Association of Candesartan vs Losartan With All-Cause Mortality in Patients With Heart Failure

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Context Angiotensin II receptor blockers (ARBs) reduce combined mortality and hospitalization in patients with heart failure (HF) with reduced left ventricular ejection fraction. Different agents have different affinity for the AT_1 receptor and may have different clinical effects, but have not been tested against each other in HF.

Objective To assess the association of candesartan vs losartan with all-cause mortality in patients with HF.

Design, Setting, and Patients An HF registry (the Swedish Heart Failure Registry) of 30 254 unique patients registered from 62 hospitals and 60 outpatient clinics between 2000 and 2009. A total of 5139 patients (mean [SD] age, 74 [11] years; 39% women) were treated with candesartan (n=2639) or losartan (n=2500). Survival as of December 14, 2009, by ARB agent was analyzed by Kaplan-Meier method and predictors of survival determined by univariate and multivariate proportional hazard regression models, with and without adjustment for propensity scores and interactions. Stratified analyses and quantification of residual confounding were also performed.

Main Outcome Measures All-cause mortality at 1 and 5 years.

Results One-year survival was 90% (95% confidence interval [CI], 89%-91%) for patients receiving candesartan and 83% (95% CI, 81%-84%) for patients receiving losartan, and 5-year survival was 61% (95% CI, 54%-68%) and 44% (95% CI, 41%-48%), respectively (log-rank $P<.001$). In multivariate analysis with adjustment for propensity scores, the hazard ratio for mortality for losartan compared with candesartan was 1.43 (95% CI, 1.23-1.65; $P<.001$). The results persisted in stratified analyses.

Conclusion In this registry of patients with HF, the use of candesartan compared with losartan was associated with a lower mortality risk.

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ANGIOTENSIN II RECEPTOR blockers (ARBs) reduce cardiovascular mortality and heart failure (HF) hospitalization in patients with HF with reduced left ventricular ejection fraction (LVEF).[1] In patients not taking an angiotensin-converting enzyme (ACE) inhibitor and when added to an ACE inhibitor, candesartan and valsartan reduced the combined end point mortality and HF hospitalizations and morbidity.[2-4] When compared with captopril, losartan was neutral with regard to all-cause mortality and HF hospitalization.[5] A losartan dose of 150 mg/d compared with a dose of 50 mg/d reduced combined cardiovascular mortality and HF hospitalization.[6] In contrast, ARBs do not appear to be effective in HF with preserved LVEF,[7] although candesartan reduced HF hospitalization.[8]

Despite these variable effects, different ARBs have not been tested head to head. Major cardiology societies recommend ARBs for the treatment of HF with reduced LVEF but do not specify agents.[9,10] However, there are reasons to believe different agents may have different efficacy. Candesartan compared with losartan has higher binding affinity for the AT_1 receptor,[11,12] is more effective at lowering blood pressure,[13] and is associated with less de novo HF when used in hypertension.[14] In elderly patients with HF, losartan was associated with higher mortality than other ARBs.[15]

Randomized controlled trials (RCTs) minimize bias and confounding but have not been performed to address this issue. Therefore, our goal was to determine whether candesartan is asso-

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ciated with less all-cause mortality than losartan in a large cohort of unselected patients with HF.

METHODS

Study Protocol

The Swedish Heart Failure Registry (RiksSvikt) has been previously described.[16] It was created as a pilot in 2000 and introduced throughout Sweden in 2003. Inclusion criteria are clinician-judged HF. Approximately 70 variables are recorded at discharge from hospital or after clinic visit on a case report form and entered into a database managed by the Uppsala Clinical Research Center, Uppsala, Sweden. The database is run against the Swedish death registry monthly. The protocol, registration form, and annual report are available at http://www.ucr.uu.se/rikssvikt. Establishment of the registry and registration and analysis of the data was approved by a multisite ethics committee. Individual patient consent was not required or obtained.

As of December 14, 2009, there were 44 548 registrations from 30 254 unique patients from 62 hospitals and 60 outpatient clinics. Of 30 254 unique patients, 5823 received an ARB (2639 received candesartan, 2500 received losartan, 357 received valsartan, and 327 received other ARBs) at the time of the first registration. Valsartan and other ARBs were excluded due to small numbers, resulting in 5139 individuals receiving candesartan (n=2639) or losartan (n=2500) for this study.

Statistical Analysis

To avoid bias due to missing baseline characteristics, multiple imputation (n=10) was performed for variables with missing data using predictive mean matching. All subsequent analyses, except for descriptive statistics, were performed on the imputed data. To adjust for selection bias, propensity scores for each patient were estimated with logistic regression. Quintiles of the estimated propensity scores were used to divide the patients into 5 strata.[17] All patient and medical history and treatment variables (excluding outcome variables and target dose ARB with losartan dose set at 150 mg/d) were used when creating the multiple imputation data sets as well as in the estimation of the propensity scores. To evaluate the propensity scores, logistic regressions with ARB agent as outcome were performed for each of the variables with and without adjustment for propensity score strata.

Survival was charted by Kaplan-Meier method and compared with the log-rank test for all patients and separately for an LVEF of less than 40% and 40% or more. Several univariate and multivariate proportional hazard regression models with and without adjustment for interactions and propensity scores, as a covariate and strata variable, were performed, with ARB agent adjusted for single or combinations of clinically relevant variables.

Interactions between ARB agent and clinically relevant variables were estimated by a Cox proportional hazards regression model and are shown in a Forest plot. Interactions with ARB were tested for all variables in the model. The scaled Schoenfeld residuals from the proportional hazards regression model were investigated to assess the proportional hazards assumption, whereas the Martingale residuals were visually inspected to detect possible nonlinearity for the continuous variables.

Stratifications were performed by 5 clinically important variables that may affect choice of agent, prognosis, or both (year of inclusion [2001-2005 vs 2006-2009], duration of HF [<6 vs ≥6 months], age [≤70 vs >70 years], New York Heart Association [classes I-II {mild} vs III-IV {moderate to severe}], and LVEF [<40% vs ≥40%]). Losartan was available before candesartan and the cutoff at 2005-2006 was chosen because the European and US guidelines reflecting the CHARM studies[2,3,8,18] were published in 2005.[19,20]

A sensitivity analysis was performed to evaluate the effect of a possible unknown or unmeasured confounder.[21] Hazard ratios (HRs) for losartan vs candesartan adjusted for an unknown binary or continuous (normally distributed) confounder was derived assuming different hazards and distributions of the unmeasured confounder in the 2 treatments.

One clinically relevant and prespecified subgroup analysis was performed by LVEF, divided by less than 40% (n=2608) and 40% or more (n=1884) (647 patients had missing LVEF data). We also performed a prespecified analysis with target dose of 150 mg/d rather than 50 mg/d for losartan, in accordance with the HEAAL study.[6]

To test the null hypothesis that there is no difference in survival between candesartan and losartan at 1 year, 2270 patients would be needed (1135 in each group). This assumed an annual mortality rate of 8.1% (candesartan group in the CHARM-Overall trial[18]) and 11.7% (losartan group in the ELITE II trial[5]), respectively; a power of 80%; and that the 2-sided level of significance was set at .05. Statistics were performed in R version 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics and *P* values of patients and medical history and treatment for imputed data showing differences before and after adjustment for propensity scores strata are shown in TABLE 1 and TABLE 2. A total of 5139 patients were included (mean [SD] age, 74 [11] years; 39% women) in the analyses. Patients receiving candesartan were overall healthier but had lower LVEF and were less likely to reach target doses (defined as 32 mg/d and 50 mg/d for candesartan and losartan, respectively). If the target dose was set at 150 mg/d for losartan,[6] there were still more patients in the candesartan group receiving 25% or less of the target dose. The unadjusted logistic regressions revealed a number of differences in baseline characteristics between patients receiving losartan and candesartan, but after adjustment for propensity scores, there were no longer any statistically significant differences, except for dose

of ARB, with target dose set at 150 mg/d. This target dose was analyzed as a prespecified sensitivity analysis but a target dose of 50 mg/d was chosen for inclusion in multiple imputation and derivation of propensity scores. One variable, ACE inhibitor, had a *P* value of less than .10 (*P* = .07).

FIGURE 1 shows the overall survival between the 2 groups. One-year survival was 90% (95% confidence interval [CI], 89%-91%) for patients receiving candesartan and 83% (95% CI, 81%-84%) for patients receiving losartan, and 5-year survival was 61% (95% CI, 54%-68%) for patients receiving candesartan and 44% (95% CI, 41%-48%) for patients receiving losartan (log-rank $P < .001$). TABLE 3 shows HRs for all-cause mortality in patients receiving losartan vs candesartan. The univariate HR was 1.77 (95% CI, 1.58-1.99; $P < .001$) and the multivariate HR including stratification for propensity scores was 1.43 (95% CI, 1.23-1.65; $P < .001$) (HR = 0.70 for candesartan vs losartan). Only β-blockers interacted with an ARB agent ($P = .04$). TABLE 4 shows HRs for all-cause mortality for patients receiving losartan vs candesartan after adjustment for this interaction, together with interactions with 4 variables with $P < .10$ (cardiac resynchronization therapy, duration of HF, creatinine, and lung disease). Losartan remained associated with increased mortality compared with candesartan for all categories except cardiac resynchronization therapy and lung disease.

Violations to the proportional hazards assumption were detected for location and this variable was therefore included as a strata variable in all proportional hazards regression models. Stratification did not change the results. Multivariate HRs with propensity score strata were 1.41 (95% CI, 1.22-1.64; $P < .001$) for year of inclusion; 1.43 (95% CI, 1.23-1.67; $P < .001$) for HF duration; 1.48 (95% CI, 1.28-1.72; $P < .001$) for age; 1.43 (95% CI, 1.24-1.67; $P < .001$) for NYHA class; and 1.44 (95% CI, 1.24-1.67; $P < .001$) for LVEF.

Quantification of the effects of a hypothetical confounder were calculated (eTable, available at http://www.jama.com). Given an HR of 2 for all-cause mortality for the binary confounder and an approximate differ-

Table 1. Baseline Patient Characteristics and *P* Values for Imputed Data Before and After Adjustment for Propensity Scores Strata[a]

Characteristics	Candesartan (n = 2639)	Losartan (n = 2500)	*P* Value	
			Imputed	Imputed Stratified for Propensity Score
Follow-up time, median (range), d	563.0 (0-2565)	640.5 (0-2916)		
No. of dead	441	888		
Included in the Swedish Heart Failure Registry				
2001-2005	214 (8.1)	701 (28.0)	<.001	.13
2006-2009	2425 (91.9)	1799 (72.0)		
Age, mean (SD), y	72.0 (11.5)	75.3 (10.2)	<.001	.54
Sex				
Male	1633 (61.9)	1483 (59.3)	.06	.86
Female	1006 (38.1)	1017 (40.7)		
Civil status				
Married	1621 (64.6)	1378 (60.1)	<.001	.92
Single	890 (35.4)	916 (39.9)		
Clinic				
Medicine	1116 (44.6)	1123 (47.7)	.001	.91
Cardiology	1371 (54.8)	1198 (50.9)		
Geriatric	14 (0.6)	32 (1.4)		
Location				
Inpatient	1202 (45.5)	1519 (61.8)	<.001	.67
Outpatient	1437 (54.5)	981 (39.2)		
Duration of heart failure, mo				
<6	1061 (40.2)	736 (29.4)	<.001	.57
≥6	1578 (59.8)	1764 (70.6)		
NYHA class[b]				
I	234 (11.0)	164 (9.0)	<.001	.98
II	1068 (50.0)	734 (40.3)		
III	770 (36.0)	840 (46.2)		
IV	65 (3.0)	82 (4.5)		
LVEF, %				
<30	692 (29.0)	628 (29.8)	.02	>.99
30-39	701 (29.4)	587 (27.9)		
40-49	511 (21.4)	404 (19.2)		
≥50	481 (20.2)	488 (23.2)		
QRS duration, mean (SD), ms	111.9 (28.9)	114.0 (28.2)	<.001	.93
Potassium, mean (SD), mEq/L	4.5 (1.2)	4.4 (1.1)	<.001	.76
Heart rate, mean (SD), beats/min	71.9 (14.8)	72.7 (14.7)	.09	>.99
Creatinine, mean (SD), mg/dL	1.25 (0.64)	1.37 (0.70)	<.001	.61
MAP, mean (SD), mm Hg	92.6 (13.9)	91.5 (13.4)	.003	.79
Hemoglobin, mean (SD), g/dL	13.3 (1.7)	13.1 (1.7)	<.001	.84
Smokers				
Current	207 (10.0)	172 (9.4)	.41	>.99
Former	934 (45.0)	868 (47.4)		
Never	935 (45.0)	791 (43.2)		

Abbreviations: LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NYHA, New York Heart Association.
SI conversions: To convert creatinine to µmol/L, multiply by 88.4; hemoglobin to g/L, multiply by 10.0.
[a] Data are presented as No. (%) unless otherwise specified. Percentages may not total 100 due to rounding.
[b] NYHA class I indicates no symptoms; NYHA class II, symptoms with moderate exertion; NYHA class III, symptoms with mild exertion; and NYHA class IV, symptoms at rest.

ence of 30% between the 2 ARBs in the probability of having the confounder, the HR for losartan vs candesartan would no longer be statistically significant. Alternatively, the corresponding numbers would have to be an HR of 3 and a difference in probability of 20% (eTable). For a normally distributed continuous confounder, if the difference in mean units between the 2 ARBs were at least 0.3 and the HR for the confounder were larger than 1.005 per unit, the HR for losartan vs candesartan would no longer be statistically significant (eTable).

In prespecified subgroup analysis according to LVEF, patients with an LVEF of 40% or more were older, more commonly women, and had more atrial fibrillation, but were otherwise healthier than patients with an LVEFof less than 40%. For patients with an LVEF of less than 40%, 1-year survival for candesartan and losartan was 91% (95% CI, 89%-92%) and 82% (95% CI, 80%-85%), respectively; and 5-year survival was 68% (95% CI, 60%-76%) and 44% (95% CI, 40%-49%), respectively ($P<.001$). For patients with an LVEF of 40% or more, the corresponding data for candesartan and losartan were 91% (95% CI, 89%-93%) and 86% (95% CI, 83%-88%) for 1-year survival and 54% (95% CI, 40%-72%) and 50% (95% CI, 44%-56%) for 5-year survival, respectively ($P<.001$).

The HRs for losartan vs candesartan were similar for an LVEF of less than 40% and an LVEF of 40% or more, and similar to the whole population (all were statistically significant in favor of candesartan). For an LVEF of less than 40%, the univariate HR was 2.08 (95% CI, 1.76-2.46; $P<.001$) and the multivariate HR including propensity score strata was 1.41 (95% CI, 1.14-1.76; $P=.002$). For an LVEF of 40% or more, the univariate HR was 1.42 (95% CI, 1.17-1.73; $P<.001$) and the multivariate HR including propensity score strata was 1.37 (95% CI, 1.06-1.79; $P=.02$).When the target dose of losartan was set at 150 mg/d, the HR adjusted only for dose was 1.91 ($P<.001$) and the HR from the multivariate model stratified for propensity score strata was 1.36 ($P=.02$). The propensity scores and the multiple imputations used in the LVEF subgroup and losartan dose of 150 mg/d analyses were the same as those derived for the full population and target dose of losartan of 50 mg/d.

No additional subgroup analyses were performed. However, interactions between ARB agent and clinical parameters were estimated and are shown in FIGURE 2.

Table 2. Baseline Characteristics of Medical History and Treatment and *P* Values for Imputed Data Before and After Adjustment for Propensity Scores Strata

Characteristics	No. (%) of Patients		*P* Value	
	Candesartan (n = 2639)	Losartan (n = 2500)	Imputed	Imputed Stratified for Propensity Score
Medical History				
Hypertension	1411 (55.0)	1296 (53.7)	.40	.88
Ischemic heart disease	1286 (50.7)	1461 (60.6)	<.001	.70
Dilated cardiomyopathy	366 (14.4)	297 (12.5)	.06	.93
Hypertrophic cardiomyopathy	49 (1.9)	63 (2.7)	.09	.88
Valve disease	468 (18.4)	501 (21.4)	.01	.78
Atrial fibrillation	1149 (43.8)	1222 (49.4)	<.001	.91
Diabetes mellitus	764 (29.2)	844 (34.0)	<.001	.94
Lung disease	413 (16.2)	515 (21.3)	<.001	.87
History of PCI and/or CABG surgery	773 (29.7)	803 (33.0)	.02	.93
Pacemaker	298 (11.4)	382 (15.5)	<.001	>.99
Cardiac resynchronization therapy	78 (3.0)	105 (4.3)	.01	.95
Implantable cardioverter defibrillator	87 (3.3)	96 (3.9)	.24	.97
Heart transplantation	7 (0.3)	12 (0.5)	.22	.97
Medical Treatment				
ACE inhibitor	420 (16.0)	76 (3.1)	<.001	.07
β-Blocker	2295 (87.1)	2049 (82.3)	<.001	.73
Aldosterone antagonist	802 (30.6)	904 (36.4)	<.001	.84
Diuretic	2065 (78.4)	2190 (87.8)	<.001	.74
Digoxin	440 (16.8)	500 (20.1)	.002	.88
Insulin	416 (15.9)	484 (19.5)	<.001	.93
Oral antidiabetic	362 (13.8)	380 (15.3)	.11	>.99
Aspirin	1281 (48.7)	1260 (50.5)	.19	.81
Oral anticoagulants	1056 (40.2)	997 (40.1)	.93	.89
Statin	1335 (50.8)	1245 (50.0)	.56	.95
Nitrates	459 (17.5)	632 (25.4)	<.001	.61
Amiodarone	81 (3.3)	84 (3.6)	.61	.87
Sotalol	14 (0.5)	29 (1.2)	.02	.87
Inotropic agent	35 (1.4)	44 (1.9)	.21	.92
Target dose of ARB				
Losartan, 50 mg/d				
≤25%	970 (36.8)	204 (8.2)	<.001	.24
26%-50%	714 (27.1)	330 (13.2)		
51%-75%	77 (2.9)	15 (0.6)		
≥76%	878 (33.3)	1951 (78.0)		
Losartan, 150 mg/d				
≤25%	970 (36.7)	549 (22.0)	<.001	<.001
26%-50%	714 (27.1)	1501 (60.0)		
51%-75%	77 (2.9)	445 (17.8)		
≥76%	878 (33.3)	5 (0.2)		

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; PCI, percutanoues coronary intervention.

COMMENT

Our findings show that in an unselected HF population, candesartan was associated with lower all-cause mortality compared with losartan. The difference was significant even after adjustment for propensity scores and numerous clinical variables, including dose, potential interactions, and after stratification and quantification of potential residual confounding of a reasonable magnitude. The variables adjusted for included those that might affect choice of agent (selection bias) and outcome (confounders). However, we cannot eliminate the possibility that residual confounding explains some of the association. In prespecified subgroups, our findings persisted with both an LVEF of less than 40% and an LVEF of 40% or more.

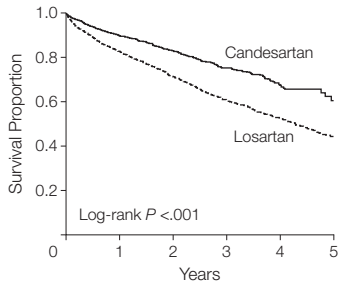
There are mechanistic reasons to believe candesartan may be more effective than losartan. Angiotensin II receptor blockers competitively block the AT_1 receptor. Candesartan has 4 binding sites on the AT_1 receptor and losartan has 2 binding sites.[22] In vitro studies have shown that losartan binds loosely and has a dissociation half-life of seconds to minutes, yielding "surmountable" antagonism. Candesartan binds tightly and has a dissociation half-life of 120 minutes, yielding "insurmountable" antagonism. Losartan has an active metabolite EXP3174, but even this has looser binding to the AT_1 receptor.[11,23-25] A point mutation at Lys^{199} decreases the affinity 45-fold for candesartan but only 5-fold for losartan.[26] Rat studies have shown candesartan to be 10 to 30 times more potent than losartan, and concentrations required for displacement of 50% radioligand were 0.9 nmol/L for candesartan and 8.9 nmol/L for losartan.[12]

Clinical studies in hypertension also suggest that candesartan may be more effective than losartan. Both candesartan (16 mg/d) and losartan (100 mg/d) improved endothelial function, measured by flow-mediated vasodilation, but only candesartan lowered plasma levels of plasminogen activator inhibitor 1 and monocyte chemoattractant protein 1.[27] Candesartan inhibited the angiotensin II–induced increase in renal filtration fraction and the aldosterone secretion significantly more than losartan.[28] Candesartan (16 mg/d) compared with losartan (100 mg/d) was more effective at lowering blood pressure, and after a forced missed dose, patients receiving losartan but not candesartan returned to pretreatment blood pressure,[29] consistent with the affinity observations above. A meta-analysis suggests that candesartan is more effective at lowering blood pressure.[13] In a registry study of hypertension, candesartan compared with losartan was associated with less de novo HF[14] and, in a registry study of elderly patients with HF, losartan was associated with worse survival than irbesartan, valsartan, and candesartan.[15]

In HF, ARBs have not been compared head to head, but studies of candesartan are larger and more conclusively positive than studies of losartan. The CHARM program is the largest and most positive and conclusive set of studies.[2,3,8,18] A meta-analysis of 38 080 patients from 24 trials revealed that most studies comparing ARB vs placebo were with candesartan and yielded a reduction in both mortality (odds ratio [OR], 0.83; 95% CI, 0.69-1.00) and HF hospitalization (OR, 0.64; 95% CI, 0.53-0.78); most studies comparing ARB vs ACE inhibitors were with losartan and yielded neutral effects (OR, 1.06; 95% CI, 0.90-1.26 for mortality and OR, 0.95; 95% CI, 0.80-1.13 for HF hospitalization); and most studies of ARB on top of ACE inhibitors were with candesartan and were overall neutral with respect to mortality (OR, 0.97; 95% CI, 0.87-1.08) but beneficial with respect to HF hospitalization (OR, 0.77; 95% CI, 0.69-0.87).[1]

Registry studies have advantages compared with RCTs. Inherent to RCTs are strict inclusion/exclusion criteria that limits applicability to many patient groups (eg, elderly patients). Patients are carefully monitored, which may dilute any differences between therapies had they played out under normal clinical follow-up. Strict inclusion criteria and careful monitoring also yield good prognosis. Indeed, RCTs of ARBs have attempted to augment risk by requiring hospitalization before inclusion but have still mainly demonstrated reductions in disease-specific morbidity such as HF hospitalization rather than all-cause mortality.[30] In contrast, our registry study provides information useful for every day clinical care of a broad unselected HF population,

Figure 1. Kaplan-Meier Estimates of Survival of Patients Receiving Candesartan and Losartan



No. at risk

Candesartan	2639	1739	957	426	125	30
Losartan	2500	1692	1097	646	359	178

Table 3. Proportional Hazard Regression Models for All-Cause Mortality for Losartan vs Candesartan[a]

Losartan vs Candesartan	Hazard Ratio (95% CI)
Univariate model	1.77 (1.58-1.99)
Multivariate model	
Adjusted for age and sex	1.56 (1.39-1.75)
Adjusted for duration of heart failure	1.71 (1.52-1.92)
Adjusted for hypertension	1.77 (1.58-1.99)
Adjusted dose of 50 mg/d[b]	2.53 (2.22-2.88)
Adjusted dose of 150 mg/d[c]	1.91 (1.67-2.18)
Adjusted for ACE inhibitor, β-blocker, and aldosterone antagonist	1.71 (1.52-1.93)
Multivariate final model	
Final	1.43 (1.23-1.65)
With propensity scores covariate	1.41 (1.22-1.64)
With propensity scores strata	1.43 (1.23-1.65)

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval.
[a] $P<.001$ for all univariate and multivariate models.
[b] Target dose of 50 mg/d for losartan and 32 mg/d for candersartan.
[c] Target dose of 150 mg/d for losartan and 32 mg/d for candesartan.

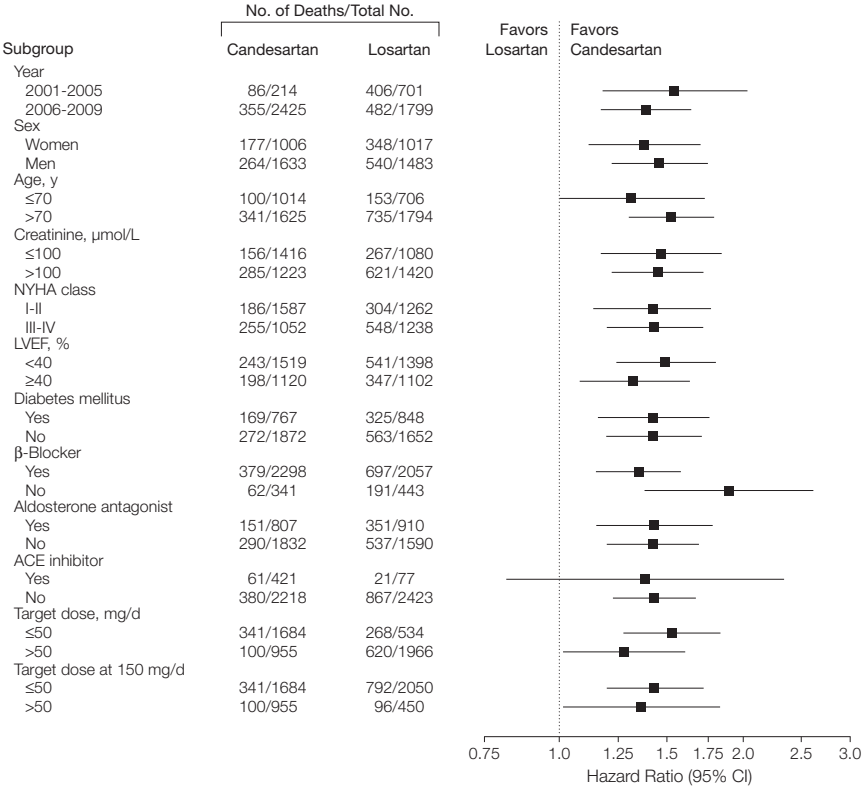
and our findings of reduced mortality with candesartan interacted statistically only with β-blocker therapy but no other parameters, making them broadly applicable. The reasons for this interaction are not readily apparent.

Table 4. Multivariate Final Analysis With Propensity Score Strata and Interaction for Losartan vs Candesartan

Multivariate Final Analysis	Hazard Ratio (95% CI)	*P* Value	
		Main Effect	Interaction
β-Blocker			
No	1.90 (1.39-2.60)	<.001	.04
Yes	1.35 (1.15-1.57)	<.001	.04
Cardiac resynchronization therapy			
No	1.45 (1.25-1.68)	<.001	.09
Yes	0.82 (0.42-1.58)	.55	.09
Duration of heart failure, mo			
<6	1.72 (1.35-2.20)	<.001	.05
≥6	1.33 (1.12-1.56)	<.001	.05
Creatinine[a]	1.51 (1.18-1.93)	<.001	.07
Lung disease			
No	1.52 (1.29-1.79)	<.001	.06
Yes	1.17 (0.90-1.51)	.24	.06

Abbreviation: CI, confidence interval.
[a]For creatinine=100 μmol/L (1.13 mg/dL).

Figure 2. Hazard Ratios for All-Cause Mortality for Losartan vs Candesartan From the Multivariate Model Stratified for Propensity Scores and Interaction With Selected Subgroups



ACE indicates angiotensin-converting enzyme; CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Assocation. Continuous and categorical variables with more than 2 levels were dichotomized at clinically relevant cutoff for presentation purposes. For variables with missing data, this number is the mean of the 10 imputations.

The magnitude of the difference in association with mortality was large. The HR for all-cause mortality of losartan compared with candesartan was 1.43 (candesartan vs losartan, 0.70) overall and similar in the LVEF of less than 40% and the LVEF of 40% or more comparisons. In comparison, in the CHARM-Overall study,[18] the adjusted HR for overall mortality was 0.90 ($P=.03$). The adjusted HRs for cardiovascular death and HF hospitalization was 0.70 ($P<.001$) in the CHARM-Alternative study,[2] 0.85 ($P=.01$) in the CHARM-Added study,[3] and 0.86 ($P=.051$) in the CHARM-Preserved study.[8] The magnitude of our findings may be due to chance, but RCTs may understate "real world" differences, and it is conceivable that candesartan is better than losartan by a magnitude similar to placebo.

The survival in the overall population of our study was quite high. This may be explained by 54.5% of patients being registered as outpatients. Inpatient registration was indeed an independent predictor of mortality. However, inpatient vs outpatient registration did not affect the differences between losartan vs candesartan (location was included in all our models and there was no interaction between ARB agent and location).

Our study has limitations. First, the diagnosis of HF in the Swedish Heart Failure Registry is clinical and does not require objective evidence of HF. A majority of patients had echocardiography data (87%) but only 31% had (N-terminal pro) brain natriuretic peptide, and in patients with preserved LVEF, there were no formal diagnostic criteria. Indeed, a larger proportion of patients with preserved LVEF had concomitant lung disease and some of these may not have had HF. Nonetheless, ARBs are effective mainly in HF with reduced LVEF and, in our study, candesartan was associated with lower mortality than losartan in this subgroup. In a registry study, treatment may change over time and

adherence is not monitored, and our study reflects only agent, dose, and coexisting HF therapy at the time of inclusion. However, this is true in intention-to-treat randomized studies as well.

In addition, our study is limited by its nonrandomized character and there are potential biases and confounders that may be responsible for our findings. First, choice of ARB agent may be subject to selection bias and we cannot determine whether hypertension or HF or diabetes was the primary indication. The Swedish Heart Failure Registry contains clinical variables that may affect choice of agent, such as hypertension, diabetes, and duration of HF. These were accounted for in the derivation of a propensity score for each patient, adjusted for in multivariate regression and examined in tests for interaction with ARB agent (duration of HF was also stratified). Because losartan has been available longer than candesartan, earlier inclusion in the Swedish Heart Failure Registry may entail a higher likelihood of receiving losartan. Indeed, year of inclusion in the Swedish Heart Failure Registry was skewed toward later years for candesartan. However, year of inclusion was corrected for by the propensity score, did not interact with ARB agent, and was stratified for, and candesartan remained associated with lower mortality than losartan.

Second, the efficacy of different ARB agents is subject to confounding. The Swedish Heart Failure Registry contains numerous variables that may affect outcomes independent of ARB agent, such as age, LVEF, NYHA class, renal function, dose of ARB, and treatment with other HF drugs, and patients treated with losartan were less healthy (except for better LVEF). However, these were included in propensity scores and multivariate analysis and examined for interactions with ARB agent. Also, important variables were examined in stratifications, without changing the results. Earlier inclusion may also entail less utilization of evidence-based therapies. However, concomitant HF therapies were included in the propensity score and multivariate analysis. In addition, the importance of up-titration of doses is well known. Indeed, the HEAAL study[6] showed that losartan dose of 150 mg/d compared with 50 mg/d was associated with less combined cardiovascular mortality and HF hospitalization. However, even after adjustment for a target does of 150 mg/d, losartan remained associated with higher mortality than candesartan did in our study.

Nonetheless, we cannot rule out that the benefits with candesartan are due to potential unknown confounders. The quantification of residual confounding suggests that to invalidate the results, a potential confounder or combination of confounders would have to have both a strong association with all-cause mortality and also be considerably likely to affect the choice of losartan vs candesartan. We are unaware of any previously described variables and find it unlikely (but cannot rule out) that there exists unknown variables, which are not adjusted for in our analysis, have a relatively strong association with all-cause mortality, and would be likely to affect the choice of losartan vs candesartan.

In conclusion, our findings suggest that candesartan is associated with less all-cause mortality than losartan. However, clinical decision making should await supportive evidence of this observed association. Ideally, different ARB agents should be tested against each other in RCTs. It would also be important and perhaps more feasible to confirm our findings in other large HF registries.

Author Contributions: Dr Lund and Ms Benson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Eklind-Cervenka, Rosenqvist, Lund.
Acquisition of data: Eklind-Cervenka, Dahlström, Edner, Lund.
Analysis and interpretation of data: Eklind-Cervenka, Benson, Dahlström, Edner, Rosenqvist, Lund.
Drafting of the manuscript: Eklind-Cervenka, Edner, Lund.
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Statistical analysis: Eklind-Cervenka, Benson, Edner, Lund.
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Administrative, technical, or material support: Dahlström, Edner, Lund.
Study supervision: Edner, Rosenqvist, Lund.
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