Association of Treatment With Losartan vs Candesartan and Mortality Among Patients With Heart Failure

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Context The benefit of angiotensin II-receptor blockers (ARBs) in heart failure is thought to be a class effect, but no head-to-head randomized trials have compared individual ARBs. Results from observational studies suggest that losartan may be associated with increased mortality in patients with heart failure compared with other ARBs.

Objective To assess the hypothesis that losartan use is associated with increased all-cause mortality in heart failure patients as compared with candesartan.

Design, Setting, and Participants We conducted a nationwide Danish registry–based cohort study, linking individual-level information on hospital contacts, filled prescriptions, and potential confounders. Patients aged 45 years and older with first-time hospitalization for heart failure in 1998-2008 were identified from the Danish National Patient Registry. New users of losartan and candesartan were selected for inclusion in the study cohort.

Main Outcome Measures We used Cox proportional hazards regression to compare the risk of all-cause mortality in users of losartan and candesartan.

Results Among 4397 users of losartan, 1212 deaths occurred during 11 347 person-years of follow-up (unadjusted incidence rate [IR]/100 person-years, 10.7; 95% CI, 10.1-11.3) compared with 330 deaths during 3675 person-years among 2082 users of candesartan (unadjusted IR/100 person-years, 9.0; 95% CI, 8.1-10.0). Compared with candesartan, losartan was not associated with increased all-cause mortality (adjusted hazard ratio [HR], 1.10; 95% CI, 0.96-1.25) or cardiovascular mortality (adjusted HR, 1.14; 95% CI, 0.96-1.36). Compared with high doses of candesartan (16-32 mg), low-dose (12.5 mg) and medium-dose losartan (50 mg) were associated with increased mortality (HR, 2.79; 95% CI, 2.19-3.55 and HR, 1.39; 95% CI, 1.11-1.73, respectively); use of high-dose losartan (100 mg) was similar in risk (HR, 0.71; 95% CI, 0.50-1.00).

Conclusions Among patients with heart failure, overall use of losartan compared with candesartan was not associated with an increased mortality risk. Although low doses of losartan were associated with increased mortality, there was no increased mortality comparing high-dose losartan against the highest doses of candesartan.

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Angiotensin II-receptor blockers (ARBs) are recommended for use in heart failure[1] patients who are angiotensin-converting enzyme (ACE) inhibitor intolerant.[2,3] In heart failure patients, candesartan and valsartan reduce morbidity and mortality when compared with placebo.[4,5] No placebo-controlled trial of losartan has been conducted, but evidence from a randomized clinical trial (RCT) suggests an effect in heart failure comparable to the ACE inhibitor captopril.[6] Although the benefit of ARBs in heart failure is generally regarded as a class effect and the different ARBs are used interchangeably, no head-to-head RCTs have been performed to compare the effects of different ARBs.

Results from observational studies comparing clinical effectiveness of losartan to other ARBs, although conflicting,[7,8] indicate that losartan may be associated with increased mortality in patients with heart failure. In particular, a recent cohort study found that use of losartan, as compared with candesartan, was associated with an increased risk of all-cause mortality.[9] However, a considerably smaller proportion of losartan users received the full-target dose compared with candesartan users, which may have favored an apparent superiority of candesartan.[10]

We conducted a nationwide registry-based cohort study to assess the hypothesis that use of losartan is associated with increased all-cause mortality in heart failure patients as compared with candesartan.

METHODS

We conducted a prospective study in a historic cohort of patients with heart failure who initiated treatment with

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candesartan or losartan during the 1998-2008 study period. The primary study outcome was all-cause mortality and the secondary outcomes were cardiovascular mortality (including cerebrovascular mortality) and all-cause mortality according to dose of candesartan and losartan. The study was approved by the Danish Data Protection Agency. Ethics approval is not required for registry-based research in Denmark.

From the Danish Civil Registration System,[11] we defined a source population consisting of all individuals living in Denmark in 1995 and of those aged 45 years or older in 1998-2008. Using the participants' unique civil registration number, we linked individual-level information on hospital contacts, drug use, and potential confounders.

From the source population, we identified patients with heart failure using the Danish National Patient Registry.[12] This nationwide registry documents all hospital admissions since 1977 and all emergency department visits and outpatient contacts since 1995. Diagnoses are coded according to *International Classification of Diseases, Tenth Revision* (*ICD-10*) since 1994, and before then, *ICD-8*. We included patients with an incident hospitalization for heart failure after 45 years of age and January 1, 1998. Patients with heart failure were identified using *ICD-8* codes 427.09-427.11, 427.19, 428.99, 782.49, and *ICD-10* codes I50.x, I11.0, I13.0, and I13.2. The Danish National Patient Registry has demonstrated high validity in the identification of heart failure with positive predictive values of a diagnosis of heart failure ranging between 81% and 100%.[13-15]

Information on use of ARBs from 1995-2008 was obtained from the Danish National Prescription Registry.[16] This nationwide registry holds detailed individual-level information on all prescriptions filled at Danish pharmacies, including the recipients' civil registration number, anatomic therapeutic chemical classification code (ATC), date of filling the prescription, number of tablets, and tablet strength in milligrams. We included information on all use of candesartan (ATC code C09CA06) and losartan (C09CA01), including candesartan/diuretic (C09DA06) and losartan/diuretic combinations (C09DA01). The remaining ARBs available in Denmark, eprosartan (C09CA02), valsartan (C09CA03), irbesartan (C09CA04), telmisartan (C09CA07), and olmesartan (C09CA08), were categorized together as a single group of other ARBs.

Information on potential confounding variables for the study patients—prior use of other selected drugs, prior hospital diagnoses, and demographic characteristics—was obtained from the National Prescription Registry, the National Patient Registry, and the Civil Registration System, respectively. Information on causes of death classified according to *ICD-10* codes was obtained from the nationwide Danish Cause of Death Register.[17]

Statistical Analysis

Follow-up started on the date of filling the first prescription for candesartan or losartan after incident hospitalization for heart failure. Patients were censored on the date of death, disappearance, emigration, or filling a prescription of an ARB agent other than the one initially used or end of study (December 31, 2008), whichever occurred first.

We compared new users of candesartan with new users of losartan, using treatment status defined as a time-varying variable. Study patients who filled a prescription for any ARB less than 3 years prior to study entry were considered prevalent users and excluded. The study patients were observed prospectively for current treatment status. Patients were classified as ongoing users of candesartan or losartan from the date of filling a prescription for the respective drug. Provided that a new prescription was filled prior to the prescription end date, patients remained classified as ongoing users. If patients did not fill a new prescription, treatment status was changed to former user of the respective drug from the prescription end date. Patients who later filled a new prescription to resume treatment were again classified as ongoing users.

Thus, the sum of all person-time during which a patient was classified as an ongoing user, irrespective of whether this was 1 contiguous period or several periods interrupted by former user episodes, represented this patient's total person-time of ongoing use. The prescription duration was estimated on the basis of the number of tablets in the prescription and, to avoid gaps between prescriptions in continuous treatment, 1 tablet was counted as 2 days of use. A sensitivity analysis in which 1 tablet indicated 1 day of use was also conducted. To prevent overaccumulation of treatment days, any overlap between prescriptions was disregarded.

For the primary analysis, we used Cox proportional-hazards regression to estimate hazard ratios (HRs) and 95% CIs for all-cause mortality among users of losartan as compared with users of candesartan. For the secondary analyses, we estimated HRs to compare the risk of cardiovascular mortality. We also analyzed all-cause mortality according to dosage of losartan and candesartan. During the study period, losartan was available in tablet strengths of 12.5, 50, and 100 mg and candesartan in 4, 8, 16, and 32 mg. Use of different doses of losartan (12.5, 50, and 100 mg) and low doses of candesartan (4 and 8 mg) were compared with use of high doses of candesartan (16 and 32 mg). A sensitivity analysis with a candesartan tablet strength of 32 mg as the reference category was also performed. Current drug dosage was prospectively determined from the tablet strength of the latest filled prescription and participants could thus change dosing schedule during follow-up.

Effect estimates were adjusted for distribution quintiles of the propensity score for starting losartan treatment.[18] The propensity score was estimated using logistic regression. As predictors for losartan treatment, we included sex, age group (in 5-year intervals), socioeconomic status, degree of

urbanization, time since first hospitalization for heart failure (<1 year, 1-2 years, 3-4 years, ≥5 years), year of first hospitalization for heart failure (1998-2000, 2001-2003, 2004-2006, 2007-2008), number of hospital admissions in the last year, use of other selected drugs in the last 3 years, and selected comorbidities in the last 3 years (TABLE 1 shows all variables in the propensity score model). Additionally, we included all estimable 2-way interactions between the predictors in the model. Study participants with a propensity score outside the common range of candesartan users and losartan users were excluded from the study population to reduce unmeasured confounding from patients at the extreme ends of the propensity score distribution.[19]

Table 1. Baseline Characteristics of Candesartan and Losartan Users in Nationwide Cohort of Patients With First-Time Hospitalization for Heart Failure, Denmark, 1998-2008

	No. (%)		
	Candesartan (n = 2082)	Losartan (n = 4397)	*P* Value[a]
Age, mean (SD), y	71.7 (10.6)	72.7 (10.4)	<.001
Male sex	1130 (54)	2419 (55)	.58
Year of first heart failure hospitalization			
1998-2000	478 (23)	1614 (37)	<.001
2001-2003	485 (23)	1539 (35)	
2004-2006	706 (34)	903 (21)	
2007-2008	413 (20)	341 (8)	
Years since first heart failure hospitalization, median (IQR)	0.8 (0.3-2.6)	0.5 (0.1-1.9)	<.001
Employment status			
Employment with unknown, basic, or no qualifications	191 (9)	322 (7)	.04
Employment with medium-level qualifications	42 (2)	68 (2)	
Employment with high-level qualifications	36 (2)	78 (2)	
Self-employed/spouse working also	64 (3)	127 (3)	
Outside labor market[b]	336 (16)	661 (15)	
Pensioned	1413 (68)	3141 (71)	
Degree of urbanization, population density/km^2			
≤49 Inhabitants	107 (5)	298 (7)	<.001
50-99 Inhabitants	614 (29)	1241 (28)	
100-199 Inhabitants	430 (21)	900 (20)	
≥200 Inhabitants	182 (9)	378 (9)	
Residence in Copenhagen suburbs	553 (27)	1004 (23)	
Residence in Copenhagen	196 (9)	576 (13)	
Comorbidities in the last 3 y			
Other ischemic heart disease	995 (48)	2195 (50)	.11
Myocardial infarction	410 (20)	1001 (23)	<.001
Diabetes	357 (17)	821 (19)	.14
Chronic pulmonary disease	353 (17)	843 (19)	.03
Cardiomyopathy	203 (10)	375 (9)	.11
Stroke	196 (9)	328 (7)	<.001
Peripheral vascular disease	173 (8)	424 (10)	.08
Unstable angina	149 (7)	388 (9)	.02
Renal disease	133 (6)	239 (5)	.12
Cancer	116 (6)	260 (6)	.58
Obesity	100 (5)	202 (5)	.71
Peptic ulcer disease	83 (4)	166 (4)	.68
Rheumatic disease	64 (3)	114 (3)	.27
Dementia	21 (1)	48 (1)	.76
Liver disease	15 (1)	34 (1)	.82

(continued)

The proportional hazards assumption was assessed by a Wald test for the interaction between each independent variable and underlying time on treatment. If a variable was not constant over time, an interaction term was included in the model.

All statistical tests were 2-sided with *P* values of less than .05 indicating statistical significance. From posthoc power calculations, we estimated that the study had 80% power to detect an HR of at least 1.17 in losartan users. Statistical analyses were performed using SAS software version 9.2.

RESULTS

From a source population of 2 915 481 individuals, we identified 120 871 patients with an incident hospitalization for heart failure between 1998 and 2008. Among these, 6637 initiated candesartan or losartan treatment during the study period. The C statistic of the propensity score model indicated good prediction of losartan treatment (C=0.78). A total of 158 patients with a nonoverlapping propensity score were excluded. Thus, we had a final study cohort of 6479 patients; 2082 users of candesartan and 4397 users of losartan. FIGURE 1 shows a detailed account of the cohort selection.

Patient characteristics at the time of study entry are presented in Table 1. Compared with candesartan users, losartan users were older; started ARB treatment sooner after first heart failure hospitalization; were more likely to live in Copenhagen and less likely to live in the Copenhagen suburbs; had a higher prevalence of myocardial infarction, unstable angina and chronic pulmonary disease and lower prevalence of stroke; had more use of nitrates and antianxiety drugs and less use of ACE inhibitors, platelet inhibitors and anticoagulants, β-blockers, statins, spironolactone, and proton-pump inhibitors; and were more likely to have been hospitalized within the last year.

During 19 491 person-years of follow-up, there were 2378 deaths in the study population. Among these, 330 occurred during ongoing candesartan use

(unadjusted incidence rate [IR]/100 person-years, 9.0; 95% CI, 8.1-10.0) and 1212 during ongoing losartan use (unadjusted IR/100 person-years, 10.7; 95% CI, 10.1-11.3). The median treatment duration was 1.1 years for candesartan users (interquartile range [IQR], 0.4-2.5 years) and 1.8 years for losartan users (IQR, 0.5-4.1 years). Median overall follow-up was 1.9 years for candesartan users (IQR, 0.8-3.4 years) and 2.7 years for losartan users (IQR, 1.1-5.1 years). FIGURE 2 shows the crude survival curves for patients initiating treatment with candesartan and losartan. Follow-up was prematurely ended for 437 patients (4 because of emigration; 433 because of switching to another ARB agent). Among candesartan users, 612 patients (29%) changed dosing schedule during follow-up compared with 1115 (26%) among losartan users. The mean (SD) number of dosages was 1.3 (0.6) among candesartan users and 1.3 (0.5) among losartan users.

Table 1. Baseline Characteristics of Candesartan and Losartan Users in Nationwide Cohort of Patients With First-Time Hospitalization for Heart Failure, Denmark, 1998-2008 (continued)

	No. (%)		
	Candesartan (n = 2082)	Losartan (n = 4397)	*P* Value[a]
Use of other drugs in the last 3 years			
Platelet inhibitors and anticoagulants	1702 (82)	3476 (79)	.01
ACE inhibitors	1670 (80)	3381 (77)	<.001
Loop diuretics	1623 (78)	3490 (79)	.19
β-Blockers	1413 (68)	2614 (59)	<.001
NSAIDs	1030 (49)	2125 (48)	.39
Statins	974 (47)	1690 (38)	<.001
Calcium channel-blockers	784 (38)	1677 (38)	.71
Spironolactone	724 (35)	1413 (32)	.03
Thiazide diuretics	717 (34)	1551 (35)	.51
Proton pump inhibitors	690 (33)	1289 (29)	<.001
Nitrates	673 (32)	1635 (37)	<.001
Anti-obstructive pulmonary drugs	643 (31)	1339 (30)	.73
Digoxin	636 (31)	1433 (33)	.10
Antianxiety drugs	465 (22)	1121 (25)	<.001
Antidepressants	457 (22)	909 (21)	.24
Antidiabetics	354 (17)	793 (18)	.31
Antiarrhythmics	204 (10)	405 (9)	.45
H_2-Antagonists	142 (7)	356 (8)	.07
Immunosuppressants	30 (1)	56 (1)	.58
No. of hospitalizations in the last year			
0	505 (24)	786 (18)	<.001
1	823 (40)	1836 (42)	
2	388 (19)	891 (20)	
≥3	366 (18)	884 (20)	

Abbreviations: ACE, angiotensin-converting enzyme; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a] Determined using the 2-sided *t* test for continuous variables and the 2-sided χ^2-test for categorical variables.
[b] Includes individuals who are unemployed, students, and those on sick or parental leave.

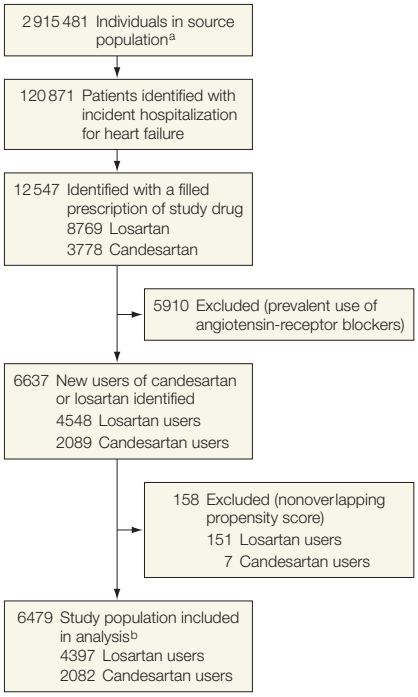
The HRs for all-cause mortality in losartan users as compared to candesartan users are presented in TABLE 2. We observed a crude increased risk of death associated with use of losartan as compared to candesartan (HR, 1.25; 95% CI, 1.10-1.41). This association persisted after adjustment for age only (HR, 1.19; 95% CI, 1.05-1.34). However, after propensity score adjustment, no significantly increased risk could be observed (HR, 1.10; 95% CI, 0.96-1.25). The propensity score–adjusted risk of death was somewhat higher among men compared with women but not significantly (HR, 1.14; 95% CI, 0.96-1.36 vs HR, 1.04; 95% CI, 0.86-1.26; *P* = .56). Patients were also observed for the secondary outcome of cardiovascular mortality. Use of losartan was not significantly associated with an increased risk of cardiovascular mortality compared with candesartan use (propensity score–adjusted HR, 1.14; 95% CI, 0.96-1.36).

In FIGURE 3, we present HRs for all-cause mortality associated with specific doses of losartan and low and medium doses of candesartan compared with high doses of candesartan. The Wald test for homogeneity showed significantly different effects between different doses of losartan ($P < .01$). Use of 12.5 mg of losartan was associated with a more than 2-fold increased risk of mortality as compared with high doses of candesartan (HR, 2.79; 95% CI, 2.19-3.55). Treatment with 50 mg of losartan was similarly less effective compared with high doses of candesartan (HR, 1.39; 95% CI, 1.11-1.73). However, there was no increased risk associated with use of 100 mg of losartan (HR, 0.71; 95% CI, 0.50-1.00). Use of 4 mg of candesartan (HR, 2.12; 95% CI, 1.61-2.80) was associated with increased mortality, whereas use of 8 mg of candesartan was not (HR, 1.30; 95% CI, 0.99-1.71).

We performed several sensitivity analyses to validate the robustness of the results. Use of losartan was not associated with increased all-cause mortality when days of prescription duration was set to equal the number of tablets in the prescriptions (HR, 1.15; 95% CI, 0.99-1.34). Inclusion of all potential confounders in a multivariable model instead of the propensity score did not change the results (HR, 1.08; 95% CI, 0.95-1.22). Similarly, an intention-to-treat analysis with the initial treatment carried forward did not change the results materially (HR, 1.02; 95% CI, 0.92-1.13). Additionally, we used loop diuretic dose as a proxy for heart failure severity[20]; loop diuretic dose was included in the model in 4 categories of mean dose used between heart failure diagnosis and start of ARB use (0-40 mg/d, 41-80 mg/d, 81-160 mg/d, and >160 mg/d). Adjusting for loop diuretic dose had no effect on the

estimates for all-cause mortality (HR, 1.09; 95% CI, 0.96-1.24). When reanalyzing mortality according to dosage schedule using 32 mg of candesartan as the reference category, there was a significantly increased risk associated with 12.5 mg of losartan (HR, 3.59; 95% CI, 1.69-7.62), but not 50 mg or 100 mg or losartan (HR, 1.78; 95% CI, 0.84-3.77 and HR, 0.91; 95% CI, 0.41-2.01, respectively).

Figure 1. Enrollment of Patients With Heart Failure in Cohort of Candesartan and Losartan Users, Denmark 1998-2008



[a]Individuals living in Denmark by 1995, aged 45 years or older between 1998 and 2008.
[b]Individuals with a propensity score within the common range of candesartan and losartan users.

COMMENT

In this comparative study, we evaluated the potential association between use of losartan and mortality in heart failure patients compared with use of candesartan. Overall, use of losartan was not associated with increased all-cause mortality or cardiovascular mortality. Compared with high doses of candesartan, use of low- and medium-dose losartan was associated with increased mortality, as was low-dose candesartan, but use of high-dose losartan was not.

Our finding of no significant overall association between losartan use and increased risk of all-cause mortality as compared with candesartan use contrasts with the results reported by Eklind-Cervenka et al[9] (HR, 1.43; 95% CI, 1.23-1.65), who addressed this hypothesis in a Swedish heart failure registry. There are several possible explanations for this finding. Comparison of treatment group baseline characteristics showed that in both studies, losartan users were on average older with more cardiovascular comorbidity. Unlike the study by Eklind-Cervenka et al[9] we were able to include a wide range of comorbidities (including noncardiovascular disease), co-medications, and health status markers in order to better account for baseline treatment group differences with respect to frailty and general health. Failure to properly account for these differences may likely exaggerate the benefit of candesartan.

The observed differences may additionally be attributed to issues related to dosage of candesartan and losartan. The recommended target dose for candesartan in heart failure is 32 mg per day. For losartan, the target dose may be between 50 and 150 mg per day. However, in RCTs, the daily dose of 150 mg of losartan has been found to have significantly better efficacy in heart failure as compared to that of 50 mg of losartan.[21] The study by Eklind-Cervenka et al,[9] showed large differences in the proportion of users achieving target dose or close to target dose in the 2 treatment groups. Specifically, when the target dose of losartan was defined as 150 mg, users of candesartan were much more likely to achieve high-dose treatment as compared to losartan users. Thus, the higher average relative dose among candesartan users may have led to an overestimation of the overall comparative effectiveness of candesartan.

Other observational studies have reported conflicting results comparing the risk of all-cause mortality associated with use of losartan, candesartan, and other ARBs. In a recent small cohort study, Desai et al[7] found no difference in all-cause mortality between 4 different ARBs, including candesartan and losartan. In contrast, Hudson et al[8] reported a significantly lower risk of all-cause mortality after use of irbesartan (HR, 0.65; 95% CI, 0.53-0.79), valsartan (HR, 0.63; 95% CI, 0.51-0.79), and candesartan (HR, 0.71; 95% CI, 0.57-0.90) as compared to losartan. In the latter study, however, full-target doses of other ARBs were consistently compared with 50 mg of losartan.

Compared with previous observational studies, our data provide a more detailed insight into the complexity of the association between losartan use and mortality risk in heart failure. Specifically, our findings suggest differential effects on mortality across increasing losartan doses as compared with high-dose candesartan, whereas lower doses of losartan (12.5 and 50 mg) were associated with increased mortality risk,

Figure 2. Survival and Follow-up of Candesartan and Losartan Users With Heart Failure

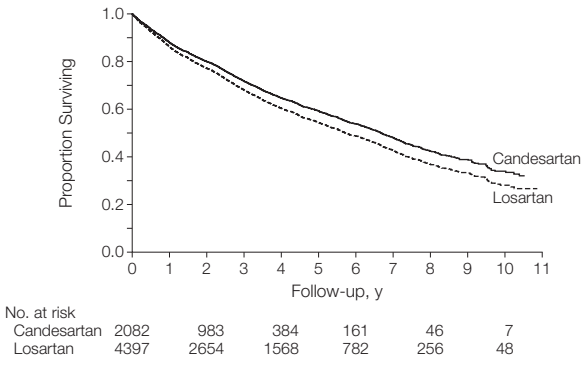


Table 2. Association Between Use of Losartan vs Candesartan in Patients with Heart Failure and Risk of All-Cause and Cardiovascular Mortality

Mortality	No. of Patients	No. of Deaths	Person-Years of Follow-Up	HR (95% CI)		
				Crude	Age-Adjusted[a]	Propensity Score–Adjusted[b]
All-cause overall						
Candesartan	2082	330	3675	1 [Reference]	1 [Reference]	1 [Reference]
Losartan	4397	1212	11 347	1.25 (1.10-1.41)	1.19 (1.05-1.34)	1.10 (0.96-1.25)
Women						
Candesartan	952	156	1700	1 [Reference]	1 [Reference]	1 [Reference]
Losartan	1978	545	5224	1.19 (1.00-1.42)	1.13 (0.94-1.35)	1.04 (0.86-1.26)
Men						
Candesartan	1130	174	1974	1 [Reference]	1 [Reference]	1 [Reference]
Losartan	2419	667	6123	1.30 (1.10-1.54)	1.22 (1.04-1.45)	1.14 (0.96-1.36)
Cardiovascular overall						
Candesartan	2082	174	3675	1 [Reference]	1 [Reference]	1 [Reference]
Losartan	4397	675	11 347	1.34 (1.14-1.59)	1.28 (1.08-1.51)	1.14 (0.96-1.36)

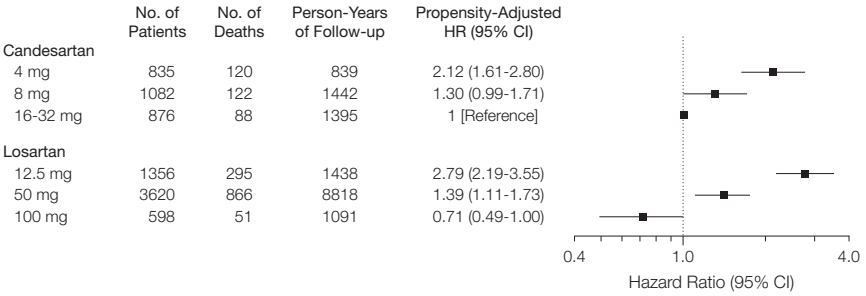
Abbreviation: HR, hazard ratio.
[a] Adjusted for age in 5-year intervals.
[b] Adjusted for propensity scores categorized in quintiles. Propensity scores included all variables shown in Table 1 and all estimable 2-way interactions between these variables.

as compared with high doses of candesartan. There was no increased risk of using a high dose of losartan (100 mg) as compared with high doses of candesartan. The relationship between the ARB dose used and mortality risk was also evident among patients using different doses of candesartan, with those using low doses at significantly increased risk of death compared with those using high doses. Given these findings, it cannot simply be concluded that any single drug of losartan and candesartan is superior to the other in patients with heart failure, but rather that differential effects may be expected according to the dose achieved. However, given that these findings stem from observational data and that the magnitude of the differences between different doses seem large, an alternative explanation to the differential effects across losartan doses (and across candesartan doses) is the possibility of unmeasured confounding because of frailty (eg, patients with frailty and advanced heart failure tolerating only low doses of losartan and because of the severity of heart failure being more likely to die than patients who tolerate high candesartan doses).

This study has several strengths worth mentioning. First, use of ARBs was determined from a comprehensive nationwide drug registry on filled prescriptions. This eliminated recall bias and improved precision regarding the timing of drug use and the current drug dosage. Because drug use was treated as a time-varying variable, we were (in contrast to traditional intention-to-treat designs) able to estimate effects of on-treatment exposure. The new user design eliminated potential bias from prevalent ARB use.[22] Furthermore, propensity scores derived from a nonparsimonious propensity model, including a wide range of health status markers, were used to minimize confounding by indication.

Several limitations of this study should also be acknowledged. First, there is no information on clinical measures of heart failure severity that are associated with mortality, eg, left ventricular ejection fraction. Second, for the purpose of the study, filling of a drug prescription was assumed to be interchangeable with actual drug use. If one of the drugs was truly associated with increased mortality, non-use of dispensed drugs would bias the results toward no effect. Third, this study did not include information on prescribed drug dose, and drug strength of the latest filled prescription was therefore used as a proxy. In dose-specific analyses, candesartan use of 16 to 32 mg was set as the reference category. Although this is comparable to the CHARM trial, in which the mean achieved dose was 24 mg, the 16- to 32-mg candesartan category might not have been the ideal comparison group to 100 mg of losartan. To address this, we conducted sensitivity analyses with 32 mg of candesartan as the reference category. Fourth, the possibility of residual confounding exists due to unmeasured baseline health differ-

Figure 3. All-Cause Mortality in Candesartan and Losartan Users With Heart Failure



ences that may exist between the treatment groups. In particular, users of losartan were on average older with more severe cardiovascular comorbidity, factors which are associated with frailty and other unmeasured risk factors for death. Fifth, we could not evaluate whether higher doses of either candesartan or losartan were associated with increased risk for adverse effects. Given the nationwide coverage of the study, it is likely that this cohort is representative of patients with first-time hospitalization for heart failure. However, results might not be generalizable to patients with heart failure earlier on in the natural process of disease.

CONCLUSION

This large, nationwide cohort study of patients with heart failure found no significantly increased risk of all-cause mortality associated with use of losartan as compared with candesartan. Whereas lower doses of losartan were associated with increased mortality risk as compared with higher doses of candesartan, there was a decreasing risk of mortality with increasing losartan dose; and no significantly increased mortality risk was observed when comparing the highest dose of losartan against the highest doses of candesartan. These findings do not support the hypothesis of differential effects of specific ARBs in patients with heart failure.

Author Contributions: Mr Svanström had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Svanström, Pasternak, Hviid.
Acquisition of data: Svanström, Hviid.
Analysis and interpretation of data: Svanström, Pasternak, Hviid.
Drafting of the manuscript: Svanström.
Critical revision of the manuscript for important intellectual content: Svanström, Pasternak, Hviid.
Statistical analysis: Svanström.
Obtained funding: Hviid.
Study supervision: Hviid.
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