

# Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers Are Associated With Improved Outcome but Do Not Prevent New-Onset Atrial Fibrillation After Acute Myocardial Infarction

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**Background**—Treatment with renin-angiotensin system (RAS) inhibitors might restrain the structural/electrical remodeling associated with atrial fibrillation (AF). Limited evidence exists regarding the potential benefits of RAS inhibition post-acute myocardial infarction (AMI) in patients with AF. This study sought to assess the association between RAS inhibition and all-cause mortality and new-onset AF in patients with/without congestive heart failure (CHF) post-AMI.

**Methods and Results**—Patients hospitalized for AMI between 2006 and 2012 were identified in Swedish registries. Patients were stratified in 4 subgroups; patients with CHF and AF (n=11 489); patients with CHF without AF (n=31 676); patients with AF without CHF (n=10 066); and patients without both CHF and AF (n=59 417). Patients exposed to RAS inhibition were compared to nontreated. Three-year risk of all-cause mortality and new-onset AF was assessed using adjusted Cox regression analyses. At discharge, 83 291 (73.9%) patients received RAS inhibition. RAS inhibition was associated with lower 3-year risk of all-cause mortality in CHF patients with AF, adjusted hazard ratio (HR) with 95% CI 0.75 (0.70–0.81), CHF patients without AF, HR 0.65 (0.60–0.69), AF patients without CHF, HR 0.82 (0.75–0.90), and in patients without CHF and AF, HR 0.76 (0.72–0.81), respectively. RAS inhibition was not associated with lower 3-year risk of new-onset AF in patients without AF but with/without CHF; HR 0.96 (0.84–1.10) and 1.12 (1.02–1.22), respectively.

**Conclusions**—RAS inhibition post-AMI was associated with lower risk of all-cause mortality. In patients with/without CHF, RAS inhibition was not associated with lower incidence of new-onset AF. (*J Am Heart Assoc.* 2017;6:e005165. DOI: 10.1161/JAHA.116.005165.)

**Key Words:** atrial fibrillation • myocardial infarction

Inhibition of the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) have been shown to reduce the risk of death, reinfarction, and hospitalization for congestive heart failure (CHF) post-acute myocardial infarction (AMI) in patients with CHF and/or left ventricular dysfunction.<sup>1–5</sup> Also, ACEIs and ARBs have, in previous

studies, shown to have antiarrhythmic properties by restraining the structural and electrical remodeling associated with atrial fibrillation (AF).<sup>6–10</sup>

Current non-ST-segment elevation myocardial infarction (NSTEMI) guidelines from the United States<sup>11</sup> and Europe<sup>12</sup> recommend the use of RAS inhibitors in patients with CHF, left ventricular dysfunction, and in those with hypertension

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Accompanying Tables S1 through S5 are available at <http://jaha.ahajournals.org/content/6/3/e005165/DC1/embed/inline-supplementary-material-1.pdf>

An abstract based on the preliminary results of this work was presented as a poster at the European Society of Cardiology Congress, August 27–31, 2016, in Rome, Italy.

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or diabetes mellitus. Also, the American guidelines suggest that such therapy might be reasonable for all other patients with cardiac or vascular disease. ARBs are stated as a noninferior alternative in ACEI-intolerant patients. Similarly, the ST-segment elevation myocardial infarction (STEMI) guidelines from the United States<sup>13</sup> and Europe<sup>14</sup> state that ACEIs or ARBs are recommended for all patients with CHF and left ventricular dysfunction, and that it is reasonable for all other patients without contraindications. AF guidelines from the United States<sup>15</sup> and Europe<sup>16</sup> recommend RAS inhibition as a reasonable upstream therapy that might be considered in patients with CHF and left ventricular dysfunction to prevent new-onset AF. At the same time, these guidelines stress that RAS inhibition is not beneficial for primary prevention of new-onset AF in patients without cardiovascular disease.

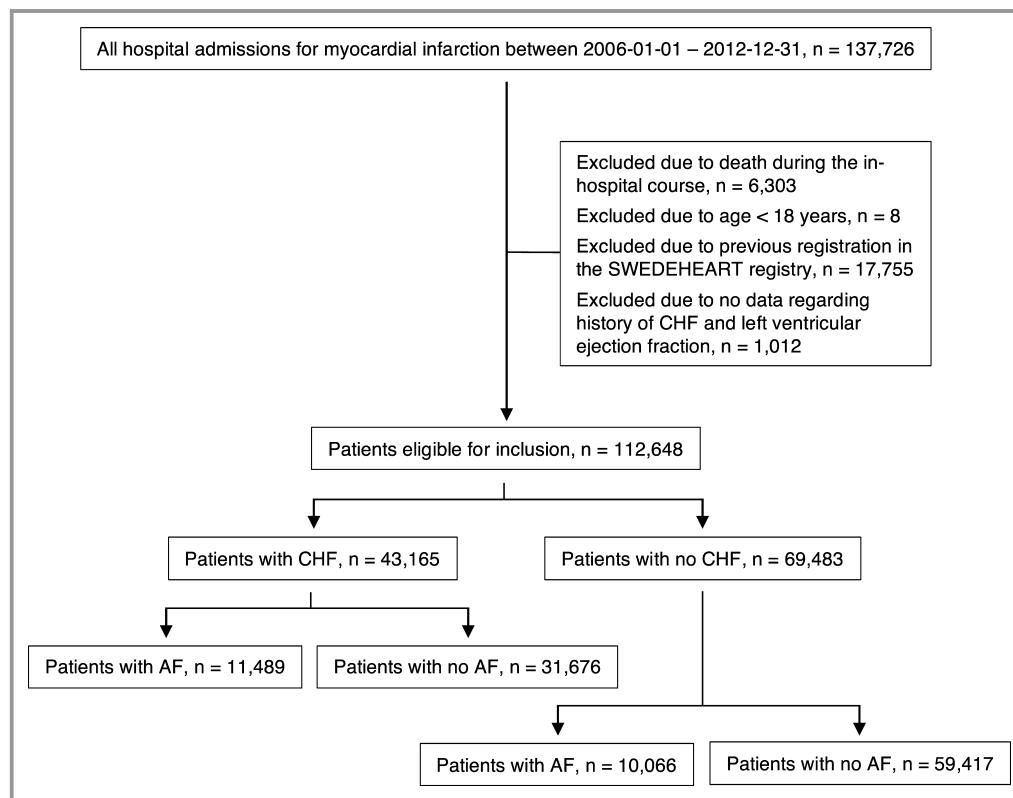
It is still unclear whether or not ACEIs and ARBs are beneficial for patients with AF post-AMI. Moreover, it is uncertain whether ACEIs and ARBs are effective upstream therapies for prevention of new-onset AF post-AMI. With this study we sought to answer the following questions: (1) Is RAS inhibition associated with lower risk of all-cause mortality, cardiovascular mortality, recurrent AMI, and stroke in patients with and without CHF and/or AF post-AMI? (2) In patients

with no history or in-hospital diagnosis of AF post-AMI, is RAS inhibition associated with reduced risk of new-onset AF?

## Methods

### Study Population

This is a retrospective, observational cohort study including all patients admitted to all coronary care units in Sweden (n=72). Data in this study were obtained from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.<sup>17</sup> SWEDEHEART is nationwide and includes all consecutive patients admitted to coronary care units because of symptoms indicative of acute coronary syndrome. Patients included in the registry do not provide written consent, but are informed about their inclusion in the registry and have the possibility to opt out. In the present study, patients aged above 18 years discharged alive after their first AMI between 2006 and 2012 were included. Patients with no history of CHF and with missing data regarding left ventricular ejection fraction (LVEF) were excluded (see Figure 1). The last follow-up date for included patients was on December 31, 2013.



**Figure 1.** Selection of study population. AF indicates atrial fibrillation; CHF, congestive heart failure; SWEDEHEART, Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies.

## Data Collection and Data Linkage With Other Registries

Information about comorbidities at arrival, patient presentation at admission, hospital course, and medication at arrival and discharge was obtained from SWEDEHEART and was enriched with data from the National Patient Registry and the National Dispensed Drug Registry. The National Patient Registry, which has previously been shown to have high validity, is a mandatory registry for all hospitals in Sweden and includes diagnoses for all patients seeking hospital care since 1987.<sup>18</sup> The National Dispensed Drug Registry includes data about all prescribed drug purchases in Sweden, including anatomical therapeutic chemical classification codes, dates, dosages, and quantities for every prescription since July 2005.<sup>19</sup> The data linkage was approved and performed by the National Board of Health and Welfare in Sweden using the unique 10-digit civic registration number. The ethics committee at Karolinska Institute, Stockholm, approved the study protocol. See Table S1 for more details regarding data collection, data linkage, and variable definition.

## Definition of Exposure

The main exposure was treatment with ACEI and/or ARB, either at hospital discharge as registered in the SWEDEHEART registry, or if an ACEI or ARB was dispensed within 7 days from discharge according to the National Dispensed Drug Registry. For ACEI and ARB, the duration of treatment after discharge was estimated to last 3 months. Thereafter, each drug purchase from the pharmacy within 6 months, as captured in the National Dispensed Drug Registry, resulted in the patient being considered exposed to the medication for an additional 6 months. An interruption gap of 6 months or above resulted in an assumption of drug discontinuation and a censoring from the on-treatment analysis. In accord with this, a drug dispense of ACEI or ARB in a previously unexposed patient resulted in censoring from the on-treatment analysis. Ongoing treatment with ACEI or ARB before index AMI was based on data entered in SWEDEHEART at hospital arrival, or if an ACEI or ARB was dispensed within 6 months before admission.

## Definition of Outcomes

The efficacy outcome in this study was all-cause mortality. Additional outcomes included cardiovascular mortality, recurrent AMI, and stroke (ischemic or hemorrhagic) within 3 years from discharge. Also, the risk of new-onset AF was estimated in a subgroup of patients with no history of AF before discharge. Data on outcome were based on observations in the National Patient Registry and in the National Cause of Death Registry (see Table S2). When analyzing outcome,

patients were censored after 3 years from discharge or at the end of follow-up. For all-cause mortality, no other censoring scheme was applied. For cardiovascular mortality, recurrent AMI, stroke, and new-onset AF, patients were also censored for all-cause mortality.

## Statistical Analyses

Statistical analyses were performed on all patients meeting the inclusion criteria. Results were described according to treatment with ACEI and/or ARB versus no such treatment, with follow-up started at the time of discharge. Patients were stratified and analyzed in 4 different subgroups; patients with CHF and AF; patients with CHF without AF; patients without CHF and with AF; and patients without both CHF and AF. Demographic and baseline characteristics were reported using percentages for categorical variables and with median and interquartile range (IQR) for continuous variables. Categorical variables were compared using Pearson's  $\chi^2$  test, and continuous variables were compared using the Wilcoxon signed-rank test. The association between drug treatment and outcome was studied in an on-treatment analysis. Kaplan–Meier survival plots were used to illustrate outcome in relation to drug treatment. Unadjusted and adjusted Cox proportional hazards models were reported using hazard ratios (HR) with 95% confidence interval (CI). In the adjusted model, potential clinical cofounders were accounted for and included: age (3-knot restricted cubic spline); sex; diabetes mellitus; hypertension; peripheral vascular disease; previous stroke; type of infarction (STEMI or NSTEMI); Killip class on admission; new-onset AF during hospital course; LVEF; creatinine level (3-knot restricted cubic spline); discharge hospital (as a  $\Gamma$  distributed random frailty effect); percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during the in-hospital course; and concomitant medication at discharge (oral anticoagulants, aspirin, P2Y<sub>12</sub>-inhibitors,  $\beta$ -blockers, diuretics, digoxin, and statins). Tests for interactions were performed to determine whether the association of ACEI and/or ARB treatment with outcome was similar in patients with AF and those without AF and were calculated using z-tests based on the results from the two separate cohorts in the Cox proportional hazards models. For missing data, multiple imputation with chained equations was performed, generating 25 imputed data sets using the above adjustment variables, including outcome, as predictors.<sup>20</sup>

Four sensitivity analyses were conducted. In the first sensitivity analysis, an intention-to-treat analysis was performed in which drug treatment with ACEI and/or ARB at discharge was accounted for, censoring only at the end of follow-up or for mortality. Second, a complete case analysis was performed excluding patients with any missing data (n=75 547). Third, a propensity-score-matched analysis was

conducted in which propensity scores were estimated using random-effects logistic regression models with ACEI and/or ARB at discharge as outcome and all other variables above as explanatory variables. In the fourth sensitivity analysis, ACEI and ARB were analyzed separately. Finally, we also assessed for differences in the following subgroups; age  $\leq 75$  years versus age  $>75$  years; NSTEMI versus STEMI; and hypertension versus no hypertension.

All analyses were performed using R statistics software (version 3.1.0; R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Study Population and Baseline Characteristics

In this study, all consecutive patients admitted because of a first AMI between 2006 and 2012 in all coronary care units in Sweden were included ( $n=137\,726$ ). A proportion of patients were excluded from the final study population because of in-hospital mortality ( $n=6303$ ), age under 18 years ( $n=8$ ), previous registration in SWEDEHEART ( $n=17\,755$ ), and because of missing data regarding both CHF and LVEF ( $n=1012$ ). After all exclusions, a total of 112 648 patients remained (see Figure 1).

The study population had a median age of 72 years, and 35.5% were women. At discharge, a total of 83 291 (73.9%) were treated with ACEI and/or ARB. Table 1 shows the characteristics of the patients included stratified by use of ACEI and/or ARB. Compared to patients not discharged on treatment with RAS inhibition, those receiving such treatment were more often male and more likely to have a history of diabetes mellitus, hypertension, AMI, previous PCI, and CABG. Patients discharged on RAS inhibition were more likely to have an STEMI, left ventricular dysfunction, or a discharge diagnosis of CHF. Also, patients on ACEI and/or ARB more often underwent PCI during the index hospitalization. At discharge, patients on RAS inhibition were more often prescribed aspirin, P2Y<sub>12</sub> inhibitors, oral anticoagulants,  $\beta$ -blockers, calcium-channel blockers, diuretics, and statins.

### All-Cause Mortality, Cardiovascular Mortality, Recurrent AMI, and Stroke

A total of 17 121 patients died within 3 years from discharge. Figure 2 illustrates unadjusted Kaplan–Meier curves for all-cause mortality within 3 years postdischarge. For all-cause mortality, the cumulative incidence rate per 100 person years for patients treated with ACEI/ARB versus nontreated was 18.8 and 9.0, respectively. In patients with CHF at baseline, treatment with RAS inhibition was associated with a lower 3-year risk of all-cause mortality, both in patients with a

diagnosis of AF and in those with no diagnosis of AF, adjusted HR with 95% CI 0.75 (0.70–0.81) and 0.65 (0.60–0.69), respectively. Similar associations were observed in patients with no diagnosis of CHF, with or without AF at baseline, adjusted HR 0.82 (0.75–0.90) and 0.76 (0.72–0.81), respectively.

The unadjusted event rate of 3-year cardiovascular mortality is presented in Table 2. After adjustment for confounding factors, treatment with ACEI/ARB was associated with a lower risk of cardiovascular mortality, HR 0.81 (0.78–0.85). Similar findings were observed in patients with CHF at baseline. For patients with no diagnosis of CHF and with AF at baseline, there was a borderline trend toward lower cardiovascular mortality after adjustments, HR 0.91 (0.82–1.02). For patients without both CHF and AF, there was a significant association with reduced cardiovascular mortality, adjusted HR 0.91 (0.84–0.99).

The 3-year event rate for AMI is presented in Table 2. After adjustments, treatment with ACEI/ARB was significantly associated with a lower rate of AMI, HR 0.95 (0.92–0.98). A similar association was noted among a subgroup of patients with CHF at baseline, irrespectively if they had AF or no AF. For patients without CHF at baseline, no beneficial association was observed with ACEI/ARB in regard to recurrent AMI.

The unadjusted cumulative incidence rate per 100 person-years of 3-year stroke was 2.1 in patients exposed to ACEI/ARB versus 2.6 in nontreated patients. After adjustments, the association of ACEI/ARB with risk of 3-year stroke was similar to nontreated patients, adjusted HR 0.96 (0.89–1.03). In a subgroup of patients with CHF and without AF at baseline, ACEI/ARB was associated with a lower risk of stroke, adjusted HR 0.80 (0.68–0.95). However, this association was not observed among the other subgroup of patients.

### New-Onset AF

In patients with no history of AF or in-hospital diagnosis of AF, the cumulative incidence rate per 100 person-years of 3-year new-onset atrial fibrillation was 2.9 in patients treated ACEI/ARB versus 2.9 in nontreated patients (see Figure 3; Table 2). After adjustment for patient, hospital, and treatment characteristics, ACEI/ARB was not associated with a lower risk of new-onset AF, adjusted HR 1.07 (1.00–1.15). A similar lack of association was observed among patients with or without CHF.

### Sensitivity Analyses

Similar results to the main analyses were observed in an intention-to-treat analysis (Table S3), a complete case analysis (Table S4), a propensity score analysis (Table S4), and when ACEI and ARB were analyzed separately (Table S5).

**Table 1.** Baseline Table

	All Patients (n=112 648)	No ACEI/ARB (n=29 357)	ACEI/ARB (n=83 291)	P Value
<b>Demographics</b>				
Age, median (IQR), y	72 (62–81)	74 (62–83)	71 (62–79)	<0.001
Sex, women	39 987 (35.5)	11 729 (40.0)	28 258 (33.9)	<0.001
Smoking, n=106 886	25 714 (24.1)	6451 (23.8)	19 263 (24.1)	<0.001
Body mass index, median (IQR), n=97 204	26 (24–29)	25 (23–28)	27 (24–29)	<0.001
<b>Admission year</b>				
2006	16 949 (15.0)	5783 (19.7)	11 166 (13.4)	
2007	17 264 (15.3)	5177 (17.6)	12 087 (14.5)	
2008	16 311 (14.5)	4453 (15.2)	11 858 (14.2)	
2009	15 387 (13.7)	3877 (13.2)	11 510 (13.8)	
2010	15 466 (13.7)	3469 (11.8)	11 997 (14.4)	
2011	15 616 (13.9)	3287 (11.2)	12 329 (14.8)	
2012	15 655 (13.9)	3311 (11.3)	12 344 (14.8)	
<b>Comorbidities and presentation at admission</b>				
Diabetes mellitus	27 149 (24.1)	4959 (16.9)	22 190 (26.6)	<0.001
Hypertension	67 436 (59.9)	13 571 (46.2)	53 865 (64.7)	<0.001
MI	29 330 (26.0)	7087 (24.1)	22 243 (26.7)	<0.001
CHF	12 039 (10.7)	2903 (9.9)	9136 (11.0)	<0.001
Peripheral vascular disease	6143 (5.5)	1618 (5.5)	4525 (5.4)	0.61
Stroke	13 038 (11.6)	3618 (12.3)	9420 (11.3)	<0.001
Any bleeding	7390 (6.6)	2174 (7.4)	5216 (6.3)	<0.001
Chronic obstructive pulmonary disease	7855 (7.0)	2262 (7.7)	5593 (6.7)	<0.001
Dementia	616 (0.5)	282 (1.0)	334 (0.4)	<0.001
Cancer diagnosis within 3 years	3160 (2.8)	1033 (3.5)	2127 (2.6)	<0.001
Previous PCI	12 727 (11.3)	2667 (9.1)	10 060 (12.1)	<0.001
Previous CABG	9461 (8.4)	2100 (7.2)	7361 (8.8)	<0.001
<b>Hospital course</b>				
STEMI	36 472 (32.4)	6949 (23.7)	29 523 (35.4)	<0.001
PCI	63 821 (56.7)	12 621 (43.0)	51 200 (61.5)	<0.001
CABG	3935 (3.5)	1181 (4.0)	2754 (3.3)	<0.001
Creatinine, median (IQR), μmol/L, n=110 143	83 (70–102)	84 (70–106)	83 (70–100)	<0.001
Decompensated heart failure (Killip ≥II), n=108 078	15 524 (14.4)	3886 (13.8)	11 638 (14.6)	0.003
LVEF <50%, n=82 026	35 679 (43.5)	4924 (27.1)	30 755 (48.2)	<0.001
CHF (including history of)	43 165 (38.3)	7136 (24.3)	36 029 (43.3)	<0.001
New-onset AF	9853 (8.9)	2635 (9.2)	7218 (8.9)	0.08
AF (including history of)	21 555 (19.1)	5936 (20.2)	15 619 (18.8)	<0.001
<b>Discharge medication</b>				
Aspirin	104 283 (92.8)	26 459 (90.5)	77 824 (93.6)	<0.001
P2Y <sub>12</sub> inhibitors	86 889 (77.2)	19 770 (67.6)	67 119 (80.6)	<0.001
Oral anticoagulants	7921 (7.0)	1655 (5.7)	6266 (7.5)	<0.001
β-blockers	100 285 (89.1)	24 537 (83.8)	75 748 (91.0)	<0.001
Calcium-channel blockers	17 711 (15.7)	4327 (14.8)	13 384 (16.1)	<0.001

Continued

**Table 1.** Continued

	All Patients (n=112 648)	No ACEI/ARB (n=29 357)	ACEI/ARB (n=83 291)	P Value
Digoxin	3613 (3.2)	1016 (3.5)	2597 (3.1)	0.003
Diuretics	37 220 (33.1)	8834 (30.2)	28 386 (34.1)	<0.001
Nitrates	19 301 (17.2)	5874 (20.1)	13 427 (16.2)	<0.001
Statins	94 871 (84.3)	21 382 (73.1)	73 489 (88.3)	<0.001

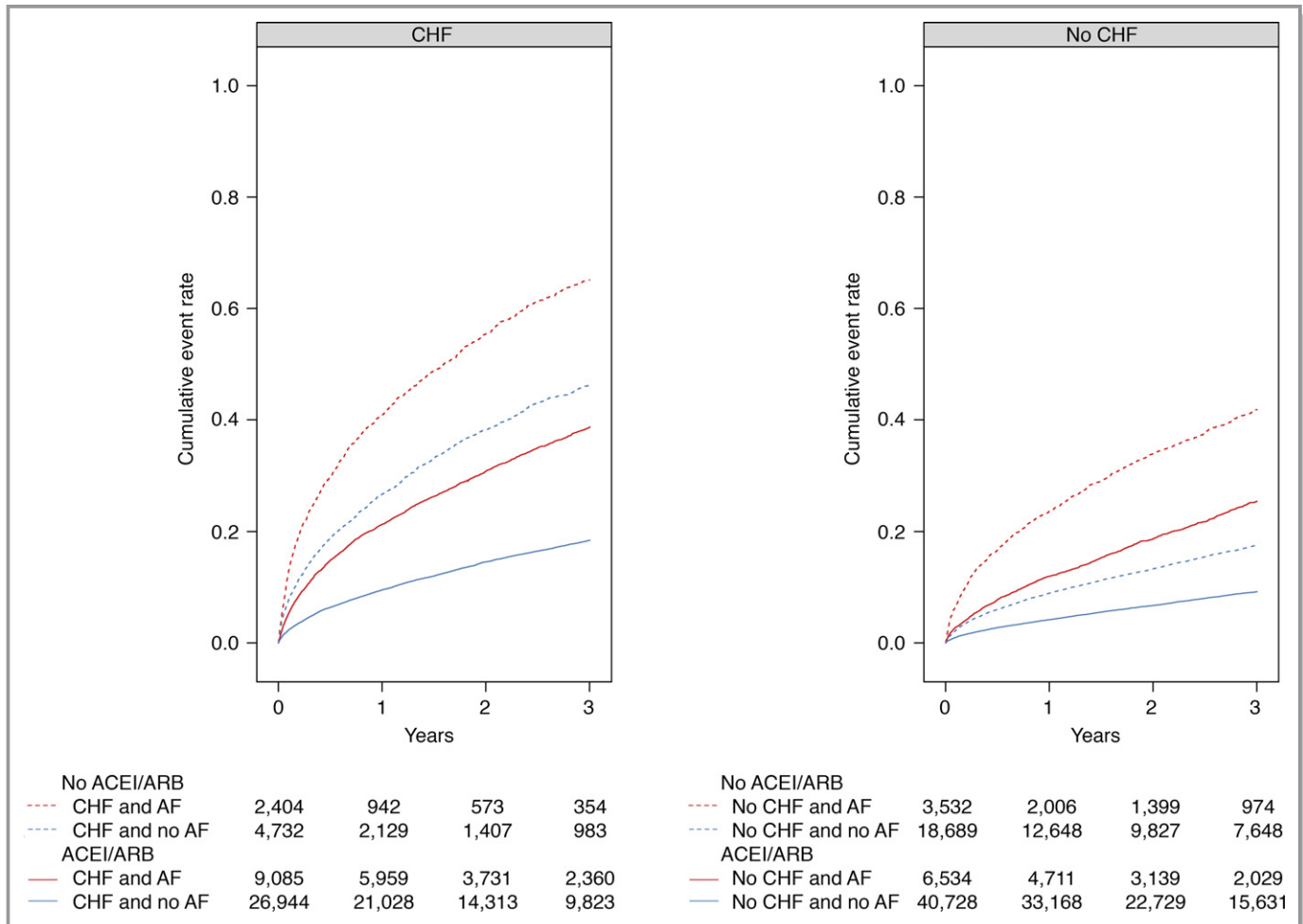
Patient characteristics, admission year, and clinical and in-hospital characteristics of acute myocardial infarction patients in relation to treatment with ACEI and/or ARB at discharge. Demographic and baseline characteristics were reported using percentages for categorical variables or with median and IQR for continuous variables (as noted). ACEI indicates angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; CHF, congestive heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

**Subgroup Analysis**

All-cause mortality did not show significant heterogeneity in subgroup analysis, with 2 exceptions. The association between lower risk of all-cause mortality and treatment with ACEI/ARB appeared to be diminished in 2 subgroup of patients without CHF and with AF at baseline, in patients with STEMI and in those with no hypertension (see Figure 4).

**Discussion**

This study shows that RAS inhibition in patients with AMI was associated with a lower risk of all-cause mortality. This association was consistent among patients with or without CHF and with or without AF at baseline. A similar beneficial association was observed for cardiovascular mortality in all patients, and for recurrent AMI in patients with CHF,

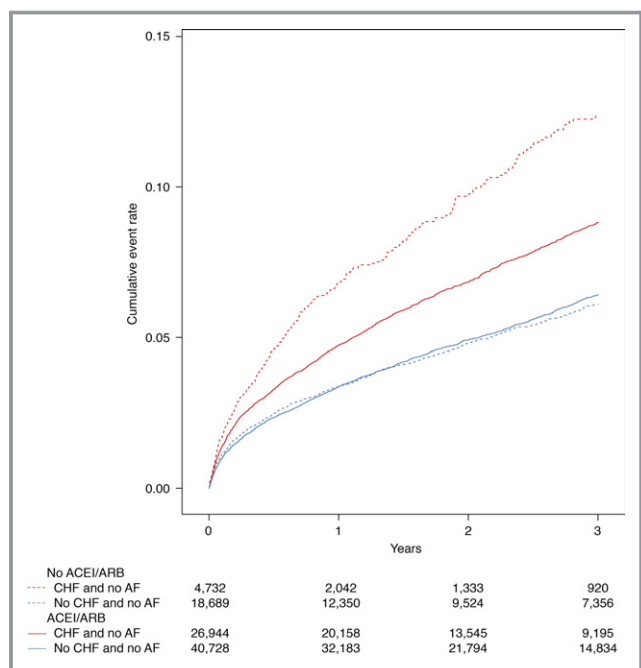


**Figure 2.** Kaplan–Meier plots depicting outcome for patients with and without CHF and AF. Kaplan–Meier plots depicting the cumulative incidence curve for all-cause mortality stratified by use of ACEI and/or ARB. ACEI indicates angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CHF, congestive heart failure.

**Table 2.** Outcome in Relation to Treatment

Outcomes, No. of Events/Person Time in units of 100 years (Event Rate)	Stratification						P Value for Interaction	P Value for Interaction
	All Patients (n=112 648)	CHF and AF (n=11 489)	CHF and No AF (n=31 676)	P Value for Interaction	No CHF and AF (n=10 066)	No CHF and No AF (n=59 417)		
All-cause mortality	17 121/2121.4 (8.1)	3964/176.1 (22.5)	5474/590.7 (9.3)	...	2383/173.5 (13.7)	5300/1181.1 (4.5)	...	
No ACE/ARB	6115/477.9 (12.8)	1134/25.3 (44.9)	1450/57.1 (25.4)	...	1119/53.2 (21.0)	2412/342.3 (7.0)	...	
ACE/ARB	11 006/1643.5 (6.7)	2830/150.8 (18.8)	4024/533.6 (7.5)	...	1264/120.3 (10.5)	2888/838.8 (3.4)	...	
Unadjusted HR	0.53 (0.52–0.55)	0.45 (0.42–0.49)	0.32 (0.30–0.34)	<0.001	0.51 (0.47–0.55)	0.49 (0.46–0.52)	0.42	
Adjusted HR	0.73 (0.71–0.76)	0.75 (0.70–0.81)	0.65 (0.60–0.69)	0.003	0.82 (0.75–0.90)	0.76 (0.72–0.81)	0.18	
Cardiovascular mortality	11 015/2121.4 (5.2)	2854/176.1 (16.2)	3660/590.7 (6.2)	...	1546/173.5 (8.9)	2955/1181.1 (2.5)	...	
No ACE/ARB	3732/477.9 (7.8)	809/25.3 (32.0)	970/57.1 (17.0)	...	696/53.2 (13.1)	1257/342.3 (3.7)	...	
ACE/ARB	7283/1643.5 (4.4)	2045/150.8 (13.6)	2690/533.6 (5.0)	...	850/120.3 (7.1)	1698/838.8 (2.0)	...	
Unadjusted HR	0.58 (0.56–0.60)	0.47 (0.43–0.50)	0.33 (0.31–0.35)	<0.001	0.56 (0.50–0.61)	0.56 (0.52–0.60)	0.98	
Adjusted HR	0.81 (0.78–0.85)	0.78 (0.71–0.86)	0.67 (0.62–0.73)	0.02	0.91 (0.82–1.02)	0.91 (0.84–0.99)	0.94	
MI	20 802/1889.7 (11.0)	3092/150.2 (20.6)	6551/518.8 (12.6)	...	2427/149.8 (16.2)	8732/1070.9 (8.2)	...	
No ACE/ARB	5609/432.4 (13.0)	713/21.1 (33.7)	1179/50.1 (23.5)	...	898/46.6 (19.3)	2819/314.6 (9.0)	...	
ACE/ARB	15 193/1457.2 (10.4)	2379/129.0 (18.4)	5372/468.7 (11.5)	...	1529/103.3 (14.8)	5913/756.2 (7.8)	...	
Unadjusted HR	0.85 (0.82–0.87)	0.68 (0.62–0.73)	0.61 (0.57–0.65)	0.05	0.81 (0.75–0.88)	0.89 (0.85–0.93)	0.06	
Adjusted HR	0.95 (0.92–0.98)	0.86 (0.78–0.94)	0.84 (0.79–0.90)	0.73	0.97 (0.88–1.06)	1.02 (0.97–1.07)	0.35	
Stroke	4620/2080.6 (2.2)	910/169.1 (5.4)	1244/579.3 (2.1)	...	848/166.7 (5.1)	1618/1165.4 (1.4)	...	
No ACE/ARB	1198/468.9 (2.6)	170/24.2 (7.0)	208/55.7 (3.7)	...	297/51.1 (5.8)	523/337.9 (1.5)	...	
ACE/ARB	3422/1611.7 (2.1)	740/145.0 (5.1)	1036/523.7 (2.0)	...	551/115.6 (4.8)	1095/827.5 (1.3)	...	
Unadjusted HR	0.84 (0.79–0.90)	0.79 (0.67–0.94)	0.57 (0.49–0.67)	0.01	0.84 (0.73–0.97)	0.85 (0.77–0.95)	0.83	
Adjusted HR	0.96 (0.89–1.03)	1.02 (0.85–1.22)	0.80 (0.68–0.95)	0.06	1.03 (0.88–1.20)	0.98 (0.87–1.10)	0.58	
New-onset AF	4928/1713.3 (2.9)		2105/566.3 (3.7)			2823/1147.0 (2.5)		
No ACE/ARB	1110/388.7 (2.9)		303/54.8 (5.5)			807/333.9 (2.4)		
ACE/ARB	3818/1324.6 (2.9)		1802/511.5 (3.5)			2016/813.1 (2.5)		
Unadjusted HR	1.03 (0.96–1.10)		0.71 (0.63–0.80)			1.03 (0.95–1.12)		
Adjusted HR	1.07 (1.00–1.15)		0.96 (0.84–1.10)			1.12 (1.02–1.22)		

Number and incidence rate of events and crude and adjusted hazard ratios for outcomes stratified by ACEI and/or ARB treatment in patients with and without congestive heart failure and atrial fibrillation. Crude event rates were calculated according to the number of events per 100 person-years. Unadjusted and adjusted HR is given with a 95% confidence interval. ACEI indicates angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CHF, congestive heart failure; HR, hazard ratio; MI, myocardial infarction.



**Figure 3.** Kaplan–Meier plot depicting new-onset AF for patients with and without CHF. Kaplan–Meier plot depicting the cumulative incidence curve for new-onset AF stratified by use of ACEI and/or ARB. ACEI indicates angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CHF, congestive heart failure.

irrespective of AF. No favorable association was observed with ACEI and/or ARB in regard to new-onset AF.

Several trials, such as the Survival and Ventricular Enlargement (SAVE) trial,<sup>1</sup> the Acute Infarction Ramipril Efficacy (AIRE) trial,<sup>2</sup> and the Trandolapril Cardiac Evaluation (TRACE) trial,<sup>3,4</sup> have shown that ACEI lower rates of mortality and cardiovascular mortality in patients with CHF post-AMI. This observation has also been supported by a meta-analysis based on the 3 aforementioned trials.<sup>21</sup> Similar beneficial results have been shown with ARB in the Valsartan in Acute Myocardial Infarction (VALIENT) trial.<sup>5</sup> Moreover, there are data supporting that RAS inhibition might be beneficial for all post-AMI patients, not only those suffering from CHF.<sup>22,23</sup> The lower risk of mortality observed in our study, and in previous trials, might be a result of reduction in myocardial infarct expansion, ventricular remodeling, and ventricular dilatation observed with RAS inhibition.<sup>24,25</sup>

The association between RAS inhibition and recurrent AMI is still controversial. The SAVE trial showed a lower risk,<sup>1</sup> and the TRACE trial showed no association between RAS inhibition and recurrent AMI.<sup>3</sup> In our study, the observed risk of recurrent AMI was lower among patients with CHF treated with ACEI and/or ARB. Studies have suggested that ACEIs do not appear to be associated with a reduced process of atherosclerosis.<sup>26</sup> However, the reduced risk of AMI might be

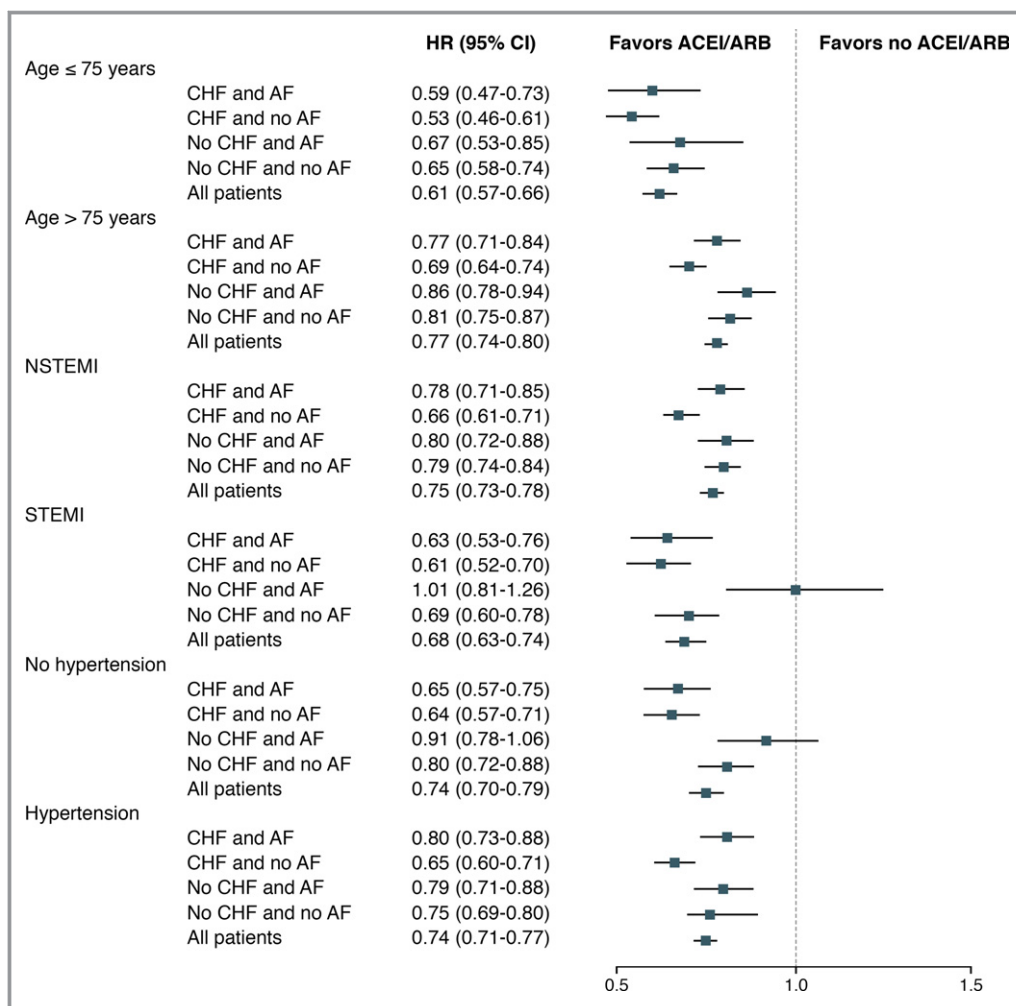
attributed to other possible mechanisms, such as improved endothelial function, a reduced risk of left ventricular hypertrophy, and renal protection.<sup>27,28</sup>

In this study, we found no association between ACEI/ARB and risk of stroke among patients without CHF and in those with both CHF and AF. This is similar to, and in contrast to, other trials on patients with coronary artery disease.<sup>29–31</sup> In a meta-analysis<sup>32</sup> based on the 3 cited trials on patients with coronary artery disease, a significant reduction in stroke rate was observed, although this was mainly driven by one of the trials, the Heart Outcomes Prevention Evaluation (HOPE) trial.<sup>29</sup> Moreover, the divergence between our results and the meta-analysis could be because of different inclusions criteria and because of differences between patient characteristics in trials and in routine care.

In this study, RAS inhibition in patients with no history of AF, or in-hospital finding/diagnosis of AF, was not associated with a lower risk of new-onset AF during a 3-year follow-up. A similar finding was observed in patients with and without CHF at baseline. In comparison, post-hoc analyzes of randomized, controlled trials in patients with CHF but without known AF have suggested that RAS inhibition might reduce the incidence of new-onset AF.<sup>33–35</sup> In contrast, 2 prospective, randomized trials on patients with AF did not show beneficial effects of RAS inhibition with regard to future AF burden similar to our findings.<sup>36,37</sup> Explanatory mechanisms for the possible antiarrhythmic property of RAS inhibition, such as restrained electrical and structural remodeling, have been proposed in preclinical studies.<sup>7–9</sup> To our knowledge, 2 trials have studied RAS inhibition and risk of AF post-AMI. In the TRACE trial,<sup>38</sup> a lower risk of new-onset AF was observed among patients discharged with trandolapril. In contrast, the Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico-3 (GISSI-3) trial<sup>39</sup> reported no significant reduction in the risk of new-onset AF with RAS inhibition. In a meta-analysis including these 2 trials, no association was observed between RAS inhibition and risk of new-onset AF in a subgroup of post-AMI patients.<sup>40</sup> Moreover, a similar lack of association between ACE inhibition and new-onset AF was noted in the HOPE trial.<sup>41</sup>

Current practice guidelines on NSTEMI,<sup>11,12</sup> STEMI,<sup>13,14</sup> and AF<sup>15,16</sup> recommend ACEI or ARB to patients with CHF and left ventricular dysfunction. Also, the guidelines suggest that RAS inhibition might be useful for other patients with cardiac disease but without signs or symptoms of CHF. However, treatment with RAS inhibition is not stated as beneficial for the primary prevention of AF.<sup>11–16</sup> Our study confirms that ACEI and ARBs are beneficial post-AMI and associated with a lower risk of all-cause mortality, cardiovascular mortality, and, in patients with CHF, lower risk of recurrent AMI. Moreover, our study suggests that RAS inhibition is not associated with a lower risk of new-onset AF post-AMI.





**Figure 4.** Risk of all-cause mortality in prespecified subgroups. Risk of all-cause mortality in subgroup of patients stratified by use of ACEI and/or ARB. ACEI indicates angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CHF, congestive heart failure; HR, hazard ratio; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

The present study has limitations that have to be considered when interpreting the results. First, this is a retrospective, observational study and patients were not randomized to RAS inhibition. It is inevitable that residual confounding exists. However, we have a large sample size and access to detailed clinical information and were able to include many important confounders in our statistical analyses. Also, our results were confirmed in several sensitivity analyses, including complete case analysis and propensity-score-matching analysis. Second, although we were able to follow drug dispense postdischarge and could in an on-treatment analysis censor for drug initiation or discontinuation, we had no information on reasons for drug initiation or withdrawal after discharge. Also, we lack information on frequency of adverse effects, such as hyperkalemia. Finally, it is plausible that 3 years of follow-up might be too short to

capture long-term effects of RAS inhibition in preventing new-onset AF.

### Conclusions

Treatment with ACEI and/or ARB was associated with a lower risk of all-cause mortality and cardiovascular mortality in all patients post-AMI, and a lower risk of recurrent AMI was observed in patients with CHF. In patients with no AF at baseline, RAS inhibition was not associated with a lower risk of new-onset AF.

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## **SUPPLEMENTAL MATERIAL**

**Table S1.** Definition of baseline characteristics, in-hospital course, procedures and discharge medication - History of comorbidities was collected from the protocol-standardized SWEDEHEART questionnaires and was enriched with data from the National Patient Registry using the International Classification of Diseases, 9<sup>th</sup> and 10<sup>th</sup> revision. Information about angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers at discharge was derived from the SWEDEHEART questionnaire and the National Dispensed Drug Registry using Anatomical Therapeutic Chemical classification codes

<b>Variable</b>	<b>ICD-code / ATC-code</b>	<b>Comments</b>
Age	-	Derived from SWEDEHEART
Sex	-	Derived from SWEDEHEART
Smoking	-	Derived from SWEDEHEART
BMI	-	Derived from SWEDEHEART
Admission year	-	Derived from SWEDEHEART
Creatinine	-	Derived from SWEDEHEART
Diabetes mellitus	E10, E11, E12, E13, E14, 250	Derived from the National Patient Registry and SWEDEHEART based on diabetes/diabetes medication at arrival
Hypertension	I10-I15, 401-405	Derived from the National Patient Registry and SWEDEHEART
Myocardial infarction	I21-I23, 410, 412	Derived from the National Patient Registry and SWEDEHEART
Heart failure	I50, 428, K761, I971, I13.0, I13.2, I110, P290, 427.00, 427.10, 428.99	Derived from the National Patient Registry and SWEDEHEART
Peripheral vascular disease	I70-I73, 440-443	Derived from the National Patient Registry
Stroke	I60-I61, I63-I64, 430-431, 433-434	Derived from the National Patient Registry
Any bleeding	I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920- K922, I60-I62, N02, R310, R311, R318, R040-R042, R048, R049, R58, T810, I983, D629, DR029	Derived from the National Patient Registry
Chronic obstructive pulmonary disease	J40-J47, 49-496	Derived from the National Patient Registry
Dementia	G30, G31, 290, 294B	Derived from the National Patient Registry
Cancer diagnosis within 3 years	C14-C20	Derived from the National Patient Registry
Previous PCI	FNG00, FNG01, FNG02, FNG03, FNG04, FNG05, FNG06, 3080	Derived from the National Patient Registry and SWEDEHEART
Previous CABG	FNA-FNF, FNH-FNW, 3065, 3066, 3068, 3092, 3105, 3127, 3158	Derived from the National Patient Registry and SWEDEHEART
Type of infarction, NSTEMI/STEMI	-	Derived from SWEDEHEART
PCI	-	Derived from SWEDEHEART
CABG	-	Derived from SWEDEHEART
Killip class	-	Derived from SWEDEHEART
Left ventricular ejection fraction	-	Derived from SWEDEHEART
New-onset atrial fibrillation	-	Derived from SWEDEHEART
Any atrial fibrillation	I480-I484, I489, 427D	Derived from the National Patient Registry and SWEDEHEART
Angiotensin-converting enzyme inhibitors	C09A, C09B	Derived from the National Dispensed Drug Registry and SWEDEHEART
Angiotensin II receptor blockers	C09C, C09D	Derived from the National Dispensed Drug Registry and SWEDEHEART
Aspirin	-	Derived from SWEDEHEART

P2Y <sub>12</sub> inhibitors	-	Derived from SWEDEHEART
Oral Anticoagulants	-	Derived from SWEDEHEART
β-blockers	-	Derived from SWEDEHEART
Calcium channel blockers	-	Derived from SWEDEHEART
Digoxin	-	Derived from SWEDEHEART
Diuretics	-	Derived from SWEDEHEART
Nitrates	-	Derived from SWEDEHEART
Statins	-	Derived from SWEDEHEART

**Table S2.** Definition of outcomes - The National Patient Registry, The Swedish Cause of Death Registry and the International Classification of Diseases, 10<sup>th</sup> revision, was used to define the outcomes

<b>Variable</b>	<b>ICD-code</b>	<b>Comments</b>
All-cause mortality	-	Derived from the Swedish Cause of Death Registry
Cardiovascular mortality	I00-I99	Derived from the Swedish Cause of Death Registry
Myocardial infarction	I21-I22	Derived from the National Patient Registry and the Swedish Cause of Death Registry
Stroke	I60, I61, I63, 164	Derived from the National Patient Registry and the Swedish Cause of Death Registry
New-onset atrial fibrillation	I480-I484, I489	Derived from the National Patient Registry and the Swedish Cause of Death Registry

**Table S3.** Intention-to-treat analysis - Number and incidence rate of events and crude and adjusted hazard ratios for outcomes stratified by angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers treatment in patients with and without congestive heart failure and atrial fibrillation in an intention-to-treat analysis

Outcomes, No. of events / Person time per 100 years (Event rate)	All patients (n = 112,648)	Stratification					
		CHF and AF (n = 11,489)	CHF and no AF (n = 31,676)	P-value for interaction	No CHF and AF (n = 10,066)	No CHF and no AF (n = 59,417)	P-value for interaction
All-cause mortality	21,900 / 2,684.5 (8.2)	5,012 / 224.3 (22.3)	7,079 / 740.9 (9.6)	-	3,021 / 222.9 (13.6)	6,788 / 1,496.4 (4.5)	-
No ACEI/ARB	7,746 / 671.7 (11.5)	1,450 / 38.4 (37.8)	1,891 / 96.0 (19.7)	-	1,373 / 72.1 (19.0)	3,032 / 465.2 (6.5)	-
ACEI/ARB	14,154 / 2,012.8 (7.0)	3,562 / 185.9 (19.2)	5,188 / 644.9 (8.0)	-	1,648 / 150.8 (10.9)	3,756 / 1,031.1 (3.6)	-
Unadjusted HR	0.61 (0.60-0.63)	0.53 (0.50-0.56)	0.42 (0.40-0.44)	< 0.001	0.58 (0.54-0.63)	0.56 (0.53-0.59)	0.33
Adjusted HR	0.79 (0.76-0.81)	0.79 (0.74-0.84)	0.73 (0.69-0.77)	0.08	0.85 (0.79-0.92)	0.80 (0.76-0.84)	0.21
Cardiovascular mortality	13,819 / 2,684.5 (5.1)	3,576 / 224.3 (15.9)	4,581 / 740.9 (6.2)	-	1,921 / 222.9 (8.6)	3,741 / 1,496.4 (2.5)	-
No ACEI/ARB	4,749 / 671.7 (7.1)	1,039 / 38.4 (27.1)	1,237 / 96.0 (12.9)	-	855 / 72.1 (11.9)	1,618 / 465.2 (3.5)	-
ACEI/ARB	9,070 / 2,012.8 (4.5)	2,537 / 185.9 (13.6)	3,344 / 644.9 (5.2)	-	1,066 / 150.8 (7.1)	2,123 / 1,031.1 (2.1)	-
Unadjusted HR	0.64 (0.62-0.66)	0.53 (0.49-0.57)	0.41 (0.39-0.44)	< 0.001	0.61 (0.56-0.67)	0.59 (0.56-0.63)	0.63
Adjusted HR	0.83 (0.80-0.86)	0.80 (0.74-0.87)	0.74 (0.69-0.79)	0.13	0.91 (0.83-1.00)	0.88 (0.82-0.94)	0.59
Myocardial infarction	23,347 / 2,358.3 (9.9)	3,466 / 187.4 (18.5)	7,381 / 642.4 (11.5)	-	2,712 / 188.9 (14.4)	9,788 / 1,339.7 (7.3)	-
No ACEI/ARB	6,556 / 591.2 (11.1)	850 / 30.8 (27.6)	1,437 / 81.5 (17.6)	-	1,022 / 61.2 (16.7)	3,247 / 417.7 (7.8)	-
ACEI/ARB	16,791 / 1,767.1 (9.5)	2,616 / 156.6 (16.7)	5,944 / 560.9 (10.6)	-	1,690 / 127.6 (13.2)	6,541 / 922.0 (7.1)	-
Unadjusted HR	0.87 (0.85-0.90)	0.69 (0.64-0.75)	0.65 (0.61-0.69)	0.21	0.83 (0.77-0.90)	0.91 (0.87-0.95)	0.04
Adjusted HR	0.95 (0.92-0.98)	0.85 (0.78-0.93)	0.86 (0.81-0.92)	0.79	0.95 (0.88-1.04)	1.01 (0.97-1.06)	0.21
Stroke	5,782 / 2,623.2 (2.2)	1,126 / 214.2 (5.3)	1,579 / 723.8 (2.2)	-	1,033 / 212.7 (4.9)	2,044 / 1,472.5 (1.4)	-
No ACEI/ARB	1,563 / 656.8 (2.4)	233 / 36.6 (6.4)	284 / 93.3 (3.0)	-	366 / 68.9 (5.3)	680 / 457.9 (1.5)	-
ACEI/ARB	4,219 / 1,966.4 (2.1)	831 / 178.0 (4.7)	1,295 / 630.6 (2.1)	-	667 / 143.8 (4.6)	1,364 / 1,014.6 (1.3)	-
Unadjusted HR	0.91 (0.85-0.96)	0.83 (0.72-0.96)	0.69 (0.61-0.78)	0.07	0.89 (0.78-1.01)	0.90 (0.82-0.99)	0.84
Adjusted HR	1.00 (0.94-1.06)	1.01 (0.86-1.17)	0.91 (0.79-1.04)	0.33	1.05 (0.92-1.20)	1.01 (0.91-1.11)	0.64
New-onset AF	5,978 / 2,151.3 (2.8)		2,553 / 706.3 (3.6)			3,425 / 1,445.0 (2.4)	
No ACEI/ARB	1,487 / 540.6 (2.8)		438 / 90.8 (4.8)			1,049 / 449.8 (2.3)	
ACEI/ARB	4,491 / 1,610.7 (2.8)		2,115 / 615.5 (3.4)			2,376 / 995.2 (2.4)	
Unadjusted HR	1.02 (0.96-1.08)		0.74 (0.66-0.82)			1.02 (0.95-1.10)	
Adjusted HR	1.05 (0.98-1.12)		0.94 (0.84-1.05)			1.10 (1.02-1.19)	

Crude event rates were calculated according to the number of events per 100 person-years. Unadjusted and adjusted HR are given with a 95% confidence interval.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CHF, congestive heart failure; HR, hazard ratio.



**Table S4.** Complete case and propensity score analyses - Complete case and propensity score analyses with hazard ratios for outcomes stratified by angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers treatment in patients with and without congestive heart failure and atrial fibrillation

Outcomes, No. of events / Person time per 100 years (Event rate)	All patients (n = 112,648)	Stratification					
		CHF and AF (n = 11,489)	CHF and no AF (n = 31,676)	P-value for interaction	No CHF and AF (n = 10,066)	No CHF and no AF (n = 59,417)	P-value for interaction
All-cause mortality							
Complete case, adjusted HR	0.78 (0.75-0.82)	0.79 (0.72-0.87)	0.72 (0.67-0.78)	0.12	0.85 (0.74-0.98)	0.82 (0.75-0.90)	0.71
Propensity score, adjusted HR	0.72 (0.69-0.75)	0.74 (0.66-0.83)	0.63 (0.57-0.68)	0.02	0.80 (0.72-0.89)	0.78 (0.72-0.84)	0.64
Cardiovascular mortality							
Complete case, adjusted HR	0.81 (0.76-0.86)	0.79 (0.71-0.89)	0.72 (0.65-0.78)	0.14	0.91 (0.75-1.10)	0.91 (0.80-1.04)	0.98
Propensity score, adjusted HR	0.77 (0.73-0.81)	0.76 (0.67-0.87)	0.64 (0.58-0.71)	0.04	0.88 (0.77-1.01)	0.90 (0.81-1.00)	0.80
Myocardial infarction							
Complete case, adjusted HR	0.95 (0.91-0.99)	0.89 (0.79-0.99)	0.85 (0.79-0.91)	0.50	0.94 (0.82-1.08)	1.04 (0.97-1.11)	0.22
Propensity score, adjusted HR	0.94 (0.90-0.98)	0.83 (0.73-0.95)	0.83 (0.75-0.92)	0.92	0.96 (0.86-1.08)	1.02 (0.96-1.09)	0.36
Stroke							
Complete case, adjusted HR	0.98 (0.90-1.07)	0.92 (0.77-1.11)	0.90 (0.77-1.05)	0.83	1.03 (0.83-1.28)	1.03 (0.89-1.19)	1.00
Propensity score, adjusted HR	0.95 (0.87-1.04)	0.96 (0.75-1.23)	0.78 (0.62-0.98)	0.23	0.96 (0.79-1.17)	1.04 (0.90-1.21)	0.53
New-onset AF							
Complete case, adjusted HR	1.04 (0.96-1.12)		0.98 (0.87-1.11)			1.08 (0.98-1.21)	
Propensity score, adjusted HR	1.12 (1.02-1.23)		0.93 (0.78-1.12)			1.15 (1.03-1.28)	

Crude event rates were calculated according to the number of events per 100 person-years. Unadjusted and adjusted HR is given with a 95% confidence interval.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CHF, congestive heart failure; HR, hazard ratio.

**Table S5.** Outcomes stratified by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers treatment - Number and incidence rate of events and crude and adjusted hazard ratios for outcomes stratified by angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers treatment in patients with and without congestive heart failure and atrial fibrillation

Outcomes, No. of events / Person time per 100 years (Event rate)	All patients (n = 112,648)	Stratification					
		CHF and AF (n = 11,489)	CHF and no AF (n = 31,676)	P-value for interaction	No CHF and AF (n = 10,066)	No CHF and no AF (n = 59,417)	P-value for interaction
All-cause mortality	17,121 / 2,121.4 (8.1)	3,964 / 176.1 (22.5)	5,474 / 590.7 (9.3)	-	2,383 / 173.5 (13.7)	5,300 / 1,181.1 (4.5)	-
No ACEI/ARB	6,115 / 477.9 (12.8)	1,134 / 25.3 (44.9)	1,450 / 57.1 (25.4)	-	1,119 / 53.2 (21.0)	2,412 / 342.3 (7.0)	-
ACEI	8,197 / 1,197.3 (6.8)	2,102 / 108.5 (19.4)	3,073 / 402.4 (7.6)	-	913 / 80.4 (11.4)	2,109 / 606.0 (3.5)	-
ARB	2,458 / 295.4 (8.3)	653 / 32.5 (20.1)	814 / 79.2 (10.3)	-	310 / 31.0 (10.0)	681 / 152.8 (4.5)	-
ACEI, adjusted HR	0.75 (0.73-0.78)	0.77 (0.71-0.83)	0.65 (0.61-0.70)	0.003	0.85 (0.77-0.94)	0.78 (0.73-0.84)	0.16
ARB, adjusted HR	0.72 (0.68-0.76)	0.69 (0.62-0.77)	0.63 (0.57-0.70)	0.23	0.74 (0.65-0.85)	0.75 (0.68-0.82)	0.93
Cardiovascular mortality	11,015 / 2,121.4 (5.2)	2,854 / 176.1 (16.2)	3,660 / 590.7 (6.2)	-	1,546 / 173.5 (8.9)	2,955 / 1,181.1 (2.5)	-
No ACEI/ARB	3,732 / 477.9 (7.8)	809 / 25.3 (32.0)	970 / 57.1 (17.0)	-	696 / 53.2 (13.1)	1,257 / 342.3 (3.7)	-
ACEI	5,476 / 1,197.3 (4.6)	1,522 / 108.5 (14.0)	2,063 / 402.4 (5.1)	-	627 / 80.4 (7.8)	1,264 / 606.0 (2.1)	-
ARB	1,608 / 295.4 (5.4)	470 / 32.5 (14.5)	548 / 79.2 (6.9)	-	199 / 31.0 (6.4)	391 / 152.8 (2.6)	-
ACEI, adjusted HR	0.84 (0.80-0.88)	0.79 (0.72-0.87)	0.69 (0.63-0.75)	0.03	0.96 (0.85-1.08)	0.95 (0.88-1.04)	0.99
ARB, adjusted HR	0.78 (0.73-0.83)	0.72 (0.63-0.82)	0.68 (0.60-0.77)	0.52	0.79 (0.67-0.94)	0.85 (0.75-0.96)	0.54
Myocardial infarction	20,802 / 1,889.7 (11.0)	3,092 / 150.2 (20.6)	6,551 / 518.8 (12.6)	-	2,427 / 149.8 (16.2)	8,732 / 1,070.9 (8.2)	-
No ACEI/ARB	5,609 / 432.4 (13.0)	713 / 21.1 (33.7)	1,179 / 50.1 (23.5)	-	898 / 46.6 (19.3)	2,819 / 314.6 (9.0)	-
ACEI	11,534 / 1,068.7 (10.8)	1,785 / 93.7 (19.1)	4,217 / 356.2 (11.8)	-	1,087 / 69.4 (15.7)	4,445 / 549.5 (8.1)	-
ARB	3,481 / 257.7 (13.5)	590 / 27.5 (21.5)	1,108 / 68.0 (16.3)	-	417 / 26.3 (15.8)	1,366 / 135.8 (10.1)	-
ACEI, adjusted HR	0.95 (0.92-0.99)	0.86 (0.78-0.95)	0.84 (0.78-0.90)	0.61	0.98 (0.89-1.08)	1.02 (0.97-1.07)	0.47
ARB, adjusted HR	0.96 (0.91-1.01)	0.84 (0.74-0.95)	0.91 (0.83-1.00)	0.34	0.94 (0.83-1.07)	1.01 (0.93-1.09)	0.37
Stroke	4,620 / 2,080.6 (2.2)	910 / 169.1 (5.4)	1,244 / 579.3 (2.1)	-	848 / 166.7 (5.1)	1,618 / 1,165.4 (1.4)	-
No ACEI/ARB	1,198 / 468.9 (2.6)	170 / 24.2 (7.0)	208 / 55.7 (3.7)	-	297 / 51.1 (5.8)	523 / 337.9 (1.5)	-
ACEI	2,535 / 1,175.2 (2.2)	556 / 104.4 (5.3)	796 / 395.2 (2.0)	-	379 / 77.4 (4.9)	803 / 598.3 (1.3)	-
ARB	751 / 289.0 (2.6)	161 / 31.2 (5.2)	198 / 77.5 (2.6)	-	149 / 29.9 (5.0)	243 / 150.4 (1.6)	-
ACEI, adjusted HR	0.99 (0.92-1.07)	1.03 (0.85-1.25)	0.84 (0.71-0.99)	0.11	1.03 (0.87-1.21)	1.03 (0.91-1.16)	0.96
ARB, adjusted HR	1.00 (0.90-1.11)	0.97 (0.75-1.24)	0.82 (0.65-1.03)	0.33	1.08 (0.86-1.35)	0.97 (0.81-1.16)	0.45
New-onset AF	4,928 / 1,713.3 (2.9)		2,105 / 566.3 (3.7)			2,823 / 1147.0 (2.5)	
No ACEI/ARB	1,110 / 388.7 (2.9)		303 / 54.8 (5.5)			807 / 333.9 (2.4)	
ACEI	2,763 / 977.5 (2.8)		1,351 / 387.7 (3.5)			1,412 / 589.8 (2.4)	

ARB	887 / 221.6 (4.0)		369 / 75.2 (4.9)		518 / 146.4 (3.5)	
ACEI, adjusted HR	1.05 (0.97-1.13)		0.97 (0.84-1.11)		1.08 (0.99-1.19)	
ARB, adjusted HR	1.20 (1.08-1.33)		1.07 (0.90-1.28)		1.24 (1.09-1.41)	

Crude event rates were calculated according to the number of events per 100 person-years. Unadjusted and adjusted HR are given with a 95% confidence interval.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CHF, congestive heart failure; HR, hazard ratio.