Covariate adjusted reanalysis of the I-Preserve trial

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Abstract

Background: The CHARM-Preserved trial suggested that the renin-angiotensin system (RAS) inhibitor candesartan might have been beneficial in heart failure with preserved ejection fraction (HFpEF); however, this hypothesis was not supported by the findings of I-Preserve with irbesartan.

Aims: To re-analyse the results of I-Preserve, adjusting for imbalances in baseline variables that may have influenced the trial outcomes.

Methods: Cox proportional hazards models with covariate adjustment for baseline variables, including age, sex, medical history, physiological and laboratory variables.

Results: In I-Preserve, 763 (37.0%) participants in the placebo group and 742 (35.9%) in the irbesartan group experienced the primary composite outcome (death from any cause or hospitalization for heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke). The prespecified analysis of this outcome, stratifying for use of ACEi at baseline, gave a hazard ratio (HR) of 0.95 (95% confidence interval, 0.86-1.05); p=0.35. Adjusting the effect of treatment for key prognostic baseline variables, gave a HR of 0.89 (0.80-0.99); p=0.033. Similar findings were observed for the composite of cardiovascular death or HF hospitalization.

Conclusion: Adjusting for imbalances in baseline variables that influence outcomes (or the response to therapy or both) can improve the power around the estimate of the effect of treatment and may alter its statistical significance. Along with the CHARM-Preserved results, these findings suggest that angiotensin-receptor blockers may have a modest effect in HFpEF.

Key-words: heart failure with preserved ejection fraction; irbesartan; covariate adjustment; treatment effects.

INTRODUCTION

Although it is commonly stated that heart failure with preserved ejection fraction (HFpEF) is a condition for which no treatment has yet been shown to reduce morbidity or mortality, in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved trial, fewer individuals treated with candesartan experienced the composite outcome of a first admission to hospital for worsening heart failure or death from cardiovascular causes: 333 (22.0%) in the candesartan group compared with 366 (24.3%) in the placebo group, giving a hazard ratio (HR) of 0.89 (95% CI 0.77–1.03; p=0.118); for first heart failure hospitalization alone, the corresponding number were 241 (15.9%) and 276 (18.3%), respectively, giving a HR of 0.85 (0.72-1.01; p=0.072).[1] There was no reduction in cardiovascular death. In a prespecified secondary analysis of CHARM-Preserved, baseline characteristics were used to adjust for imbalances in variables that might affect outcomes. For the primary composite outcome, the resulting *adjusted* HR was 0.86 (0.74-1.00; p=0.051) and for first heart failure hospitalization the adjusted HR was 0.84 (0.70-1.00; p=0.047). Coupled with the primary and secondary analyses of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT), these findings suggest that blocking the renin-angiotensin-aldosterone system (RAAS) might be beneficial in HFpEF, at least in preventing heart failure hospitalization.[2-5] However, one large trial appears to be inconsistent with this hypothesis i.e. the Irbesartan in patients with heart failure and preserved ejection fraction trial (I-Preserve) which reported no benefit from irbesartan. There are several potential explanations for this discrepancy. First, the hypothesis that RAAS blockade is beneficial in HFpEF could be wrong. Second, the primary composite outcome in I-Preserve, which was death from any cause or hospitalization for a cardiovascular cause (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke), was quite different than in CHARM-Preserved and TOPCAT and may have been less sensitive to the effect of RAAS-blocking treatment. Third, imbalances in baseline variables that might have affected outcomes (or the response to irbesartan or both) were not adjusted for in I-Preserve, as in the secondary analysis of CHARM-Preserved. We examined these possibilities further by conducting a *post hoc* exploration of the effect of adjusting for a variety of baseline variables on

the response to treatment with irbesartan in I-Preserve. We also examined the unadjusted and adjusted effect of irbesartan on both the prespecified primary outcome in I-Preserve and the narrower, more disease-specific, composite outcome used in CHARM-Preserved (which was essentially the same as used in TOPCAT).

METHODS

Study design and objectives

The design and results of I-Preserve are published. In brief, 4,128 patients who were at least 60 years of age and had New York Heart Association (NYHA) functional class II, III, or IV HF and a left ventricular ejection fraction (LVEF) of at least 45% and echocardiographic, electrocardiographic or radiologic evidence supporting a diagnosis of HF were enrolled. Patients in NYHA functional class II were required to have had a HF hospitalization within the previous 6 months. Patients with a systolic blood pressure of less than 100 mmHg or more than 160 mmHg or a diastolic blood pressure of more than 95 mmHg, were excluded, as were individuals with substantial laboratory abnormalities (such as a haemoglobin level of less than 11 g per decilitre, a creatinine level of more than 2.5 mg per decilitre [221 μmol per litre], or liver-function abnormalities. The median follow-up was of 4.1 years. In the primary analysis of I-Preserve, no adjustment beyond stratification for angiotensin converting enzyme (ACE) inhibitor use at baseline was performed.[6]

Statistical analysis

Cox proportional hazards models stratified for the prior use if angiotensin-converting enzyme inhibitors (ACEi) were used as described in the primary analysis of the trial.[6, 7] Given the exploratory nature of this report, we developed three models adjusting for variables previously used in other I-Preserve prognostic models and those thought to have potential impact on prognosis and/or the treatment effect. The "Model 1" was adjusted for a previously published I-Preserve prognostic model,[8] that included age, sex, body mass index (BMI), heart rate, systolic blood pressure, haemoglobin, estimated glomerular filtration rate (eGFR), atrial fibrillation (AF) on ECG, diabetes mellitus, history of chronic obstructive pulmonary disease (COPD) or asthma, history of a myocardial infarction (MI), history of hypertension, history of stroke, LVEF, hospitalization for HF in the

previous 6 months, NYHA class, pulmonary congestion on chest radiograph, presence of jugular venous distension, serum albumin (log transformed), serum sodium, and neutrophil count (log transformed). Additionally, we built a simplified model (*Model 2*) using only the variables in Model 1 that are routinely available in clinical practice[9]. The variables included in *Model 2* were: 1) demographics – age and sex; 2) physiological/laboratory measurements - BMI, heart rate, systolic blood pressure, haemoglobin, eGFR; 3) medical history – AF on ECG, diabetes mellitus, valvular disease, history of COPD or asthma, history of MI, history of stroke and 4) measures of heart failure status - LVEF, duration of HF superior to 1 year, hospitalization for HF in the previous 6 months, NYHA class III or IV, and pulmonary congestion on chest radiograph. These variables were incorporated in a multivariate model ordered by the z-scores of each variable in the model. Finally, we built a third model (*Model 3*), using the variables in model 2 as well as NT-proBNP. Because NT-pro BNP was not measured in 16% of patients (*Supplemental Table 1*), we imputed all the variables with missing values using chained equations (MICE) and ran the estimates over 20 imputed datasets.[10] We also performed an additional model incorporating the top 5 prognostic variables without missing values, and the Model 2 with imputation.

These variables were reported by investigators by means of check boxes on a case-report form or measured as part of the central laboratory investigations in the trial.

All analyses were performed using STATA (Stata® version 15). A p value <0.05 was considered statistically significant. The robust variance estimator was used to compute all the presented models.

RESULTS

Baseline characteristics

The baseline characteristics of patients in each treatment group are shown in **Table 1**. The treatment groups were generally well matched, with no statistically significant difference between groups. However, as discussed below, there were small imbalances between treatment groups in baseline variables that might affect outcomes (or the response to irbesartan or both).

Independent predictors of outcome in I-Preserve

Because *Model 2* was the model with the most readily available variables, we focused on this model, although the adjusted outcomes for models 1 and 3 are also reported. The *Model 2* variables ordered by the strength of the association with the outcome of cardiovascular death or heart failure hospitalization, as measured by the z-score, are shown in **Table 2**. Of the 15 significant variables listed (excluding randomized treatment), 11 were slightly more adverse in the irbesartan group (male sex, NYHA class, heart rate, LVEF, pulmonary congestion on chest x-ray, previous myocardial infarction, diabetes, valvular disease, eGFR below 60 ml/min/1.73m^2, duration of heart failure >1 year, and chronic obstructive pulmonary disease/asthma), 3 were equally distributed between the two treatment groups (prior heart failure hospitalization, history of atrial fibrillation, and haemoglobin concentration) and one (age) favoured irbesartan.

Effect of irbesartan on the prespecified primary outcome in I-Preserve

In I-Preserve, 763 (37.0%) participants in the placebo group and 742 (35.9%) in the irbesartan group experienced the primary composite outcome (death from any cause or hospitalization for heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke). The prespecified analysis of this outcome, stratifying for use of ACEi at baseline, gave a hazard ratio (HR) of 0.95 (95% confidence interval, 0.86-1.05); p=0.35. Adjusting for the variables in *Model 1* or *Model 2* each gave an adjusted HR of 0.89 (0.80-0.99); p-value =0.033. Adding NT-pro BNP (*Model 3*) gave an adjusted HR of 0.90 (0.81-1.00); p-value =0.061 (**Table 3**). Using only the top five prognostic variables without missing data (i.e. HFH in the previous 6 months, age, diabetes, atrial fibrillation and previous MI), the HR (95%CI) was 0.95 (0.86-1.04); p-value =0.29. The Model 2 with data imputation gave a HR (95%CI) of 0.90 (0.82-1.00); p-value =0.054.

Effect of irbesartan on the composite outcome of cardiovascular death or HF hospitalization

A substantially smaller number of patients experienced the narrower composite outcome of cardiovascular death or HF hospitalization: 533 (25.9%) in the placebo group and 520 (25.2%) in the irbesartan group. Analysis of this composite as pre-specified, stratifying for use of ACEi at baseline,

gave a HR of 0.95 (0.85-1.08); p=0.44. Further adjustment for the additional baseline variables described above in *Model 1* gave a HR of 0.87 (0.77-0.99); p=0.037, for *Model 2* a HR of 0.87 (0.77-0.99); p=0.039, and for *Model 3* a HR of 0.89 (0.79-1.01); p=0.091 (**Table 3** & **Figure 1**).

Effect of irbesartan on heart failure hospitalization and cardiovascular- and all-cause death

The effect of irbesartan on heart failure hospitalization and on cardiovascular death, individually are shown in **Table 3**. Analysis of heart failure hospitalization alone, stratifying for use of ACEi at baseline, gave a HR of 0.95 (0.81-1.10); p=0.50. Adding the *Model 1* variables gave a HR of 0.88 (0.75-1.03); p=0.12, the *Model 2* variables a HR of 0.87 (0.74-1.02); p=0.092, and the *Model 3* variables a HR of 0.90 (0.76-1.05); p=0.18. Irbesartan did not reduce the risk of cardiovascular death or all-cause death (in the placebo group, 69% of deaths were attributed to cardiovascular causes).

DISCUSSION

While the effect of irbesartan in the primary prespecified analysis of I-Preserve was "neutral", our *post hoc* re-analysis of the trial, adjusting for widely available baseline variables, suggested that irbesartan could lead to a marginal reduction in both the risk of the original primary composite outcome (death from any cause or hospitalization for a cardiovascular cause) and the composite of heart failure hospitalization or cardiovascular death (most commonly used endpoint in heart failure trials). This marginal reduction reached statistical significance in some of the used models. Although *post hoc* analyses of this type must be interpreted with caution, our study was prompted by a prior, prespecified, analysis of CHARM-Preserved, another trial using the same type of treatment (an angiotensin receptor blocker) in the same clinical condition (HFpEF).

Even in large trials, small imbalances in variables which are important determinants of the outcomes of interest or of the effect of treatment may occur, by chance, between treatment groups.[10] Such imbalances may lead to inaccurate assessment of the effect of treatment if not accounted for in the analysis.[10, 11] Therefore, prespecifying that important baseline covariates are included in the analysis will mitigate the impact of the potential imbalances between groups in the treatment effect estimates.[12, 13] Many studies have shown that covariate adjustment of a treatment effect results in

increased statistical power.[11] This gain in statistical power is not only due to correction for potential imbalances in baseline covariates between the randomized groups, but also due to the magnitude of the prognostic impact of the covariates.[14-17] Even when the imbalances are marginal, but the prognostic impact or the potential treatment effect modification of the variable is strong, adjustment for them may have a significant influence on the estimate of treatment effect.[12, 13] Several studies have shown that adjustment of this type increases the power around the estimate of the effect of treatment and some have advocated that this is done routinely.[11] The potential benefits of adjusting for a moderate number of prognostically significant variables in trials with a large sample size far outweigh any risks of doing so (i.e. the only risk is an increase of the type I error chances when the number of adjustment variables is similar to the number of events, which is far from occurring in large trials, such as I-Preserve).[10] However, despite this, unadjusted analyses dominate in practice; only about one-fourth of the trials report covariate adjustment in their main analysis.[18] Notwithstanding, if a large treatment effect is present, this should be observed without adjustment or other mathematical modelling. However, in the context of a small treatment effect, covariate adjustment may be relevant, especially if there are important differences in baseline characteristics, as the result of the play of chance. However, any adjusted analysis, and the variables used in such an analysis, should be pre-specified.

The present *post hoc* analyses of I-Preserve exemplify some of these considerations. On close inspection of the baseline characteristics in the present trial, it can be seen there were slight differences between the treatment groups in many of the variables which were independent predictors of the outcome of interest. Moreover, of the 15 variables in our simplest predictive model (Model 2), an imbalance in 11 of these "favoured" placebo, and only 1 "favoured" irbesartan (with the other 3 balanced between the treatment groups). Collectively, these imbalances may have altered outcomes in the two randomized treatment groups, independently of the effect of irbesartan, and created the appearance of an attenuated effect of irbesartan. In other words, the cumulative adverse prognostic imbalances in the irbesartan, compared with placebo, may have resulted in a worse outcome in the irbesartan group and diminished any benefit of irbesartan. A parallel but more difficult to identify issue is whether any of these imbalances might have altered the response to irbesartan (in addition to

outcomes in the treatment group). Such effects might influence the efficacy or tolerability of irbesartan.[9]

Our findings highlight the limitations of relying on an arbitrary p-value to determine whether a trial is "positive" or not. Our data show that a p-value can vary from 0.2 to 0.05 or less, depending on whether or not adjustment is performed and if so, what variables are used.

In addition to exemplifying the potential value of adjusting the analysis of treatment effect in randomized trials, our findings suggest that RAAS blockade does have at least a modest benefit in patients with HFpEF and that I-Preserve and CHARM-Preserved do not differ to the extent previously assumed. If correct, this is clinically important for a condition without any other effective therapy. Moreover, the potential benefit of angiotensin-receptor blockers in patients with HFpEF may have contributed to the smaller-than-anticipated treatment difference between the treatment groups in the PARAGON-HF trial.[19]

Limitations

The main limitation in our study is that the covariate adjustment was not prespecified, hence this analysis should be regarded as exploratory. In addition, the gain in treatment effect-size resulting from covariate adjustment was somewhat larger than previously observed and may not be typical of what might be expected. We showed and additional relative risk reduction of 6 to 7% for each of the original primary composite outcome and the more typically used composite of heart failure hospitalization or cardiovascular death. In HF-ACTION, adjustment led to a 4% further reduction in the hazard ratio for the primary outcome in favour of exercise training (HR from 0.93 to 0.89) with a statistically significant treatment effect apparent only after adjustment.[16] In EMPHASIS-HF the prespecified covariate adjustment gave a 3% further reduction in the hazard ratio for the primary outcome in favour of eplerenone (HR from 0.66 to 0.63).[20] In GISSI-HF, covariate adjustment led to a 2% further reduction in the hazard ratio for the co-primary endpoints in favour of n-3 polyunsaturated fatty acid therapy (resulting in both becoming statistically significant, compared with the unadjusted analysis).[17] Importantly, it is essential that a covariate-adjusted approach is pre-specified, based upon existing knowledge. Covariate adjustment performed after knowledge of the trial findings (as

performed in this retrospective analysis) increases bias and limits the external validity of the findings.[21] Some important considerations on covariate adjustment are described in the **Figure 2**.

Conclusion

Slight imbalances in baseline variables which influence trial endpoints (and, potentially, the effect of the therapy under investigation) may occur, by chance, even in large randomized clinical trials. Correcting for these variables may increase the power of the treatment effect estimate. Along with the CHARM-Preserved results, these findings suggest that angiotensin-receptor blockers may have a modest benefit in HFpEF, which could have contributed to the smaller-than-anticipated difference between treatment groups in the PARAGON-HF trial. However, this inference must remain speculative, given the exploratory, post hoc, nature of our analyses.

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Disclosures

None.

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Table 1. Comparison of the baseline patients` characteristics by treatment allocation

Clinical characteristics	**Placebo**	**Irbesartan**	**p-value**
N.	2061	2067	-
Age, yr	71.7 ± 7.0	71.6 ± 6.9	0.61
Age ≥75 yr	716 (34.7%)	697 (33.7%)	0.49
Female sex	1264 (61.3%)	1227 (59.4%)	0.20
White race	1925 (93.4%)	1934 (93.6%)	0.79
NYHA class III/IV	1615 (78.4%)	1641 (79.4%)	0.44
Heart rate, bpm	71.2 ± 10.3	71.7 ± 10.6	0.16
Heart rate >70bpm	1026 (49.8%)	1033 (50.0%)	0.90
SBP, mmHg	136.0 ± 15.0	136.7 ± 15.0	0.10
SBP <120 mmHg	210 (10.2%)	194 (9.4%)	
SBP 120-140 mmHg	1216 (59.0%)	1167 (56.5%)	0.067
SBP >140 mmHg	635 (30.8%)	706 (34.2%)	
BMI, Kg/m2	29.6 ± 5.3	29.7 ± 5.3	0.46
BMI <25 Kg/m2	358 (17.5%)	321 (15.6%)	
BMI 25-35 Kg/m2	1402 (68.3%)	1432 (69.6%)	0.28
BMI >35 Kg/m2	292 (14.2%)	304 (14.8%)	
LVEF, %	59.5 ± 9.0	59.4 ± 9.3	0.62
LVEF ≤50%	406 (19.7%)	434 (21.0%)	0.30
Pulm. congestion CXR	782 (39.6%)	808 (40.5%)	0.54
Cause of HF			0.44
Ischaemia	500 (24.3%)	536 (25.9%)	
Hypertension	1304 (63.3%)	1318 (63.8%)	
HF duration >1 year	1048 (50.9%)	1079 (52.2%)	0.39
HFH prev. 6 months	906 (44.0%)	910 (44.0%)	0.97

Myocardial infarction	482 (23.4%)	487 (23.6%)	0.90
Hypertension	1816 (88.1%)	1834 (88.7%)	0.54
Atrial fibrillation	603 (29.3%)	606 (29.3%)	0.97
Diabetes	564 (27.4%)	570 (27.6%)	0.88
Valvular disease	220 (10.7%)	231 (11.2%)	0.61
COPD/Asthma	188 (9.1%)	203 (9.8%)	0.44
Stroke	201 (9.8%)	198 (9.6%)	0.85
Hemoglobin, g/dL	14.0 ± 1.5	14.0 ± 1.5	0.77
Hemoglobin ≤12 g/dL	174 (8.7%)	166 (8.3%)	0.69
eGFR, ml/min	72.5 ± 22.4	72.6 ± 22.6	0.88
eGFR ≥60 ml/min	1406 (69.6%)	1387 (68.7%)	
eGFR 45-59 ml/min	417 (20.7%)	427 (21.2%)	0.80
eGFR <45 ml/min	196 (9.7%)	205 (10.2%)	
Sodium, mmol/L	139.5 ± 3.0	139.5 ± 3.0	0.93
Potassium, mmol/L	4.5 ± 0.5	4.4 ± 0.5	0.20
Neutrophils, 10^3 cells/µL	4.5 ± 1.8	4.5 ± 1.7	0.75
NT-pro BNP, pg/mL	320 (131-946)	360 (138-987)	0.30
Treatment			
ACEi	501 (24.8%)	538 (26.0%)	0.34
Beta-blocker	1202 (58.3%)	1225 (59.3%)	0.53
Calcium channel blocker	811 (39.4%)	826 (40.0%)	0.68
Loop diuretic	1071 (52.0%)	1079 (52.3%)	0.87
Spironolactone	313 (15.2%)	320 (15.5%)	0.79
Lipid-lowering treatment	622 (30.2%)	657 (31.8%)	0.26
Antiplatelet agent	1193 (57.9%)	1223 (59.2%)	0.39

Legend: Pulm., pulmonary ; ACEi, angiotensin converting enzyme inhibitor; CXR, chest x-ray; SBP, systolic blood pressure; BMI, body mass index; LVEF, left ventricular ejection fraction; HFH, heart failure

hospitalization; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal pro brain natriuretic peptide; ACEi, angiotensin-converting enzyme inhibitor.

Table 2. Prognostic importance of the baseline clinical variables (for the outcome of cardiovascular death or heart failure hospitalization)

Variable	HR (95%CI)	z-score	P-value
HFH prev. 6 months	2.18 (1.87-2.54)	10.0	<0.001
Age (per yr)	1.05 (1.04-1.06)	8.7	<0.001
Diabetes	1.69 (1.48-1.93)	7.6	<0.001
Atrial fibrillation	1.43 (1.25-1.64)	5.2	<0.001
LVEF (per %)	0.98 (0.97-0.99)	-4.8	<0.001
Heart rate (per bpm)	1.01 (1.01-1.02)	4.6	<0.001
Previous MI	1.37 (1.19-1.59)	4.3	<0.001
eGFR (per ml/min)	0.99 (0.99-1.00)	-4.2	<0.001
Pulm. congestion CXR	1.29 (1.13-1.47)	3.8	<0.001
COPD/Asthma	1.44 (1.20-1.73)	3.9	<0.001
Male sex	1.27 (1.11-1.45)	3.4	0.001
Hb (per g/dL)	0.93 (0.89-0.97)	-3.3	0.001
NYHA III/IV	1.31 (1.11-1.54)	3.2	0.002
HF diagnosis >1yr	1.21 (1.06-1.38)	2.8	0.005
Valvular disease	1.22 (1.02-1.46)	2.2	0.027
Stroke history	1.19 (0.98-1.43)	1.8	0.075
BMI (per Kg/m^2)	1.01 (1.00-1.02)	1.6	0.11
SBP (per mmHg)	1.00 (1.00-1.00)	-0.2	0.83
Irbesartan (vs. Placebo)	0.87 (0.77-0.99)	-2.1	0.035

Legend: HF, heart failure; HFH, heart failure hospitalization; pulm., pulmonary; prev., previous; CXR, chest x-ray; COPD, chronic obstructive pulmonary disease; Hb, haemoglobin; BMI, body mass index; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure.

The p-values presented in this table are p-values from the multivariate models.

Table 3. Effect or irbesartan on different outcomes

Outcome/events	**Placebo** (n =2061)	**Irbesartan** (n =2067)	**HR (95%CI)**	**p-value**
Primary outcome				
Prespecified analysis	763 (37.0%)	742 (35.9%)	0.95 (0.86-1.05)	0.35
Model 1			0.89 (0.80-0.99)	0.033
Model 2			0.89 (0.80-0.99)	0.033
Model 3			0.91 (0.82-1.00)	0.061
CV death or HFH				
Prespecified analysis	533 (25.9%)	520 (25.2%)	0.95 (0.85-1.08)	0.44
Model 1			0.87 (0.77-0.99)	0.037
Model 2			0.87 (0.77-0.99)	0.039
Model 3			0.90 (0.79-1.02)	0.091
HFH alone				
Prespecified analysis	336 (16.3%)	325 (15.7%)	0.95 (0.81-1.10)	0.50
Model 1			0.88 (0.75-1.03)	0.12
Model 2			0.87 (0.74-1.02)	0.092
Model 3			0.90 (0.76-1.05)	0.18
CV death				
Prespecified analysis	302 (14.7%)	311 (15.1%)	1.01 (0.86-1.18)	0.92
Model 1			0.92 (0.78-1.09)	0.33
Model 2			0.92 (0.78-1.09)	0.32
Model 3			0.93 (0.79-1.09)	0.38
All-cause death				
Prespecified analysis	436 (21.2%)	445 (21.5%)	1.00 (0.88-1.14)	0.98
Model 1			0.93 (0.81-1.07)	0.30
Model 2			0.94 (0.81-1.07)	0.35

Model 3			0.93 (0.81-1.07)	0.30

Prespecified analysis: Cox proportional hazards models stratified for the prior use if angiotensin-converting enzyme inhibitors (ACEi).

Model 1, study treatment adjusted on age, sex, atrial fibrillation, diabetes mellitus, previous myocardial infarction, hypertension, COPD, HFH in the previous 6 months, presence of jugular venous distension, NYHA class III or IV, pulmonary congestion on chest radiograph, LVEF, BMI, heart rate, haemoglobin, eGFR, serum sodium, albumin, and neutrophils (model used in Jhund P. et al. Changes in N-terminal pro-B-type natriuretic peptide levels and outcomes in heart failure with preserved ejection fraction: an analysis of the I-Preserve study. Eur J Heart Fail. 2015).

Model 2, study treatment effect adjusted on age, sex, atrial fibrillation, diabetes mellitus, previous myocardial infarction, valvular disease, COPD, HFH in the previous 6 months, HF duration > 1 year, NYHA class III or IV, pulmonary congestion on chest radiograph, LVEF, BMI, heart rate, systolic blood pressure, haemoglobin, eGFR ("clinical model"; see also Table 2).

Model 3, Model 2 plus NT-pro BNP with multiple imputation for all the variables with any missing value in the model.

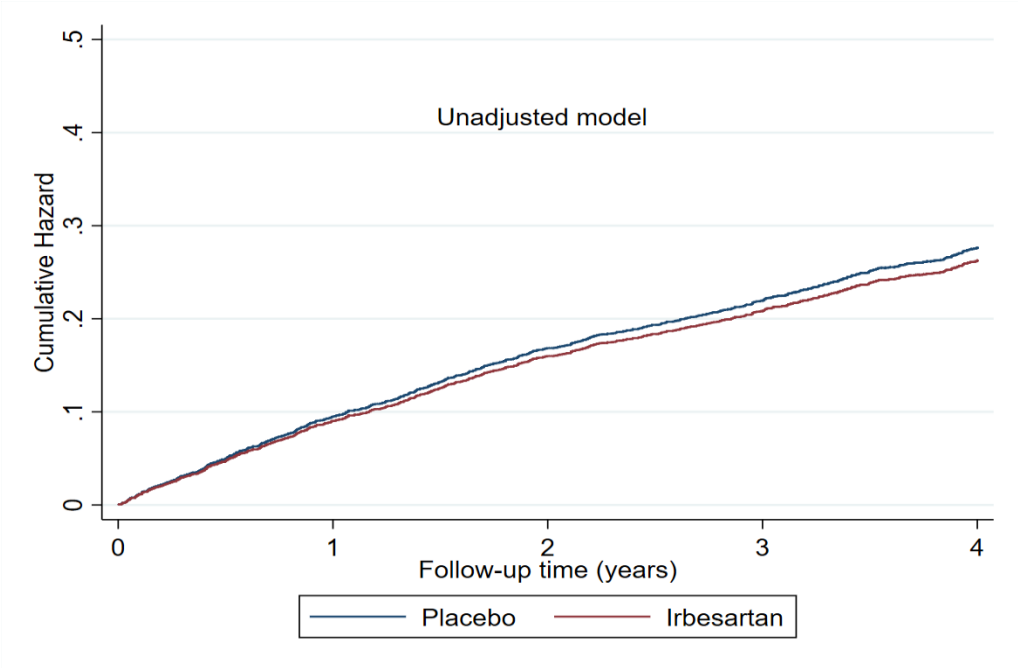
Note: The primary composite outcome was death from any cause or hospitalization for a cardiovascular cause (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke).

All models with stratification factor on the use of ACEi at baseline.

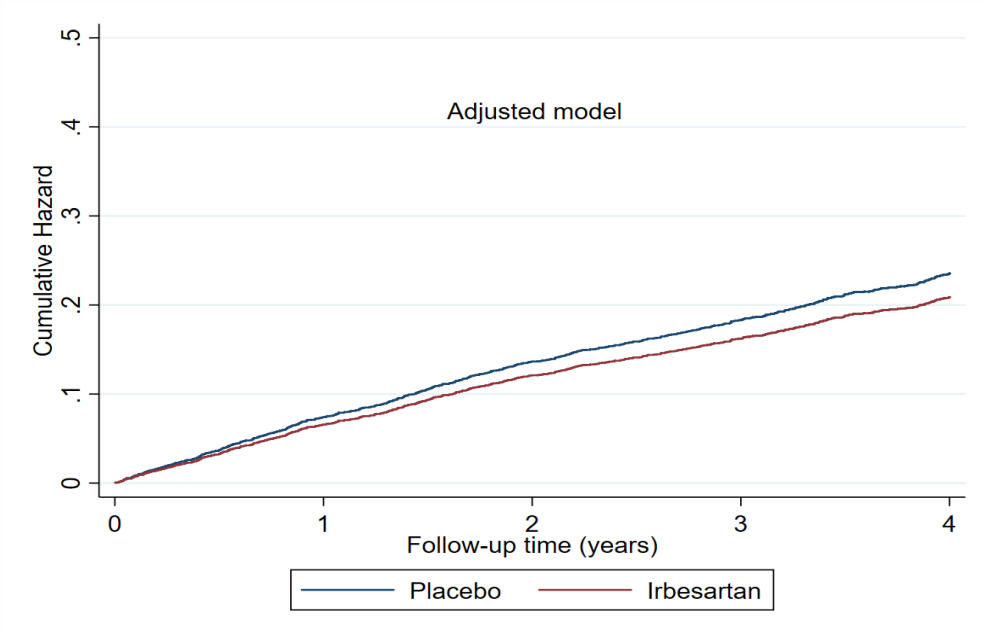
Legend: CV, cardiovascular; HFH, hospitalization for heart failure; AFib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; BMI, body mass index; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.

Figure 1. Adjusted cumulative hazard curve for the outcome of cardiovascular death or heart failure hospitalization

(A) Unadjusted model



(B) Adjusted model*



**Adjusted: study treatment effect adjusted on age, sex, atrial fibrillation, diabetes mellitus, previous myocardial infarction, valvular disease, COPD, HFH in the previous 6 months, HF duration > 1 year, NYHA class III or*

IV, pulmonary congestion on chest radiograph, LVEF, BMI, heart rate, systolic blood pressure, haemoglobin, eGFR ("Model 2"; see also Table 3). P-value for treatment effect in (A) =0.44 and in (B) =0.039.

Figure 2. Covariate adjustment in RCTs