s). Surviving patients were then invited for an interview. During this visit, the NYHA classification was determined, and the quality-of-life was measured with, among other matters, the following question, "How would you rate your quality-of-life", using a 7-point rating scale (0 = poor, 7 = excellent).

This analysis included patients who had undergone a quantitative or qualitative assessment of the left ventricular function ($n = 6806$, 64% of the entire cohort). Of these patients, 80% ($n = 5451$) reported left ventricular ejection fraction (LVEF). Patients with a LVEF $\geqslant$40%, as well as patients with a normal or mildly depressed systolic left ventricular function, as assessed by echocardiography were classified as PLVF. Patients with a LVEF $<$40%, patients with a moderate or severe left ventricular systolic dysfunction, and those with left ventricular dilatation, as assessed by echocardiography were classified as LVSD.

Statistical analysis

Continuous variables are described as mean values with their corresponding standard deviations, or as median values and corresponding 25th and 75th percentiles. Dichotomous variables are reported as absolute numbers and percentages. To evaluate the characteristics of differences in treatment and outcome between patients with and without LVSD, χ^2 tests, Student's *t*-tests or Mann Whitney U tests were applied as appropriate.

Multivariable logistic regression analysis was applied to study the relationship between LVF and all-cause mortality during the 12-week follow-up period. LVSD, age, gender, hypertension, diabetes, ischaemic heart disease, renal insufficiency, prior stroke, chronic atrial fibrillation and pharmacological treatment were forced into the regression model. We report odds ratios (OR) and corresponding 95% confidence intervals (CI). To examine the differential effect of pharmacological treatment in patients with and without LVSD, interaction terms were included in the regression model. All calculations were performed using SPSS 10.1 software package. For all tests a p value of 0.05 or less (two-sided) was considered statistically significant.

We acknowledge the fact that the discussion on how to define preserved left ventricular function in patients with heart failure is still ongoing, and that choice may be challenged.[11–14] Therefore, we repeated all analyses using different thresholds. We first analysed quantitative LVEF $<$40% vs. LVEF $\geqslant$40% (excluding patients with only qualitative assessment of the LV function), and secondly LVEF $<$40% vs. LVEF $>$50% (excluding patients with a LVEF $\geqslant$40% and $\leqslant$50%). Since the results of these analyses were highly consistent, we only report on our original choice.

Results

Patient characteristics

The mean age (SD) of the 6806 patients was 69 (±13) years and 41% were female. A substantial proportion of patients had ischaemic heart disease (64%), a history of hypertension (54%), documented diabetes (27%) or chronic atrial fibrillation (24%). The median duration of the index hospitalisation was 10 days (interquartile range: 6—16).

Patients not in the analysis ($n = 3895$) were older and included more females. Fewer patients were known with an ischaemic heart disease, while a history of stroke was more common in these patients. Furthermore, out of the analyses, most patients (68%) were admitted to a general internal medicine ward, as compared to the patients who

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Table 1 Differences in characteristics of patients with preserved and depressed left ventricular function

	Patients with known left ventricular function			Patients not in the analysis ($n = 3895$)
	PLVF ($n = 3148$)	LVSD ($n = 3658$)	p^a	
Age (mean, SD)	71 ± 12	67 ± 13	<0.001	76 ± 11.6
Women (%)	1739 (55)	1065 (29)	<0.001	2216 (57)
Men >70 years (%)	666 (21)	961 (26)	<0.001	1039 (27)
Women >70 years (%)	1099 (35)	607 (17)	<0.001	1748 (45)
Co-morbidity				
Hypertension (%)	1845 (59)	1829 (50)	<0.001	2005 (52)
Diabetes mellitus (%)	816 (26)	1016 (28)	0.09	1075 (28)
Ischaemic heart disease (%)	1851 (59)	2508 (69)	<0.001	2060 (53)
Previous revascularisation (%)	377 (12)	674 (18)	<0.001	291 (8)
Renal insufficiency (%)	155 (5)	220 (6)	0.05	296 (8)
Prior stroke (%)	492 (16)	501 (14)	0.02	814 (21)
Chronic atrial fibrillation (%)	795 (25)	827 (23)	0.01	860 (22)
LVEF (mean, SD)	56 ± 9.8	33 ± 10.9	<0.001	n.a.
Speciality at admission (%)			<0.001	
General internal medicine	1299 (42)	1164 (32)		2659 (68)
Cardiology/cardiovascular surgery	1615 (51)	2288 (63)		769 (20)
Other	231 (7)	197 (5)		458 (12)
Duration of index hospitalisation in days (median, IQR)	10 (6—16)	10 (6—15)	0.26	9 (5—14)
Contribution of heart failure to index admission (%)	1189 (38)	1904 (52)	<0.001	1141 (29)

LVEF, left ventricular ejection fraction.
[a] The *p* value refers to the statistical difference between PLVF and LVSD.

were in the analysis (Table 1). The comparison between patients with and without LVSD revealed that almost half of all patients ($n = 3148$, 46%) had PLVF. Patients with PLVF were on average 4 years older and more often women (55% vs. 29%, $p < 0.001$) than patients with LVSD (Table 1). Patients with PLVF were also more likely to have a history of hypertension (59% vs. 50%, $p < 0.001$) and chronic atrial fibrillation (25% vs. 23%, $p = 0.01$), whereas ischaemic heart disease (59% vs. 69%, $p < 0.001$) was more prevalent in those with LVSD. Patients with PLVF were more likely to be hospitalised in general internal medicine than those with LVSD (42% vs. 32%, $p < 0.001$) and contribution of heart failure to index admission was less prominent (38% vs. 52% $p < 0.001$).

Pharmacological treatment

Table 2 gives an overview of the pharmacological treatment during hospitalisation in patients with or without LVSD. The vast majority of patients received diuretics (87% vs. 85%, $p = 0.01$), most often loop diuretics. The use of loop diuretics was the sole enrolment criterion in 5% of all patients (2% and 10% in patients with and without LVSD, respectively). Patients with LVSD were more likely to receive ACE-inhibitors or Angiotensin II receptor blockers (ARBs) (82% versus 62% in PLVF, $p < 0.001$), as well as β-blockers (46% and 39%, $p < 0.001$) or cardiac glycosides (41% vs. 31%, $p < 0.001$). Calcium channel blockers was the only class of agents that was prescribed significantly more often in patients with PLVF than in patients with LVSD (28% vs. 16%, $p < 0.001$).

Pharmacological treatment (multivariable analysis)

Patients receiving ACE-inhibitors had lower 12-week death rates than those not receiving ACE-inhibitors (OR 0.55, 95% CI 0.43-0.71; Fig. 1). Similar results were observed in relation to treatment with β-blockers (OR 0.61, 95% CI 0.48-0.77) and statins (OR 0.59, 95% CI 0.43-0.81). In contrast, treatment with IV inotropic agents was associated with worse outcome (OR 5.53, 95% CI 4.07-6.95). Patients receiving cardiac glycosides, diuretics and nitrates had similar 12-week mortality as those not receiving these agents. Of particular interest was the lack of statistical evidence for a heterogeneous effect of any agent between patients both with and without LVSD (P for interaction, all >0.05).

Outcome

The incidence of all-cause mortality during the 12-week follow-up, although high in both groups, was higher in patients with LVSD than those without (12% vs. 10%, OR 1.35, 95% CI 1.13—1.62). No significant differences were observed in the need for re-admission (22% versus 21%), time to first re-admission or number of days that patients were hospitalised during the follow-up period (Table 3). NYHA classification at follow-up did not differ between

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Table 2 Differences in pharmacological treatment between patients preserved and depressed left ventricular function

	PLVF ($n = 3148$)	LVSD ($n = 3658$)	p
ACE-inhibitors (%)	1839 (58)	2848 (78)	<0.001
Angiotensin II receptor blockers (%)	140 (4)	218 (6)	0.005
ACE or ARB (%)	1956 (62)	3009 (82)	<0.001
β-Blockers (%)	1231 (39)	1679 (46)	<0.001
Calcium channel blockers (%)	867 (28)	583 (16)	<0.001
Cardiac glycosides (%)	986 (31)	1512 (41)	<0.001
Diuretics (%)	2679 (85)	3188 (87)	0.01
Loop diuretic (%)[a]	2431 (91)	2952 (93)	0.01
Thiazide diuretic (%)[a]	343 (13)	381 (12)	0.32
i.v. inotropic agents (%)	204 (7)	380 (10)	<0.001
Nitrates (%)	1451 (46)	1811 (50)	0.005
Spironolactone (%)	527 (17)	1070 (29)	<0.001
Statins (%)	668 (21)	937 (26)	<0.001

[a] The proportions may add up more than 100% as some patients received both diuretics.

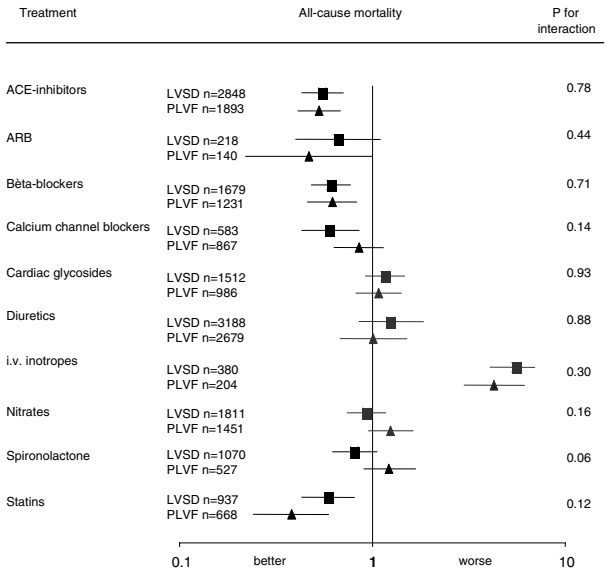

Fig. 1 All cause mortality with respect to pharmacological treatment. Adjusted for age, gender, hypertension, diabetes, ischaemic heart disease, renal failure, prior stroke, chronic atrial fibrillation and pharmacological treatment. LVSD: left ventricular systolic dysfunction PLVF: preserved left ventricular function.

patients with and without LVSD (25% and 24% had NYHA III/IV, respectively). More patients with LVSD (29%) viewed their quality of life as "quite poor" to "very poor" as compared to 23% in the preserved group ($p = 0.04$).

Outcome (multivariate analysis)

After adjustment for age, gender, co-morbidity and pharmacological treatment, patients with LVSD had higher mortality than patients with PLVF (OR 1.4, 95% CI 1.1-1.6, $p = 0.001$). No differential effect of the presence or absence of left ventricular systolic function on all-cause mortality was observed in subgroups of patients according to clinical characteristics, except for diabetes ($p = 0.03$) (Fig. 2).

Discussion

Almost half of heart failure patients enrolled in the EuroHeart Failure Survey with left ventricular function determination had preserved left ventricular function. This group of patients had different patient characteristics to that of patients with LVSD, including advanced age, a higher proportion of women, and a history of hypertension and chronic atrial fibrillation. Furthermore we observed a higher mortality in patients with LVSD, but mortality was high in both groups.

Our findings are in agreement with prior reports suggesting that patients with LVSD are at increased risk for mortality.[15–21] However, there is growing recognition that heart failure caused primarily by abnormalities in relaxation/diastole represents a substantial proportion of all heart failure patients and is also associated with a high morbidity and mortality. We showed that 12-week mortality was high in both groups, whereas every fifth patient, regardless of LV function, was re-admitted within 12 weeks. In the recently published CHARM-Preserved trial, 24% of patients in the placebo arm experienced a composite endpoint of cardiovascular death or hospital admission for heart failure, while 18.5% of these patients were hospitalised for heart failure over 36.6 months of follow-up.[22] The cardiovascular mortality among these patients was 58% lower than in CHARM patients with low LVEF <40%.[23,24]

The definition of heart failure with preserved systolic function or diastolic heart failure remains a matter of controversy[12,25] and a difficult exercise in clinical practice. This probably explains why clinical trials have been lacking and guidelines on the management of this subset of patients remain mainly speculative.[6] So far, only a subset of patients enrolled in the DIG trial with EF >45% and the CHARM preserved arm have extensively studied the effect of Digoxin and Candesartan, respectively in PLVF patients. Digoxin reduced heart failure hospitalisations and the Angiotensin II receptor blockers (ARB) reduced cardiovascular hospitalisations in these trials.[22,26] Our analysis on the large EuroHeart Failure

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Table 3 Differences in outcome between patients with preserved and depressed left ventricular function

	PLVF ($n = 3148$)	LVSD ($n = 3658$)	p
Total mortality (%)[a]	307 (10)	425 (12)	0.01
Re-admission <12 weeks (%)	676 (22)	759 (21)	0.47
Time to 1st re-admission in days (median, IQR)	29 (10—54)	28 (10—53)	0.66
Hospitalisation time in days during follow-up (median, IQR)	11 (6—22)	11 (5—22)	0.30
12-week follow-up interview[b] (n, %)	1124 (36)	1304 (36)	
NYHA classification			0.64
Class I/II (%)	844 (76)	965 (75)	
Class III/IV (%)	270 (24)	327 (25)	
Quality-of-life			0.04
Very good—quite good (%)	516 (46)	545 (42)	
Average (%)	340 (30)	380 (29)	
Quite poor—very poor (%)	257 (23)	369 (29)	

NYHA, New York Heart Association classification.
[a] Patients who died during index hospitalisation or within the 12-week follow-up period.
[b] Only patients who attended the 12-week follow-up interview.

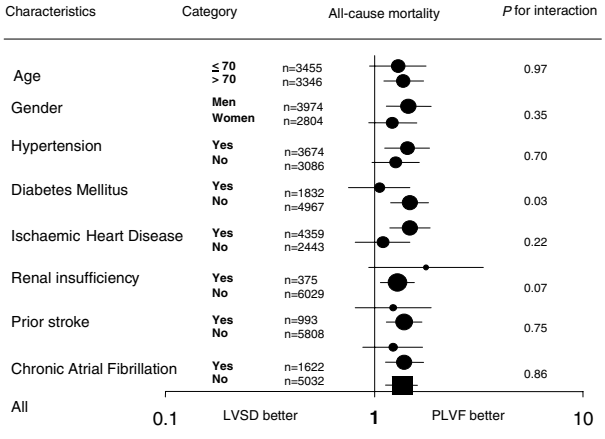

Fig. 2 Relation between left ventricular systolic function and mortality in subgroup of patients according to patient characteristics. Adjusted for age, gender, hypertension, diabetes, ischaemic heart disease, renal failure, prior stroke, chronic atrial fibrillation and pharmacological treatment.

Survey population provides additional information on the specific clinical profile of patients with PLVF and the way these patients are treated in Europe.

We included only patients with a known LV function, thus excluding 3895 patients (36%) of whom we had no information in this context. However, according to the guidelines, echocardiography is encouraged in all heart failure patients.[5,6] The high percentage of patients who could not be included in this secondary analysis reflects the lack of this diagnostic procedure in patients with proven or suspected heart failure.

As discussed in the main article of the EuroHeart Failure Survey[8], adherence to the guidelines regarding ACE-inhibitors was observed in a majority of patients with a documented ventricular dysfunction, whereas treatment with β-blockers was clearly under-prescribed. As mentioned earlier, treatment guidelines lack evidence-based recommendations for patients with a preserved left ventricular function. It is therefore not possible to compare the treatment of these patients with the guidelines. Moreover, since more patients with PLVF were hospitalised in general internal medicine as compared to those with LVSD, this could clearly affect management. Although there is currently no evidence available from randomised controlled trials on treatment of patients with a preserved LVF with ACE-inhibitors or β-blockers, a considerable percentage of these patients were treated with the above mentioned drugs (58% and 39%, respectively). For ACE-inhibitors, the rate of prescription among this hospitalised preserved LVF group compares favourably to the rate reported in CHARM Preserved (58% vs. 18.6%) whereas the use of β-blockers (39% vs. 55.5%) was lower than in the clinical trial.[22] In CHARM preserved there was a statistically marginal effect of the ARB candesartan on the outcome of cardiovascular mortality or heart failure hospitalisations. However, the total number of these hospitalisations, both for patients and episodes, was significantly reduced in this trial. The use of cardiac glycosides was significantly lower in the PLVF group although the rate of atrial fibrillation was slightly greater in the LVSD group. The relatively high rate of prescription of calcium channel blockers in the preserved group, one of the few drugs that are (according to the guidelines) indicated in this subgroup of patients, probably reflects the greater proportion of patients with a history of hypertension.

This study is the first to compare the effects of pharmacological treatment in patients with or without LVSD. We would like to stress however, that one should be very cautious in interpreting these observational data. Use of ACE-inhibitors or β-blockers was associated with improved survival, reflecting either the effects of treatment or patient selection. Therapy with diuretics, cardiac glycosides and nitrates seemed to have no influence on mortality, whereas those treated with an intravenous inotropic agent had a worse prognosis

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indicating the poor clinical condition of patients needing intravenous support with these drugs. Interestingly, this analysis revealed no interaction between the apparent effects of treatment on mortality and the presence or absence of LVSD.

Our study also observed the sub-optimal use of diagnostic procedures to evaluate LVF in daily practice, as 3895 patients were left out of this analysis due to the absence of this evaluation. Knowing the cardiac function is of great importance, as the guidelines primarily focus on heart failure patients with LVSD.[6] Given the limited number of randomised trials conducted in PLVF patients, the treatment of these patients is referred to as highly speculative. Several ongoing trials specifically address the interest of β-blockers (SENIOR), ACE-Inhibitors (PEP {CHF} or ARBs {I-Preserve}) in the setting of patients with preserved systolic function. Taking this into account one could argue that a large majority of the 10701 patients in the EuroHeart Failure Survey did not receive evidence-based treatment. This was mainly due to the missing evidence of cardiac dysfunction and the absence of evidence-based treatment aiming at PLVF patients. In order to provide optimal treatment to all heart failure patients, we should be more aware of the under-utilisation in evaluating the LVF. Furthermore, we would like to stress that the observed absence of a heterogeneous effect between patients with or without LVSD does not mean that patients with PLVF will derive the same benefit from pharmacological treatment as those with LVSD. This observation deserves confirmation in randomised trials. Thus the evaluation of LVF remains an area for improvement.

This study has certain limitations that should be taken into account when interpreting the results. It should be noted that surveys like the EuroHeart Failure Survey are prone to information and selection bias. Since a limited number of centres were recruited across the 24 countries, interpretation of the results must be cautious due to a potential centre effect. However our findings, with respect to the proportion of patients with PLVF and use of various treatments, were in agreement with the IMPROVEMENT survey, which was performed by primary care physicians in the same European countries.[27]

Furthermore, we acknowledge the fact that only 64% of our overall population had undergone an assessment of the left ventricular function and cannot exclude selection bias, as the excluded patients slightly differed from those in the analysis. Nevertheless, our findings regarding patients with heart failure are in line with other observational studies.[15–17,21] By design, the EuroHeart Failure survey included clusters of university hospitals and general hospitals. We cannot therefore extend our observation to the overall heart failure population as this selection of centres might impact on the patients' profile and treatment modalities. The selection of patients studied here was based on the record of the value of ejection fraction whatever the method used. We also used an arbitrary threshold of 40% to separate depressed and preserved or mildly reduced systolic function. However, a sensitivity analysis showed comparable results whatever the threshold for ejection fraction used. Finally, the impact of the various cardiovascular medications was made in the context of an observational study, not of a randomised trial.

In conclusion, this study showed that a high percentage of hospitalised heart failure patients had PLVF. Although major statistical differences exist regarding clinical characteristics and treatment, morbidity and mortality was high in both groups. A considerable number of patients in the preserved group were treated with drugs (ACE-inhibitors and β-blockers) that have a documented impact on survival in patients with a depressed LV systolic ventricular function. Although there was still under-utilisation of these drugs according to the guidelines in the depressed group, far more patients in this group received ACE-inhibitors or β-blockers compared to patients with a preserved ventricular function. Finally, only a limited number of patients were treated by ARBs in both groups. A comparison of the effect of pharmacological treatment, in the context of an observational study did not reveal an interaction of the treatment effect on mortality between LVSD and PLVF.

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