Assessment of Long-Term Effects of Irbesartan on Heart Failure With Preserved Ejection Fraction as Measured by the Minnesota Living With Heart Failure Questionnaire in the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) Trial

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Background—The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was used in a large, multinational, randomized, placebo-controlled trial to measure adverse effects of heart failure with preserved ejection fraction (HF-PEF) on patients' lives and the effects of irbesartan.

Methods and Results—Patients with symptomatic HF-PEF were randomly assigned to irbesartan (up to 300 mg daily) or placebo. The MLHFQ was administered at baseline (n=3605), month 6 (n=3137), month 14 (n=2904), and the end of study (median, 56 months, n=2205). Baseline MLHFQ scores of 43±21 indicated that HF-PEF had a substantial adverse effects. Estimated retest reliability was 0.80. Baseline MLHFQ scores were associated with other measures of the severity of heart failure including symptoms, signs of congestion, cardiac structure, and time to hospitalizations or deaths attributed to heart failure. Slight improvement in shortness of breath or fatigue was associated with significant improvement in MLHFQ scores (−5.9 and −5.0, $P<0.0001$). Compared with placebo, further improvement in MLHFQ scores was not observed with irbesartan after 6 months (mean adjusted difference, 0.4; 95% confidence interval, −0.8 to 1.7), 14 months (0.5; 95% confidence interval, −0.9 to 1.8), or the end of study (2.0; 95% confidence interval, −4.1 to 0.01).

Conclusions—The MLHFQ scores are a reliable, valid, and sensitive measure of the adverse impact of HF-PEF on patients' lives. Irbesartan did not substantially improve MLHFQ scores during a long period of follow-up.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00095238.

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Key Words: diastolic heart failure ■ ARBs ■ quality of life

Patients with heart failure often seek medical care for relief of symptoms, functional limitations, and psychological distress. The MLHFQ is a measure of heart failure as indicated by these adverse effects on patients' lives that has been widely used in clinical trials of heart failure with reduced ejection (HF-REF).[1–3] The effects of treatments for HF-PEF on MLHFQ scores have not been studied as extensively. The predominant cause of HF-PEF, nature of the cardiac dysfunction, and affected population (more prevalent among elderly women) differ from HF-REF. However, HF-PEF and HF-REF lead to the same symptoms and functional limitations and affect patients' lives in similar ways.[4–6]

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The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial enrolled a large number of patients with symptomatic HF-PEF to test whether irbesartan can reduce mortality and cardiovascular hospitalizations and secondarily the adverse impact of HF-PEF on patients' lives as measured by the MLHFQ.[7] A cursory report of the

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Table 1. Study MLHFQ Data

	Baseline	6 Months	14 Months	End of Study
Missing responses, n (%)*				
0	3148 (76)	2740 (76)	2508 (86)	1912 (85)
1 (imputed)	283 (6.8)	266 (7.4)	245 (8.4)	191 (8.5)
2 (imputed)	118 (2.8)	90 (2.5)	108 (3.7)	74 (3.3)
3 (imputed)	56 (1.4)	41 (1.1)	43 (1.5)	28 (1.2)
4–20 (excluded)	45 (1.1)	36 (1.0)	29 (0.8)	35 (1.0)
Missing or blank MLHFQ form	478 (12)	468 (13)	699 (19)	1400 (39)
Deaths	0 (0)	58 (1.6)	160 (4.4)	766 (21)
Reason unknown	478 (12)	410 (11)	539 (15)	634 (18)
Distribution† of MLHFQ scores				
No. of patients	3605	3137	2904	2205
Total score	42 (28–58)	32 (18–46)	30 (17–45)	30 (15–45)
Physical dimension‡	22 (15–29)	16 (10–23)	16 (9–23)	16 (8–23)
Emotional dimension	8 (3–13)	5 (2–10)	5 (2–10)	5 (2–10)
Cronbach α				
Total score	0.92	0.92	0.93	0.94
Physical dimension	0.91	0.91	0.92	0.93
Emotional dimension	0.85	0.86	0.87	0.88

MLHFQ indicates Minnesota Living with Heart Failure Questionnaire.

*Percentage of the 4128 enrolled in the study at baseline and percentage of the number with baseline scores (n=3605) at subsequent visits.

†Median (25th to 75th percentiles).

‡See Table 2 for definition of dimensions.

MLHFQ data indicated irbesartan did not have a significant effect during the first 6 months of follow-up.[8] When a theoretically useful treatment for HF does not improve a patient-reported outcome measure such as the MLHFQ, the reliability, validity, and sensitivity of the data need to be examined in-depth. The only other major randomized, controlled trial of treating HF-PEF with an angiotensin-II receptor blocker did not examine its effects on MLHFQ scores.[4] Therefore, we conducted in-depth analyses of the MLHFQ data from the I-PRESERVE Trial including longer follow-up and assessments of the reliability, validity, and sensitivity to change in this pivotal multinational trial.

Methods

The I-PRESERVE Trial design has been published.[9] Briefly, qualifying patients were ≥60 years old with New York Heart Association (NYHA) class II–IV symptoms and an ejection fraction >45%. Patients who had not been hospitalized due to heart failure during the previous 6 months were required to have NYHA class III or IV symptoms with corroborative evidence of heart failure, or a substrate for HF-PEF, such as ECG or echocardiographic evidence of left ventricular hypertrophy or, if atrial fibrillation was absent, left atrial enlargement. Treatment with an angiotensin-converting enzyme inhibitor was permitted in up to one-third of enrolled patients who had specific indications such as diabetes or atherosclerotic cardiovascular disease.

Patients (n=4128) were enrolled in 25 countries. The primary end point was a composite of death from any cause or the first blindly adjudicated hospitalization for a protocol-specified cardiovascular cause (worsening heart failure, unstable angina, myocardial infarction, ventricular or atrial dysrhythmia, or stroke). The composite outcome of the first hospitalization or death due to heart failure was used to examine the predictive validity of the MLHFQ.

Investigators asked participating patients to complete the MLHFQ at baseline, 6 and 14 months after random assignment, and the end of study visit. Each of the 21 questions asked the patients to indicate how much a possible effect of heart failure prevented them from living as they wanted during the past month (30 days), using a scale from 0 (not present or no effect), 1 (very little), 2, 3, 4, or 5 (very much). The entire MLHFQ and its physical and emotional dimensions were scored by summing responses. Patients were also asked how much their shortness of breath and fatigue had changed since starting study treatment using a 7-point scale of markedly, moderately, or slightly improved or worsened or unchanged. Both patients and investigators reported their global assessment of change in heart failure using the same 7-point scale.

An echocardiography substudy that enrolled 745 subjects in sinus rhythm to examine the effects of irbesartan on left atrial size, left ventricular hypertrophy, and indices of diastolic function provided several echocardiographic measures of HF-PEF that were analyzed to help validate the MLHFQ.[10]

Data Analysis

First, the number of missing MLHFQ responses was examined at each visit, and imputation was used to fill-in questionnaires with ≤3 missing responses. Each missing value was predicted by regression of questions with missing responses on the best subset of responses to other questions. Other study variables were not used for imputation to avoid biasing estimates of their relationships to MLHFQ scores. The prediction error inherent in using a single imputed value probably would lead to underestimation of relationships to other variables. There were no substantial differences in results when the data are analyzed without the imputed values (complete MLHFQ only). Questionnaires with >3 missing responses were excluded.

Distributions of patients' responses are summarized as mean±SD. Internal consistency of the MLHFQ was assessed by Cronbach α coefficient, a function of the mean pairwise correlation between responses to all 21questions. Absent repeated

baseline administration of the MLHFQ when patients were clinically stable, retest reliability was estimated using a path model of the correlations between baseline, month 6, and month 14 scores to account for any changes in what is being measured during the widely spaced measurements.[11]

Relationships to clinical assessments of HF-PEF including several echocardiographic measures were examined by linear regression analysis with robust standard errors to assess validity of the MLHFQ. Conceptually speaking, symptoms of HF-PEF should be directly related to MLHFQ scores. Signs and pathophysiologic measures of HF-PEF should be indirectly related to the MLHFQ scores, depending on how strongly each relates to perceived symptoms, functional limitations, and psychological effects of HF-PEF.

Some MLHF questions may be more or less applicable or important, depending on the patients' culture, lifestyle, roles, sex, activities, and so forth. For example, working to earn a living might be less important to elderly retired subjects. The MLHFQ scores were related to the patients' age, sex, and country, using multivariable regression analysis to adjust for any differences in assessments of HF-PEF and comorbidity.

To examine predictive validity, baseline MLHFQ scores and changes thereof during the first 6 months of follow-up were related to times to subsequent hospitalizations or death attributed to heart failure by fitting Cox regression models. The proportional hazards assumption was tested using standardized Schoenfeld residuals. An interaction between MLHFQ scores and follow-up time was tested and added to model changes in the hazard ratio (HR). Cox regression models with dummy variables representing discrete follow-up intervals, and their interaction with MLHFQ scores were also used to estimate the variation HRs during follow-up. All Cox models included age and sex as covariates and were stratified by country. Clinical correlates of MLHFQ scores and comorbidities were not included because they could represent the same variation as MLHFQ scores.

To further evaluate construct validity and sensitivity to differences between groups, changes in MLHFQ scores after 6 months were compared by ANOVA of groups defined by patients' or investigators' ratings of changes in dyspnea, fatigue, global assessments of heart failure, and NYHA class. Whenever the main effect of the change categories was significant (all were $P<0.00001$), the MLHFQ scores in the "no change category" were compared with other categories of change, using a Bonferroni adjustment for multiple post hoc comparisons.

Changes in the MLHFQ scores in the groups randomly assigned to irbesartan or placebo were compared by linear regression analyses that included baseline MLHFQ scores, age, sex, country, all baseline clinical assessments that were associated with MLHFQ scores including several comorbidities (a history of stable angina, diabetes mellitus, peripheral vascular disease, tobacco use, ethanol abuse, chronic obstructive pulmonary disease and cancer), treatment with an angiotensin-converting enzyme inhibitor, and hospitalization for heart failure within 6 months before enrollment. Analyses at the end of study also included time to discontinuation of the randomly assigned treatment and use of medications typically prescribed for HF-REF. Each follow-up visit was analyzed separately due to declining numbers of subjects. Confidence intervals (98.3%) were adjusted for comparing the treatment groups at 3 follow-up times ($1-0.05/3=1-0.0167=0.983$). In addition, a longitudinal mixed effects regression model of the individual changes in MLHFQ scores at the 6-month, 14-month, and end-of-study (month 55 on average) visits on time, treatment, and their interaction was used to estimate the overall effect of irbesartan on mean MLHFQ scores and rates of change. The intercepts (6-month change scores) and slopes (linear rates of change between 6 months and the end of study) were specified to be random effects with unstructured covariance.

Stata software (version 10.1) was used for all analyses. Unless stated otherwise, probability values and confidence intervals are reported without adjustment for multiple comparisons.

Table 2. Baseline Distribution of MLHFQ Responses

Question About …	Response >0 (%)	Responses,* Mean±SD
1. Swelling in ankles, legs	76	1.9±1.5
2. Need to sit or lie down†	89	2.6±1.4
3. Difficulty walking, climbing stairs†	93	3.2±1.4
4. Difficulty with house or yard work†	88	2.8±1.6
5. Difficulty going places away from home†	82	2.6±1.7
6. Difficulty sleeping well†	77	2.1±1.6
7. Difficulty doing things with family or friends†	67	1.7±1.5
8. Difficulty working to earn a living	51	1.6±1.8
9. Difficulty with recreational activities	71	2.2±1.8
10. Difficulty with sexual activities	42	1.3±1.8
11. Eating less likeable foods	71	1.8±1.6
12. Shortness of breath†	94	3.2±1.4
13. Fatigue, tiredness, or low energy†	95	3.2±1.3
14. Hospital stay	39	1.1±1.6
15. Costing money for medical care	67	2.0±1.8
16. Treatment side effects	40	0.8±1.3
17. Being a burden family or friends‡	48	1.2±1.5
18. Loss of self-control‡	56	1.3±1.5
19. Worry‡	81	2.2±1.6
20. Difficulty with concentration, memory‡	76	2.0±1.6
21. Feeling depressed‡	71	1.9±1.6

MLHFQ indicates Minnesota Living with Heart Failure Questionnaire.

*Question was whether the possible effect of heart failure was present and prevented the patient from living as they wanted during the past month ranging from 0 (no), 1 (very little), to 5 (very much). Higher scores indicate that heart failure with preserved ejection fraction more adversely affected patients' lives.

†Questions included in the physical dimension.

‡Questions included in the emotional dimension.

Results

Table 1 summarizes the MLHFQ data collected at each visit. Most respondents completed all 21 questions. Questions about sexual activities (7.7%) and working to earn a living (5.6%) were most frequently unanswered at baseline (and throughout the trial). The median (25–75th percentile) MLHFQ score at baseline was 42 (28–58). Cronbach α for the total score was consistently ≥ 0.92. Estimated retest reliability of the total score was 0.80 (0.80 and 0.71 for the physical and emotional dimension scores).

Shortness of breath, fatigue, and difficulty walking or climbing stairs had the greatest impact on these patients with HF-PEF (Table 2). Swelling in the lower extremities was common but had little impact. Sexual difficulties, hospital stays, and side effects of treatments were either not applicable during the past month (the reference period for the questions) or had little adverse impact on the majority of subjects.

Relationship to Clinical Assessments

Table 3 shows progressively higher (worse) MLHFQ scores with worse NYHA class or peripheral edema. Scores were higher when signs of circulatory congestion including pulmonary rales, jugular venous distention, and an enlarged liver

Table 3. Relationships Between Baseline MLHFQ Scores and Clinical Assessments

Clinical Assessment	Baseline Distribution*	Mean Difference† in MLFQ Score
Symptom		
NYHA class		
II	773 (21)	Reference group
III	2730 (76)	9.3 (7.7, 11.0)¶
IV	101 (3)	25.8 (21.6, 30.0)¶
Peripheral edema		
None	1658 (46)	Reference group
Trace	1102 (31)	2.7 (1.1, 4.3)¶
1–2+	762 (21)	7.7 (5.9, 9.4)¶
3–4+	70 (2)	13.7 (9.0, 18.3)¶
Hospitalization in past 6 mo	1603 (44)	0.9 (−0.4, 2.3)
Cardiovascular		
Presumed etiology of heart failure		
Hypertension	2349 (65)	−0.8 (−2.2, 0.6)
Ischemic heart disease	868 (24)	2.3 (0.7, 3.9)‖
Lung auscultation		
Clear	2483 (69)	Reference group
Wheezing only	924 (26)	4.4 (−0.04, 8.8)
Basilar rales	106 (3)	5.8 (4.3, 7.4)¶
Diffuse rales	86 (2)	14.4 (10.5, 18.4)¶
Jugular venous distension	283 (8)	7.0 (4.4, 9.5)¶
Enlarged liver	701 (19)	9.1 (7.4, 10.8)¶
S3/4 gallop	297 (8)	5.3 (2.8, 7.8)¶
LV hypertrophy detected by ECG	1146 (32)	5.4 (4.0, 6.9)¶
LVEF	59±9	−0.3/5%
>60%	1780 (49)	−1.1 (−2.5, 0.2)
NT-proBNP, pg/mL		
≤300	1456 (47)	Reference group
301–1000	889 (29)	−1.2 (−3.0, 0.5)
>1000	741 (24)	0.9 (−1.0, 2.7)
Systolic blood pressure, mm Hg	136±15	−0.2 (−0.5, −0.02)/5 mm Hg§
Diastolic blood pressure, mm Hg	79±9	0.7 (0.3, 1.0)/5 mm Hg¶
Pulse pressure, mm Hg	57±13	−0.6 (−0.9, −0.4)/5 mm Hg¶
Heart rate, beats/min	71±10	0.6 (0.3, 1.0)/5 beats/min¶
Left bundle-branch block	299 (8)	1.4 (−1.1, 3.8)
Atrial fibrillation or flutter	598 (17)	0.5 (−1.3, 2.3)
Laboratory		
Serum sodium, mEq/L		
≤135	249 (7)	−1.4 (−4.0, 1.3)
136–145	3209 (91)	Reference group
>145	82 (2)	5.4 (0.8, 9.9)§
Serum potassium, mEq/L		
≤3.5	70 (2)	−2.2 (−7.1, 2.7)
3.6–5.0	3111 (88)	Reference group
>5.0	338 (10)	2.5 (0.2, 4.8)§
Serum albumin, g/dL		
≤4.0	1493 (42)	−0.2 (−1.9, 1.5)
4.1–5.0	1000 (28)	Reference group
>5.0	1047 (30)	0.6 (−1.2, 2.4)
Blood urea nitrogen >25 mg/dL	765 (22)	0.8 (−0.9, 2.5)

(*Continued*)

Table 3. Continued

Clinical Assessment	Baseline Distribution*	Mean Difference† in MLFQ Score
Serum creatinine >1.5 mg/dL	219 (6)	−2.5 (−5.3, 0.4)
Estimated GFR, mL/min per 1.73 m^2		
≤45	331 (9)	0.6 (−1.8, 3.0)
46–60	761 (22)	1.4 (−0.3, 3.1)
>60	2450 (69)	Reference group
Hemoglobin, g/dL		
<12	336 (10)	1.2 (−1.2, 3.6)
12–15	2379 (68)	Reference group
>15	785 (22)	−0.7 (−2.4, 1.0)
Body mass index, kg/m^2	29.6±5.3	1.6 (1.0, 2.3)/5 kg/m^2¶
Medical history‡		
Stable angina	1465 (41)	3.8 (2.4, 5.2)¶
Diabetes mellitus	958 (27)	5.0 (3.4, 6.5)¶
Peripheral vascular disease	966 (27)	2.0 (0.5, 3.5)¶
Tobacco use	667 (18)	−5.0 (−6.8, −3.3)¶
Ethanol abuse	399 (11)	−8.2 (−10.3, −6.6)¶
COPD or adult asthma	328 (9)	−2.8 (−5.2, −0.5)§
Cancer	200 (6)	−4.0 (−7.0, −1.0)¶

MLHFQ indicates Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; LV, left ventricular; LVEF, LV ejection fractions reported by each investigational site that used varying methods; NT-proBNP, N-terminal pro B-type natriuretic peptide; GFR, glomerular filtration rate; and COPD, chronic obstructive pulmonary disease.

*Summarized as n (percentage) or mean±SD.

†Difference from reference group estimated as linear regression coefficients (95% confidence interval). All other patients are the reference group for all dichotomous variables.

‡History of some conditions that could have had an effect on MLHFQ scores unrelated to heart failure with preserved ejection fraction.

§$P<0.05$.

‖$P<0.01$.

¶$P<0.001$.

were present. On average, MLHFQ scores were higher in the presence of left ventricular hypertrophy on ECG, an S3 (or S4) gallop, an ischemic etiology, and higher heart rates. Conversely, MLHFQ scores were lower (better) with higher systolic and pulse pressures. The MLHFQ scores were not related to the ejection fractions, circulating levels of natriuretic peptide, or measures of renal function.

From the echocardiography substudy, left atrial diameter >4.2 cm (women) or 4.6 cm (men) was positively associated with the baseline MLHFQ scores (39%; n=603; mean difference in MLHFQ score, 3.4; $P=0.03$) as was the left ventricular mass to end-diastolic volume ratio (n=474; median, 1.8 g/mL; 25–75th percentile, 1.4–2.4; $P=0.03$), with an estimated mean difference in MLHFQ score of 2.5 g/mL. An E/A ratio of ≤0.8 (46%; n=585; mean difference in MLHFQ score, 0.7; $P=0.66$), isovolumic relaxation time >110 ms (22%; n=569; mean difference, 2.4; $P=0.22$), and lateral E/E′ ratio >15 (24%; n=446; mean difference, 3.7; $P=0.09$) were not significantly associated with MLHFQ scores.

Men had significantly lower adjusted MLHFQ scores (Table 4). Average adjusted baseline MLHFQ scores in several countries differed from the United States. Nevertheless, the estimated effect of irbesartan did not vary significantly by country (interaction probability value=0.82), sex (interaction probability value=0.24), or in the elderly (interaction probability value=0.24).

Relationship to Heart Failure Morbidity and Mortality

Of the 3605 patients who had a baseline MLHFQ score and median follow-up of 4.3 years, 616 (17%) had an adjudicated hospitalization or death attributed to heart failure. The interaction between MLHFQ scores and follow-up time was significant ($P<0.0001$), indicating that the hazard ratio (HR) decreased over time from an initial value of 1.6 per 5 points higher MLHFQ score (95% confidence interval, 1.5–1.7; $P<0.0001$). Estimates of HRs within sequential time intervals show the downward trend from the first 6-month interval (HR, 1.6; 95% confidence interval [CI], 1.51–1.65; $P<0.0001$), to the next 6-month interval (HR, 1.3; 95% CI, 1.28–1.38; $P<0.0001$), to the second (HR, 1.2; 95% CI, 1.14–1.21; $P<0.0001$) and third (HR, 1.05; 95% CI, 1.02–1.08; $P=0.002$) year of follow-up.

Changes During First 6 Months

Of the patients with a baseline MLHFQ score, 3137 (87%) had a score at 6 months. Fifty-eight (1.6%) died before the 6-month visit, and 36 (1.0%) were missing >3 MLHFQ

Table 4. Demographics in Relation to Baseline MLHFQ Scores and Irbesartan Effects

Demographic Variable	Baseline Distribution*	Difference in Baseline MLHFQ Score†	Mean Effect of Irbesartan on Change in MLHFQ Score at 6 Months†
Age, y	71±7	0.2/5 y	
≥65	2956 (82)	0.1 (−1.5, 1.8)	0.7 (−0.4, 1.9)
<65	649 (18)	Reference group	−0.9 (−3.8, 2.1)
Sex			
Female	2199 (61)	Reference group	1.2 (−0.4, 2.8)
Male	1406 (39)	−4.8 (−6.1, −3.4)¶	−0.05 (−1.7, 1.6)
Country			
United States	224 (6)	Reference group	2.9 (−3.7, 9.5)
Canada	71 (2)	9.4 (5.0, 13.8)¶	−1.4 (−7.2, 4.5)
Mexico	150 (4)	7.1 (2.2, 12.0)‖	−1.9 (−8.2, 4.3)
Argentina	363 (10)	9.1 (5.4, 12.7)¶	2.2 (−2.0, 6.4)
Brazil	145 (4)	4.1 (−0.6, 8.8)	−1.6 (−7.6, 4.4)
The Netherlands	213 (6)	−5.8 (−9.7, −2.0)‖	1.2 (−2.8, 5.3)
Germany	189 (5)	−9.8 (−13.6, −5.9)¶	1.0 (−3.4, 5.3)
France	177 (5)	1.4 (−2.9, 5.8)	2.2 (−2.5, 6.8)
Spain	227 (6)	12.6 (8.2, 16.9)¶	3.5 (−0.6, 7.7)
Belgium	131 (4)	−3.8 (−8.6, 0.9)	0.6 (−5.4, 6.6)
Poland	272 (8)	12.4 (8.3, 16.5)¶	1.0 (−2.6, 4.6)
Hungary	65 (2)	14.0 (8.2, 19.8)¶	−2.9 (−10.8, 5.0)
Czechoslovakia	107 (3)	0.5 (−4.5, 5.5)	2.7 (−5.0, 10.3)
Russia	1017 (28)	10.3 (6.7, 14.0)¶	−0.7 (−2.4, 0.9)
Other‡	254 (7)	−3.1 (−6.9, 0.7)	2.2 (−2.0, 6.4)

MLHFQ indicates Minnesota Living with Heart Failure Questionnaire.

*Summarized as n (percentage) or mean±SD.

†Mean difference (95% confidence interval) between groups adjusted for significant clinical assessments and medical history listed in Table 3 and other demographics. Tests for interaction with irbesartan effect were not significant (elderly, $P=0.24$; sex, $P=0.24$; country, $P=0.82$).

‡Other countries with <50 subjects including Australia (n=38), Denmark (n=1), Greece (n=19), Ireland (n=9), Italy (n=14), Norway (n=23), Portugal (n=26), South Africa (n=32), Sweden (n=48), Switzerland (n=1), and The United Kingdom (n=43).

§$P<0.05$.

‖$P<0.01$.

¶$P<0.001$.

responses. There was a notable improvement in MLHFQ scores in both treatment groups that persisted to the end of the study (Table 1).

Average 6-month changes in MLHFQ scores within categories of concurrent changes in symptoms, global assessments, and NYHA class are shown in Figures 1, 2, and 3. Changes in MLHFQ scores were clearly related to patient and investigator assessments of changes in heart failure symptoms. The MLHFQ scores indicated some improvement when no change was reported in other measures. The MLHFQ scores in the "slight symptom improvement" or 1 NYHA class improvement categories were significantly different ($P<0.001$) from the respective "no change" categories as were the slightly worse categories except the 3.3 higher mean

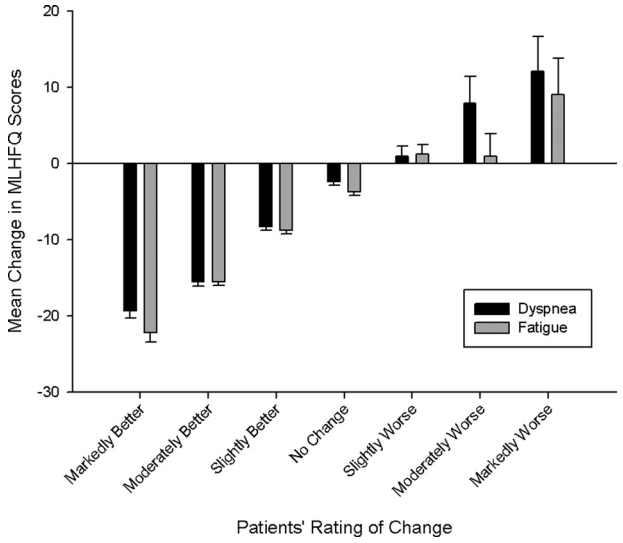

Figure 1. Mean (standard error) changes in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores within categories of patients' ratings of changes in dyspnea and fatigue during the first 6 months of treatment.

MLHFQ score in the slightly worse dyspnea subgroup (n=120).

Changes in MLHFQ scores during the first 6 months of follow-up were associated with subsequent heart failure events by Cox regression that included the baseline MLHFQ scores. The initial HR for a 5-point increase in score was 1.2 (95% CI, 1.1–1.3; $P<0.0001$). The interaction between the effect of the MLHFQ score and follow-up time was also significant ($P<0.0001$), indicating the HR decreased during follow-up.

Comparison of Changes in MLHFQ Scores in Treatment Groups

As summarized in Table 5, fewer patients had MLHFQ scores at each subsequent visit. However, the number of subjects in each

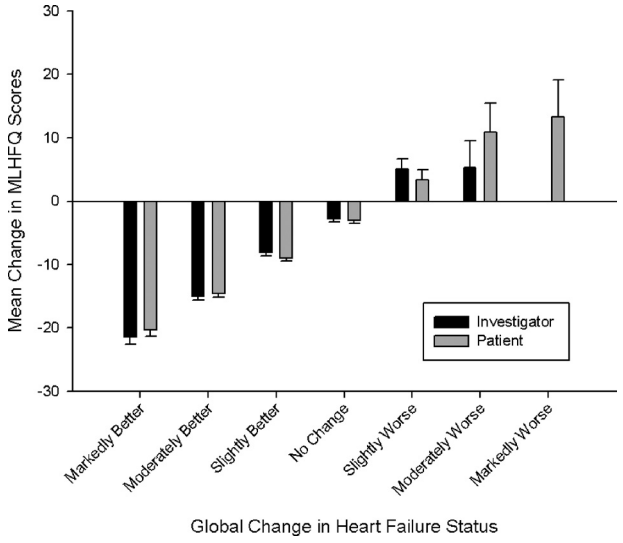

Figure 2. Mean (standard error) changes in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores within categories of patients' and investigators' global ratings of changes in heart failure during first 6 months of treatment.

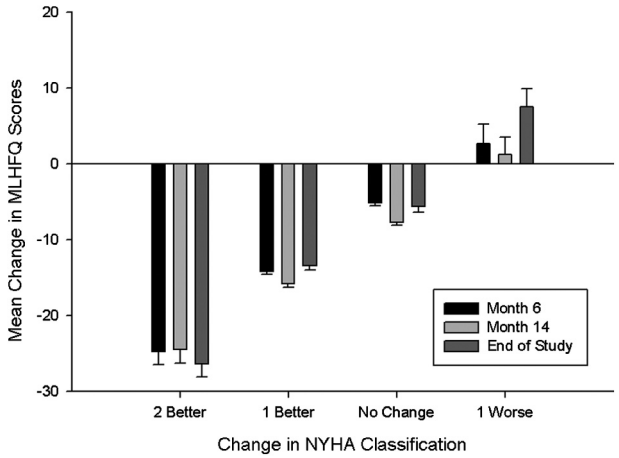

Figure 3. Mean (standard error) changes in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores within categories of changes in New York Heart Association (NYHA) class.

treatment group, distributions of baseline MLHFQ scores, percentages that discontinued the assigned treatment including interim mortality, and percentages treated with other medications that could affect MLHFQ scores were similar. The mean adjusted differences between treatment groups in the total MLHFQ score were not significant at any visit.

The longitudinal regression analysis found a very small annual rate of reduction of 0.4/y (95% CI, 0.1–0.6/y, $P=0.01$) in the initial 6-month improvement in MLHFQ scores in the placebo group. Compared with the placebo group, irbesartan prevented this slow worsening of MLHFQ scores (difference −0.6/y; 95% CI, −1.0 to −0.2; $P=0.003$). Averaging over all 3 visits, the difference in changes in MLHFQ scores between the irbesartan and placebo groups was not significant (0.8; 95% CI, −0.4 to 2.0; $P=0.20$). Separate analyses of the physical and emotional dimension scores found very similar results that are not reported.

Discussion

The median MLHF scores of 42 (quartiles 28–58) at baseline indicate HF-PEF adversely affected the lives of the majority of patients enrolled in the I-PRESERVE Trial, of whom 75% had NYHA class III symptoms at baseline. All 21 questions were pertinent to substantial proportions of these symptomatic patients and their responses were highly internally consistent, suggesting that all responses were related to the same phenomenon, presumably HF-PEF. In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study of HF-PEF, the distribution of scores among NYHA class III patients was 48 (32–67) and

Table 5. Changes in MLHFQ Scores Within Treatment Groups

	6 Months		14 Months		End of Study*	
	Irbesartan	Placebo	Irbesartan	Placebo	Irbesartan	Placebo
Subjects, n (%)†	1567 (87)	1570 (87)	1446 (81)	1458 (81)	1102 (61)	1103 (61)
Discontinued study treatment, %	6.7	7.0	13	11	40	40
Adverse event	2.9	2.8	5.7	4.3	15	13
Mortality	1.6	1.6	4.5	4.4	21	20
Concurrent meds, %						
ACE inhibitor	22	25	26	23	30	27
β-blocker	60	61	61	60	65	64
Diuretic	82	87	87	84	86	81
Loop diuretic	62	60	60	61	61	61
Spiranolactone	18	19	19	18	21	16
CaCB	34	39	40	36	40	36
Baseline score	43±21	43±21	43±21	43±20	43±21	42±20
Changes in score	−9.7±18	−9.7±17	−12.0±19	−12.2±18	−11.9±23	−9.6±23
Unadjusted mean difference (98.3% CI)						
Total score	0.0 (−1.5, 1.5)		0.2 (−1.4, 1.9)		−2.3 (−4.6, 0.01)	
Physical dimension	0.0 (−0.7, 0.7)		0.4 (−0.4, 1.2)		−0.8 (−1.9, 0.3)	
Emotional dimension	−0.1 (−0.6, 0.3)		−0.1 (−0.6, 0.4)		−0.6 (−1.3, 0.02)	
Adjusted‡ mean difference (98.3% CI)						
Total score	0.4 (−0.8, 1.7)		0.5 (−0.9, 1.8)		−2.0 (−4.1, 0.01)	
Physical dimension	0.2 (−0.5, 0.8)		0.5 (−0.2, 1.2)		−0.7 (−1.6, 0.3)	
Emotional dimension	0.0 (−0.4, 0.4)		−0.1 (−0.5, 0.4)		−0.6 (−1.2, −0.01)	

MLHFQ indicates Minnesota Living with Heart Failure Questionnaire; ACE, angiotensin-converting enzyme inhibitor; CaCB, calcium channel blocker; CI, confidence interval.

*Median, 56; interquartile range, 50–62 months after baseline visit.

†Baseline MLHFQ score included 1795 patients in the irbesartan group and 1810 in the placebo group.

‡Baseline MLHFQ score, age, sex, country, all significant baseline clinical assessments, and comorbidities (in Table 3) and whether the subject was treated with an angiotensin-converting enzyme inhibitor or hospitalized for heart failure within 6 months before enrollment are included as covariates in the regression model.

27 (15–48) for class II patients.[4]. The distributions of MLHFQ scores in the CHARM study of patients with HF-REF and NYHA class II (26, 13–47) or III (44, 25–62) heart failure were very similar. The distribution of MLHFQ scores in I-PRESERVE is also similar to other studies of HF-REF [12–14] Thus, depending on the patients' symptoms and functional limitations, heart failure has similar adverse effects on patients' lives regardless of their ejection fraction.

In-depth analysis of MLHFQ data collected by the I-PRESERVE investigators did not reveal clinically significant effects of irbesartan after 6, 14, or a median of 56 months of follow-up. This result is consistent with a much smaller open-label study of patients with HF-PEF given lower doses of irbesartan (75 mg, n=56) that did not see more improvement in MLHFQ scores after 12, 24, or 52 weeks than seen with diuretic therapy (n=50).[15] These are the only 2 studies we know that used the MLHFQ to evaluate an angiotensin receptor antagonist for HF-PEF.

The lack of an irbesartan effect could not be attributed to the measurement performance of the MLHFQ in this multinational study. The estimated retest reliability coefficient of 0.80 was sufficient for comparing treatment groups. Changes in MLHFQ scores in subgroups that had only slightly better or worse symptoms of heart failure or a change in one NYHA class were significantly different from those that did not change. The baseline MLHFQ scores were related to left atrial enlargement and left ventricular mass–to–volume ratio that were also independently associated with other study end points.[10] Baseline and changes in MLHFQ scores over 6 months were also associated with the end point of hospitalizations or deaths attributed to heart failure. Therefore, the reliability, validity, and sensitivity of the MLHFQ in this study of HF-PEF were sufficient to detect a treatment effect and similar to what has been reported in studies of patients with HF-REF.[2,12,16–18]

A substantial improvement in the MLHFQ scores occurred in both treatment groups during the first 6 months of follow-up and persisted in those followed to the end of the study. Similar improvements have been seen in some but not all studies of medications and disease management programs for patients with HF-REF.[19–24] Further unreported analysis of the MLHFQ scores in the placebo group indicated that the changes in the first 6 months were related to baseline scores (perhaps regression to the mean), country, sex, and age. Adjustments were made for all of these factors when estimating the effect of irbesartan. The 6-month estimates of the irbesartan effect did not vary significantly across countries, age groups, or sex. Thus, we do not believe the changes in MLHFQ scores seen in the placebo group during the first 6 months masked an irbesartan effect.

Although the number in each treatment group that died or were lost to follow-up were similar at each visit as were the baseline MLHFQ scores of the remaining subjects, unrecognized differences between the subjects remaining in each group and the reasons for the nonrandom losses during follow-up could have biased the long-term comparisons. Unreported comparisons of subjects that provided MLHFQ data at all follow-up visits showed essentially the same group trends and differences as did the longitudinal regression analyses.

The observed differences between countries in adjusted MLHFQ scores may be related to differences in language, culture, translation, and perhaps medical care for HF-PEF. Why women reported their lives were more adversely affected by HF-PEF is not known. The difference was not due to any particular questions. As much as possible, adjustments were made for any differences between sexes in the severity of symptoms and clinical assessments of HF-PEF, comorbidities, age, and country. The observed sex difference is consistent with other studies of patients with HF-PEF and HF-REF.[4,12,13] More to the point, the significant unexplained variation in MLHFQ scores between country and sex did not explain the lack of benefit from irbesartan.

In summary, irbesartan did not reduce the substantial adverse impact of symptomatic HF-PEF on patients' lives in the I-PRESERVE Trial. In-depth analyses indicate the lack of benefit was not due to lack of reliability, validity, or sensitivity of the MLHFQ in this large, multinational clinical trial.

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CLINICAL PERSPECTIVE

Patients with heart failure often seek medical care for relief of symptoms, functional limitations, and psychological distress that adversely affect their quality of life. The multinational Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial enrolled a large number of patients with symptomatic heart failure with preserved ejection fraction (HF-PEF) to test whether irbesartan can reduce mortality and cardiovascular hospitalizations and secondarily the adverse impact of heart failure on quality of life as measured by the Minnesota Living with Heart Failure Questionnaire. In-depth analyses indicated that the Minnesota Living with Heart Failure Questionnaire scores provided a reliable, valid, and sensitive measure of the adverse effects of heart failure with preserved ejection fraction on patients' lives. Although the quality of subjects' lives was adversely affected at baseline, there was no indication that irbesartan reduced the adverse effects during more than 4 years of follow-up.

Assessment of Long-Term Effects of Irbesartan on Heart Failure With Preserved Ejection Fraction as Measured by the Minnesota Living With Heart Failure Questionnaire in the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) Trial

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