Effectiveness by gender and age of renin-angiotensin system blockade in heart failure—A national register-based cohort study

Anna Ohlsson1 | Bertil Lindahl2,3 | Ronnie Pingel4 | Marianne Hanning1 | Ragnar Westerling1

1Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
2Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden
3Department of Medical Sciences, Uppsala University, Uppsala, Sweden
4Department of Statistics, Uppsala University, Uppsala, Sweden

Correspondence
Anna Ohlsson, Department of Public Health and Caring Sciences, Uppsala University, PO Box 564, SE-751 22 Uppsala, Sweden. Email: anna.ohlsson@pubcare.uu.se

Funding information
Swedish Research Council for Health, Working Life and Welfare, Grant/Award Number: 2015-00480

Abstract
Purpose: Investigate effectiveness by gender and age and equity implications of treatment with renin-angiotensin system blockade (RASb) in heart failure (HF) patients.

Methods: In this population-based register study, we used inpatient data from 2006 to 2010 for patients age 20 years or older with no HF hospitalization for minimum of 1 year before an index hospitalization. A wash-out period for RASb of 6 months preceding admission was used. Hospital data were linked with drug dispensation data and cause of death data. The associations between time-dependent RASb exposure and all-cause death and HF death, respectively, were examined by Cox regression models. Interactions by gender and age were also investigated on the multiplicative and additive scales.

Results: Thirty thousand seven hundred twenty-one patients were analysed. Fifty-one percent were women. Median age was 83. Fifty-three percent of women and 64% of men received RASb after the index hospitalization. Younger patients were more likely to receive RASb than older ones. One-year mortality was 28%. RASb was associated with an overall hazard ratio (HR) for all-cause death of 0.72 (95% confidence interval 0.69-0.75), and an HR of 0.85 (0.77-0.93) for HF death. Interaction analyses showed HRs for all-cause death associated with RASb between 0.12 (0.10-0.13) in the youngest, and 0.80 (0.76-0.84) in the oldest patients.

Conclusions: RASb appeared effective for women and men and for patients of all ages in this hospitalised HF cohort. No gender difference in effectiveness was found. RASb exposure was low overall, indicating a need for improved adherence to treatment guidelines. Treatment with RASb may be inequitable for women and older patients.

KEYWORDS
angiotensin receptor antagonists, angiotensin-converting enzyme inhibitor, gender, health care disparities, health equity, heart failure, pharmacoepidemiology, treatment outcome
INTRODUCTION

Efficacy of renin-angiotensin system (RAS) blocking drugs in heart failure (HF) with reduced ejection fraction (HFrEF) is established in clinical trials, where mortality reductions are seen across gender, age, and ethnicity groups. Hence, treatment guidelines recommend RAS blockade (RASb) for the vast majority of HF patients. Effective-ness studies (ie, observational studies of RASb use in HF patients) also show mortality reductions overall and that RASb is effective among elderly and female patients, although women may benefit less than men.

Although RASb reduces mortality by 16% to 40% in patients with HFrEF, under-prescription as well as gender and age inequity in RASb treatment have been demonstrated.

Equitable health care requires efficacy studies in different patient groups, as effects and side effects may vary. Women and older patients are typically underrepresented in HF research. Moreover, all patients regardless of age, gender, or sociodemographics should have equal chances of receiving effective evidence-based treatment according to need. Consequently, observational studies of effectiveness of RASb in different groups of HF patients are relevant in the context of equity in health care.

To our knowledge, no previous study has analysed total population data for RASb effectiveness according to age and gender in HF.

1.1 Aim

Building on our previously reported data, revealing less RASb treatment among female and elderly HF patients, we aimed to study the effectiveness of RASb in the same cohort.

The research questions were as follows:

- Is RASb exposure associated with mortality reduction in a hospitalised Swedish HF population?
- Does the association between RASb exposure and mortality differ by gender or age?

2 METHODS

2.1 Material

This population-based cohort study used register data from the Swedish National Patient Register, the Swedish Prescribed Drug Register, and the Swedish Cause of Death Register. The registers are held by the Swedish National Board of Health and Welfare. The coverage of the patient register is over 99% for inpatients. The Prescribed Drug Register records dispensed drugs in Sweden with 95% to 100% completeness. The Cause of Death register comprises all deaths among persons registered in Sweden at the time of death, with a coverage of 99%.

2.2 Study population

We included inpatients aged 20 years or older from the patient register discharged from hospital 1 July 2006 to 30 December 2010, who survived hospitalisation with a primary diagnosis of HF (The International Classification of Diseases [ICD-10] codes I11.0, I13.0, I13.2, I42.0, I42.3-I42.9, I50.0, I50.1, and I50.9) and had not been hospitalised for HF 1 July 2005 to 30 June 2006 nor had a RASb dispensation in the 6 months preceding hospitalisation (Figure 1). The discharge date for the first HF hospitalisation during the study period was defined as the index date. We included 30 721 patients.

2.3 Outcomes

Two outcomes were analysed separately: HF death and all-cause death. Date of death and underlying cause of death were retrieved from the cause of death register. Time was from index date until event, censoring, or end of study, ie, 31 December 2010. Subjects were followed up to 4.5 years.

2.4 Exposures

2.4.1 Renin-angiotensin system blockade

At least one dispensation of either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) at any time during follow-up was regarded as RASb exposure. Doses were not recorded. Using the date of the first dispensation after the index date,
A time-dependent exposure variable for RASb was computed, such that follow-up time before the first dispensation was defined as unexposed time, and follow-up time after the first dispensation (until death, censoring, or end of study) was defined as exposed time, to avoid survival bias. Only the first dispensation was considered, ie, exposure information was not updated. No specific assumptions regarding the length of prescription were made. Stock-piling and non-adherence were not addressed. RASb exposure was defined as protective.

### 2.4.2 Gender

Gender was categorised as woman or man. Female gender was considered protective; thus man was the reference.

### 2.4.3 Age

Age was categorised as 20 to 64 years, 65 to 74 years, 75 to 84 years, and 85 years or older. The highest age category was as the reference.

### 2.5 Covariates

Comorbidity, defined as additional ICD-10 diagnoses at any inpatient hospitalisation 1.5 years previous to and including the index hospitalisation, comprised hypertension, angina pectoris, myocardial infarction, atrial fibrillation/flutter, pacemaker, coronary artery bypass grafting (CABG), stroke, peripheral vascular disease, lung disease, renal dysfunction, diabetes mellitus, anaemia, dementia, cancer, liver disease, and rheumatic disease.

As entry time into the study varied for the subjects, hospitalisation-free time in the study period before the index hospitalisation was computed. Other HF therapies, ie, beta blocker (BB) and mineralocorticoid receptor antagonist (MRA) dispensed within 1 year following index, were recorded.

### 2.6 Statistical analysis

Descriptive statistics are reported as medians with quartiles for continuous variables or proportions and counts for categorical variables.

Cox proportional hazards regression models were fitted to estimate associations (hazard ratios [HRs]) between exposures and outcomes for all-cause death and HF death, respectively. We computed 95% confidence intervals (CI) for the estimates.

Univariate models were fitted to estimate crude HRs for each exposure. Model 2 was adjusted for age. Model 3 was adjusted for age and gender. Model 4 further included comorbidities, hospitalisation-free time, and BB or MRA medication.

To study whether the adjusted associations between RASb and the outcomes differed by gender, model 5 further included the interaction term between RASb and gender. HRs were then calculated for the combined exposures RASb and gender with the common reference category man without RASb. Similarly, in model 6, we added the
|                  | Number (%) | Distribution (%) |
|------------------|------------|------------------|
|                  | Total      | RASb             | No RASb           |
| Number (%)       | 30 732     | 17 836 (58.0)    | 12 896 (42.0)     |
|                  |            | Age 20-64       | Age 65-74         |
| Age (y)          |            | 3876 (12.6)     | 4216 (13.7)       |
| Median           | 83         | 79               | 86                |
| 25th percentile  | 74         | 69               | 80                |
| 75th percentile  | 88         | 85               | 90                |
| Age 20-64        |            | 3237 (18.1)     | 639 (5.0)         |
| Age 65-74        |            | 3197 (17.9)     | 1019 (7.9)        |
| Age 75-84        |            | 6101 (34.2)     | 3678 (28.5)       |
| Age ≥ 85         |            | 5301 (29.7)     | 7560 (58.6)       |
| Gender           |            |                  |                   |
| Women            | 15 667 (51.0) | 8233 (46.2) | 7434 (57.6) |
| Men              | 15 065 (49.0) | 9603 (53.8) | 5462 (42.4) |
| Follow-up time   |            |                  |                   |
| Total person years | 47 068 | 1-1644 | 1-1644 |
| Range            |            | 1-1643           | 1-1644            |
| Median           | 450        | 606              | 263               |
| 25th percentile  | 153        | 265              | 71               |
| 75th percentile  | 897        | 1032             | 640               |
| Comorbidity      |            |                  |                   |
| Hypertension     | 10 376 (33.8) | 6091 (34.2) | 4285 (33.2) |
| Diabetes Mellitus | 4746 (15.4) | 2745 (15.4) | 2001 (15.5) |
| Angina Pectoris  | 3662 (11.9) | 1887 (10.6) | 1775 (13.8) |
| Myocardial infarction | 5503 (17.9) | 2990 (16.8) | 2513 (19.5) |
| Atrial fibrillation/flutter | 12 791 (41.6) | 7281 (40.8) | 5510 (42.7) |
| Pacemaker        | 2026 (6.6) | 1102 (6.2) | 924 (7.2) |
| Stroke           | 2484 (8.1) | 1145 (6.4) | 1339 (10.4) |
| Renal dysfunction | 2609 (8.5) | 922 (5.2) | 1687 (13.1) |
| Vascular disease | 1045 (3.4) | 522 (2.9) | 523 (4.1) |
| Rheumatic disease | 1067 (3.5) | 506 (2.8) | 561 (4.4) |
| Lung disease     | 5456 (17.8) | 2848 (16.0) | 2608 (20.2) |
| Liver disease    | 287 (0.9) | 146 (0.8) | 141 (1.1) |

(Continues)
interaction term between RASb and age to model 4, and HRs for the combined exposures RASb and age were calculated with the common reference category 85 years or older without RASb. For HF death, interaction was estimated for gender and RASb. Event rates were too low in some age groups for age interaction analysis to be reliable. To determine interaction on the additive scale, the Relative Excess Risk due to Interaction (RERI) was calculated. RERI ≤ 0 denotes interaction, where RERI > 0 designates positive interaction, and RERI < 0 designates negative interaction. All exposures were coded as protective to facilitate interpretation of interaction effects.

Interaction was estimated for gender and RASb. Event rates were too low in some age groups for age interaction analysis to be reliable. To determine interaction on the additive scale, the Relative Excess Risk due to Interaction (RERI) was calculated. RERI ≤ 0 denotes interaction, where RERI > 0 designates positive interaction, and RERI < 0 designates negative interaction.

### Table 1 (Continued)

| Number (%) | Distribution (%) |
|------------|------------------|
| Total      | RASb No RASb Age 20-64 Age 65-74 Age 75-84 Age ≥ 85 Women Men |
| CABG       | 1720 (5.6) 1097 (6.2) 623 (4.8) 193 (5.0) 343 (8.1) 746 (7.6) 438 (3.4) 482 (3.1) 1238 (8.2) |
| Anaemia    | 3192 (10.4) 1385 (7.8) 1807 (14.0) 176 (4.5) 358 (8.5) 1021 (10.4) 1637 (12.7) 1776 (11.3) 1416 (9.4) |
| Cancer     | 2033 (6.6) 914 (5.1) 1119 (8.7) 118 (3.0) 304 (7.2) 771 (7.9) 840 (6.5) 694 (4.4) 1339 (8.9) |
| Dementia   | 1401 (4.6) 452 (2.5) 949 (7.4) 9 (0.2) 58 (1.4) 520 (5.3) 814 (6.3) 854 (5.5) 547 (3.6) |
| RASb       | 17 836 (58.0) 3237 (83.5) 3197 (75.8) 6101 (62.4) 5301 (41.2) 8233 (52.5) 9603 (63.7) |
| Beta blocker ≤ 1 y^a | 19 918 (64.8) 13 627 (76.4) 6291 (48.8) 3196 (82.5) 3145 (74.6) 6466 (66.1) 7111 (23.1) 9713 (62.0) 10 205 (67.7) |
| Mineralocorticoid antagonist ≤ 1 y^a | 10 847 (35.3) 6678 (37.4) 4169 (32.3) 1604 (41.4) 1711 (40.6) 3410 (34.9) 4122 (32.1) 5533 (35.3) 5314 (35.3) |

**Abbreviations:** CABG, Coronary Artery Bypass Grafting; RASb, renin-angiotensin system blockade.

[a]From index date.
| N = 30 721 | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 | Model 6 | RERI |
| 13 398 events (43.6%) | Crude HR | HR Adjusted for Age | HR Adjusted for Age and Gender | HR Adjusted for Age, Gender, Hospitalisation-Free Time*, Comorbidityb, and Other Medicationc | HR Adjusted for Age, Gender, Hospitalisation-Free Time*, Comorbidityb, and Other Medicationc | Interaction AgeClass * RASb | Interaction female gender * RASb |
|------------------|----------|--------------------|-----------------|----------|----------|----------------|----------------|
| RASb             | 0.46 (0.45-0.48) | 0.62 (0.59-0.64)  | 0.61 (0.59-0.63) | 0.72 (0.69-0.75) | 0.70 (0.67-0.74) | 0.80 (0.76-0.84) | 0.05 (-0.00-0.11) |
| Gender (female)  | 1.11 (1.07-1.15) | 0.85 (0.82-0.88)  | 0.91 (0.88-0.95) | 0.90 (0.86-0.94) | 0.91 (0.88-0.94) | Ref             | Ref             |
| Age              | 20-64     | 0.18 (0.16-0.19)  | 0.17 (0.15-0.18) | 0.19 (0.17-0.21) | 0.19 (0.17-0.21) | 0.29 (0.25-0.34) | Ref             |
| 65-74            | 0.36 (0.33-0.38) | 0.35 (0.32-0.37)  | 0.35 (0.33-0.37) | 0.35 (0.33-0.38) | 0.42 (0.39-0.47) | Ref             | Ref             |
| 75-84            | 0.64 (0.62-0.67) | 0.63 (0.60-0.65)  | 0.61 (0.59-0.64) | 0.61 (0.59-0.64) | 0.65 (0.62-0.68) | Ref             | Ref             |
| ≥85              | Ref       | Ref               | Ref             | Ref       | Ref       | Ref             | Ref             |
| Interaction female gender * RASb | 1.04 (0.97-1.11) | 0.70 (0.67-0.74)  | 0.80 (0.76-0.84) | Ref       | Ref       | Ref             | Ref             |
| Interaction age * RASb | 1.04 (0.97-1.11) | 0.70 (0.67-0.74)  | 0.80 (0.76-0.84) | Ref       | Ref       | Ref             | Ref             |
| RERI female gender+RASb | 0.05 (-0.00-0.11) | 0.03 (-0.03-0.09) | 0.00 (-0.05-0.05) | Ref       | Ref       | Ref             | Ref             |
| RERI age 20-64 + RASb | 0.05 (-0.00-0.11) | 0.03 (-0.03-0.09) | 0.00 (-0.05-0.05) | Ref       | Ref       | Ref             | Ref             |
| RERI age 65-74 + RASb | 0.05 (-0.00-0.11) | 0.03 (-0.03-0.09) | 0.00 (-0.05-0.05) | Ref       | Ref       | Ref             | Ref             |
| RERI age 75-84 + RASb | 0.05 (-0.00-0.11) | 0.03 (-0.03-0.09) | 0.00 (-0.05-0.05) | Ref       | Ref       | Ref             | Ref             |

Abbreviations: RASb, renin-angiotensin system blockade; RERI, Relative Excess Risk due to Interaction.

*Time in the study before the first hospitalization.

*Hypertension, diabetes mellitus, angina pectoris, myocardial infarction, atrial fibrillation/flutter, pacemaker, stroke, renal dysfunction, vascular disease, rheumatic disease, lung disease, liver disease, Coronary Artery Bypass Grafting, anaemia, cancer, dementia.

Beta blocker and mineralocorticoid receptor antagonist.
comorbidities except hypertension and CABG were more frequent in the group not receiving RASb, with the largest difference in renal dysfunction (5% vs 13%) between RASb-exposed and nonexposed patients. Among those receiving RASb, BB was more prevalent compared with the non-RASb group (Table 1).

### 3.3 Outcome

Overall, 13,398 (44%) patients died during follow-up. One-year mortality was 28%, and 2-year mortality was 37%. Death from HF occurred in 1909 patients (6%). There were 5665 (31.8%) deaths, including 796 (4.5%) HF deaths in those exposed to RASb, compared with 7733 (60.0%) and 1113 (8.6%) in those unexposed.

Table 2 shows that female gender was associated with a crude HR of more than one, which changed to 0.91 (95% CI, 0.88-0.95) after adjustment for age, hospitalisation-free time, RASb, comorbidity, and BB/MRA (model 4). Lower age was associated with a lower HR for all-cause death, the HR for 20 to 64 year old being 0.19 (0.17-0.21) (model 4). The unadjusted HR for all-cause death associated with RASb was 0.46 (0.45-0.48), and the adjusted overall HR was 0.72 (0.69-0.75) (Table 2; model 4).

Table 3 demonstrates the HRs for HF death, showing similar relations as for all-cause death. The crude HR for HF death associated with RASb was 0.47 (0.42-0.51) and the adjusted HR 0.85 (0.77-0.93).

To assess the bias of misclassification in our data, we ran analyses stratified by comorbidity diagnosis, showing small differences in HRs.

### 3.3.1 Interaction analyses

The interaction term for female gender and RASb was nonsignificant for all-cause death. There was significant interaction between lower age class and RASb for all-cause death. (Table 2; model 6). Interaction effects are also depicted as HRs for all-cause death for each exposure combination compared with a common reference category in Figure 2, showing HRs between 0.12 (0.10-0.13) in the youngest and 0.80 (0.76-0.84) in the oldest patients.

The RERI for all-cause death was not significant for gender and RASb nor age and RASb (Table 2). For HF death, the interaction term for female gender and RASb was nonsignificant (Table 3). HRs for each exposure category are presented in Figure 3. The RERI was not significant (Table 3).

### 4 Discussion

Women and older patients were less exposed to RASb than men and younger patients. Exposure to RASb was associated with a reduction in mortality for women and men alike. Interaction analysis showed a stronger association between survival and RASb for younger vs older patients.
4.1.1. Treatment

In our data, reflecting RASb treatment in Sweden 2005 to 2010, 58% were exposed to RASb. Treatment guidelines have consistently recommended RASb as first line therapy in HFrEF since 2005; however, treatment patterns could have changed since our data collection. A study of drug treatment quality in the Stockholm region in 2012 reported that 68% of HF patients in primary and secondary care were treated with RASb. According to the Swedish Board of Health and Welfare's national statistics of health care quality indicators, 61% of all hospitalised HF patients were treated with RASb in 2016 compared with 55% in 2008. Thus, available data indicate that RASb is still underused although the trend may be towards higher use.

4.1.2. Mortality

The overall all-cause mortality of 28% at 1 year and 37% at 2 years in our study is similar to other observational studies. A study of drug treatment quality in the Stockholm region in 2012 reported that 68% of HF patients in primary and secondary care were treated with RASb. According to the Swedish Board of Health and Welfare's national statistics of health care quality indicators, 61% of all hospitalised HF patients were treated with RASb in 2016 compared with 55% in 2008. Thus, available data indicate that RASb is still underused although the trend may be towards higher use.

4.1.3. Treatment effects

Our overall adjusted HR of 0.72 for all-cause death among patients exposed to RASb is comparable with a systematic overview of randomised trials reporting an OR for death of 0.74 for ACEI compared with placebo. As for observational data, Keyhan et al reported similar HRs for ACEI treatment (HR 0.80 for women and 0.71 for men), and the Euro Heart failure study found an OR of 0.5 for death within 12 weeks for RASb among hospitalised patients.
RASb was also associated with a lower risk for HF death, with an HR of 0.85 (0.77-0.93). In the SOLVD study of enalapril efficacy, the greatest mortality reduction was found among deaths attributable to progressive HF.2

4.1.4. Gender

In our study, as in other observational studies, half of the patients were women.9,11,13 Also consistent with previous reports, women had a higher adjusted overall survival than men.11 This may be partly due to the higher proportion of HF with preserved ejection fraction (HFP EF) among women and conversely to the lower prevalence of ischemic heart disease. Alternative explanations include pathophysiology, sex hormones, and remodelling in HF in men and women.14

The finding that RASb is associated with decreased mortality for both male and female HF patients is noteworthy, as earlier research has been conflicting.4,35 A review summarises that although ACEIs prevent cardiovascular death and readmissions, clinical trials have failed to show significant all-cause mortality benefit for women, possibly due to underpowered trials.14 Our data, with a representative proportion of women, reflect a survival benefit for women on RASb in agreement with other observational studies.9,11,16 Keyhan et al reported a greater risk reduction associated with RASb for men than for women.11 In contrast, we found a somewhat higher risk reduction among women, although not statistically significant.

As in previous studies, we found less RASb exposure among women15-18 and older patients.10,36 Whether this constitutes inequity in treatment is unclear, as the gender difference in treatment could be due to a higher prevalence of HFP EF among women.37

4.1.5. Age

RASb exposure decreased with higher age. RASb was associated with better survival in all age groups, but the association weakened with higher age, perhaps partially due to a higher prevalence of HFP EF among older patients.37 Our results are relevant for numerous patients, as the HF population is old. Ageing populations are a reality, notably in middle- and high-income countries. Hence, not only healthy ageing and quality of life are increasingly relevant considering equity but also health economics. HF accounts for 1% to 2% of hospital admissions in high-income settings. In Sweden and the United Kingdom, 2% of the healthcare budget goes to HF care.38 Health costs are double in HF patients compared with the general population, largely attributable to institutionalised care. RASb reduces hospitalisations3 and is cost-effective.29

4.1. Strengths and limitations

Our individual level data represent the entire Swedish population. The validity for HF as primary diagnosis in the patient register is 95%.24 In the prescribed drug register, RASb registration is around 99% complete. The validity of HF as underlying cause of death has not been studied however, and there is uncertainty concerning the validity of the outcome HF death. Our comorbidity data are limited to inpatient hospitalisation data within 1.5 years preceding the index hospitalisation, and comorbidities were likely underestimated. Notably for HF, the lack of primary care data would lead to underreporting and misclassification bias.40 The prevalence of several comorbidity diagnoses are lower than in some other studies9,11,13,41 although Shafazand et al reported comorbidity levels similar to ours, also from Swedish patient register data.33 Some comorbidities are found in similar proportions for certain groups by Keyhan et al.11

As for misclassification, we believe that our cohort was actually less affected by some comorbidity, eg, hypertension, as we excluded patients with a recent RASb dispensation, and RASb is a treatment for hypertension. Renal dysfunction is a potential confounder in our study, being associated with increased HF mortality as well as decreased RASb exposure. Gasparini et al have shown that only 12% of patients with chronic kidney disease are recognized and diagnosed in primary and secondary care.42 Underestimating renal dysfunction could introduce bias towards overestimating the association between RASb and survival. Previous studies of HF patients report renal dysfunction among 1.3% to 56%, and mostly around 15% to 30%.9,11,13,34,43,44 Those studies vary considerably regarding exhaustivity of data in time, register vs clinical data, hospitalisation data vs other care levels, de novo vs previous HF, previous RASb use, population age, renal dysfunction definitions, exclusion by serious renal dysfunction, etc. Our prevalence of renal dysfunction was 8.5% overall, and 13% among patients exposed to RASb vs 5.2% among those unexposed. Our cohort resembles a de novo HF population and an RASb-naïve one and could be less affected by comorbidity including renal dysfunction than others. Furthermore, the relation between renal dysfunction and mortality in HF is graded; the more advanced renal dysfunction, the higher the mortality.43 Clinically significant, ie, more advanced, renal dysfunction should be less likely to be underreported in the patient register. Patients with comorbid heart disease were more likely to be diagnosed with chronic kidney disease in the study by Gasparini et al. The overall HR for patients with renal dysfunction in our study was 0.78 (data not shown), which is close to the overall HR for the whole cohort of 0.72. While we cannot refute misclassification bias in comorbidity, the consistency with other studies in overall mortality and RASb-associated mortality reduction also supports the overall validity of our results.

A limitation shared with other register studies is the lack of characterisation of HFrEF/HFP EF, as the patient register does not contain data on ejection fraction (EF). RASb has not been shown to increase survival in HFP EF patients and is not recommended for HFP EF in guidelines. We were unable to validate true eligibility for RASb.

Survival bias in pharmacoepidemiology typically leads to overestimation of effects.45 A strength of our study is that we addressed this by using a time-dependent exposure covariate.
Interaction was estimated on both the multiplicative and the additive scales and risks calculated for each exposure category with a common reference, as recommended in epidemiological literature.\textsuperscript{28} While one study suggested that the RERI is valid only for risk factors and not preventive exposures,\textsuperscript{46} a later publication concluded that it may be used for preventive factors when the sample size is sufficient (more than 1000 subjects).\textsuperscript{47} We thus regard our RERI estimates as valid.

Obviously, this observational study cannot assert causation.

5 | CONCLUSIONS

We suggest that RASb is effective in hospitalised female and male HF patients of different ages, including very old patients. We found no evidence for a differential effect by gender. Exposure to RASb was associated with decreased mortality in all studied patient groups, although somewhat less in older patients. Yet, RASb exposure was low, and more pronounced so among older and female patients. There is a room for improvement in adherence to treatment guidelines. Further studies including data on EF would expand knowledge regarding equity in RASb treatment.

ETHICS STATEMENT

The study conforms to the declaration of Helsinki and was approved by the Swedish Central Ethical Review Board (reg. no. Ö 29-2011).

ACKNOWLEDGEMENTS

This study was funded by The Swedish Research Council for Health, Working Life and Welfare (Swedish: FORTE-Forskningsrådet om Hälsa, Arbetsliv och Välfärd) (grant number 2015-00480).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Anna Ohlsson \(\text{https://orcid.org/0000-0001-6897-6390}\)

REFERENCES

1. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The acute infarction Ramipril efficacy (AIRE) study investigators. Lancet 1993;342(8875):821–8. [published Online First: October 2, 1993]

2. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD investigators. N Engl J Med 1991;325(5):293–302. [https://doi.org/10.1056/nejm199108013250501 [published Online First: August 1, 1991]]

3. The CONSENSUS Trial Study Group. CONSENSUS. Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative north Scandinavian Enalapril survival study (CONSENSUS). N Engl J Med. 1987;316:1429–1435.

4. Flather MDY, Kober S, Pfeffer L, et al. ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet. 2000;355(9215):1575-1581.

5. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-overall programme. The Lancet. 2003;362(9386):759-766. [https://doi.org/10.1016/s0140-6736(03)14282-1]

6. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE investigators. N Engl J Med 1992;327(10):669–77. https://doi.org/10.1056/nejm199209303271001 [published Online First: September 13, 1992]

7. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. Eur J Heart Fail 2012;14(8):680–69. hfs105 [pii]. https://doi.org/10.1093/eurjhf/hfs105 [doi] [published Online First: July 26, 2012]

8. Brook RH, Lohr KN. Efficacy, effectiveness, variations, and quality. Boundary-crossing research. Med Care 1985;23(5):710–22. [published Online First: May 1, 1985]

9. Masoudi FA, Rathore SS, Wang Y, Havranek EP, Curtis JP. Foody Jam, Krumholz HM National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. Circulation 2004;110(6):724–31. https://doi.org/10.1161/01.cir.0000138934.28340.ed [published Online First: 2004/08/04]

10. Vorilhon C, Chenaf C, Mulliez A, Pereira B, Clerfond G, Authier N, Jean F, Motreff P, Citron B, Eschalier A, Lusson JR, Eschalier R Heart failure prognosis and management in over-80-year-old patients: data from a French national observational retrospective cohort. Eur J Clin Pharmacol 2015;71(2):251–60. https://doi.org/10.1007/s00228-014-1794-7 [published Online First: 2014/12/30]

11. Keyhan G, Chen SF, Pilote L. Angiotensin-converting enzyme inhibitors and survival in women and men with heart failure. Eur J Heart Fail 2007;9(6–7):594–601. https://doi.org/10.1016/j.ejheart.2007.03.004 [published Online First: 2007/04/28]

12. Schade CP, Hannah KL, Rezek G, Brehm JG ACE inhibitor use and mortality reduction: do controlled trial results equal clinical practice? W V Med J 2006;102(1):304–6. [published Online First: May 19, 2006]

13. Eschalier R, Chenaf C, Mulliez A, Yaloua A, Clerfond G, Authier N, Vorilhon C, Citron B, Pereira B, Jean F, Souteyrand G, Motreff P, Eschalier A, Lusson J.R. Impact of clinical characteristics and management on the prognosis of unselected heart failure patients. Cardiovasc Drugs Ther 2015;29(1):89–98. https://doi.org/10.1007/s10557-015-6572-y [published Online First: 2015/02/24]

14. Frankenstein L, Clark AL, Ribeiro JP. Influence of sex on treatment and outcome in chronic heart failure. Cardiovasc Ther 2012;30(3):182–92. https://doi.org/10.1111/j.1755-5922.2010.00253.x [published Online First: 2011/05/24]

15. Ohlsson A, Lindahl B, Hanning M, et al. Inequity of access to ACE inhibitors in Swedish heart failure patients: a register-based study. J Epidemiol Community Health 2016;70(1):97–103. https://doi.org/10.1136/jech-2015-205738 [Epub 2015 Aug 10]

16. Lam CS, Chang P, Chia SY, Sim LL, Gao F, Lee FL, Chai P, Wong RC, Seow SC, Leong GK, Yeo PS, Sim D, Chua T, Kwok BW Impact of sex on clinical characteristics and in-hospital outcomes in a multi-ethnic southeast Asian population of patients hospitalized for acute heart failure. ASEAN Heart Journal: Official Journal of the ASEAN Federation of Cardiology 2014;22(1):8. https://doi.org/10.7603/s40602-014-0008-y [published Online First: 2014/01/01]

17. Lenzen MJ, Rosengren A, Scholte op Reimer WJ, et al. Management of patients with heart failure in clinical practice: differences between men and women. Heart. 2008;94(3):e10. https://doi.org/10.1136/hrt.2006.099523 [published Online First: 2007/06/19].
negative findings: results from a systematic review and simulation study. J Clin Epidemiol 2014;67(7):821–9. https://doi.org/10.1016/j.jclinepi.2014.02.008 [published Online First: 2014/04/29]

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.