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Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Myocardial Infarction Patients With Renal Dysfunction

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ABSTRACT

BACKGROUND There is no consensus whether angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) should be used for secondary prevention in all or in only high-risk patients after an acute myocardial infarction (AMI).

OBJECTIVES This study sought to investigate whether ACEI/ARB treatment after AMI is associated with better outcomes across different risk profiles, including the entire spectrum of estimated glomerular filtration rates.

METHODS This study evaluated discharge and continuous follow-up data on ACEI/ARB use among AMI survivors (2006 to 2009) included in a large Swedish registry. The association between ACEI/ARB treatment and outcomes (mortality, myocardial infarction, stroke, and acute kidney injury [AKI]) was studied using Cox proportional hazards models (intention-to-treat and as treated).

RESULTS In total, 45,697 patients (71%) were treated with ACEI/ARB. The 3-year mortality was 19.8% (17.4% of ACEI/ARB users and 25.4% of nonusers). In adjusted analysis, significantly better survival was observed for patients treated with ACEI/ARB (3-year hazard ratio: 0.80; 95% confidence interval: 0.77 to 0.83). The survival benefit was consistent through all kidney function strata, including dialysis patients. Overall, those treated with ACEI/ARB also had lower 3-year risk for myocardial infarction (hazard ratio: 0.91; 95% confidence interval: 0.87 to 0.95), whereas treatment had no significant effect on stroke risk. The crude risk for AKI was in general low (2.5% and 2.0% for treated and nontreated, respectively) and similar across estimated glomerular filtration rate categories but was significantly higher with ACEI/ARB treatment. However, the composite outcome of AKI and mortality favored ACEI/ARB treatment.

CONCLUSIONS Treatment with ACEI/ARB after AMI was associated with improved long-term survival, regardless of underlying renal function, and was accompanied by low rates of adverse renal events. (J Am Coll Cardiol 2016;67:1687–97)

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

AKI = acute kidney injury

ARB = angiotensin receptor blocker

CI = confidence interval

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HR = hazard ratio

LVSD = left ventricular systolic dysfunction

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) should be considered for secondary prevention after an acute myocardial infarction (AMI) (1,2). ACEI use was first shown to reduce short- and long-term mortality in patients with myocardial infarction (MI) and heart failure (HF) or left ventricular systolic dysfunction (LVSD) (3–6). Subsequently, 2 trials showed noninferiority for ARBs compared with ACEIs in MI patients with evidence of HF for improving survival with better tolerability (7,8). However, there is still no clear evidence as to whether ACEI/ARB should be used in all MI patients without HF or LVSD (1,9).

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Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease (10); the cardiovascular risk increases even with slightly decreased estimated glomerular filtration rate (eGFR) and becomes 8-fold higher in patients with severe renal dysfunction (11). Patients with CKD also have worse outcomes after an acute cardiovascular event compared with patients with normal renal function (12,13). Even though patients with low eGFR are considered a high-risk group, the evidence for treating these patients with ACEI/ARB after MI is almost nonexistent as they were excluded from most trials (4–6,14,15). Importantly, ACEI or ARB use can also potentially result in acute kidney injury (AKI) and hyperkalemia, adverse events believed to be more common in CKD patients, perhaps discouraging clinicians from treating these patients with these agents. However, a recent observational study among U.S. veterans with CKD showed that use of an ACEI or ARB for any indication was associated with a 19% lower all-cause mortality (16). We aimed to investigate current use of ACEI and ARB therapy after MI to assess long-term outcomes associated with their use in routine clinical practice across different risk profiles, including the entire spectrum of estimated glomerular function.

METHODS

We analyzed consecutive MI patients admitted to Swedish coronary care units and entered in the nationwide SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry (17). The registry includes patients with symptoms suggestive of acute coronary syndromes admitted to a coronary care unit or other specialized facility, covering all Swedish hospitals (n = 72) where treatment for acute cardiac diseases is provided. Patients were included if they were admitted for an AMI between 2006 and 2009, were alive at discharge, and had a registered measurement of serum creatinine on admission (Online Figure 1). Only the first MI during this time period was considered. Patients were followed until the end of 2010. On admission, patients received written information about SWEDEHEART and other quality-of-care registries; patients are permitted to deny participation in the registry, although few exercise this right. According to Swedish law, written consent is not required because quality control is an inherent element of hospital health care. The regional ethics committee of Stockholm approved the study protocol.

Comorbidities were obtained from the SWEDEHEART registry form and supplemented with data from the National Patient Register that included diagnoses on the basis of International Classification of Diseases codes for all patients hospitalized in Sweden from 1987 and onward. History of diabetes mellitus was further confirmed with active dispensation of oral antidiabetic agents and insulin as registered in the Swedish Registry of Dispensed Drugs (18). Information on patient presentation at admission, hospital course variables, and medications at admission and discharge were also obtained from the SWEDEHEART registry.

RENAL FUNCTION ASSESSMENT. Patient eGFR was calculated from the creatinine level on admission using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) (19). The majority of creatinine assessments were performed by either enzymatic or corrected Jaffe method (alkaline picrate reaction), both of which are traceable to isotope dilution mass spectrometry standards. Creatinine measurements performed with nonstandardized methods were reduced by 5% prior to being entered into the CKD-EPI equation (20). Renal function was classified into categories of eGFR using the current International Society of Nephrology Kidney Disease Improving Global Outcomes definition (21). Because data on albuminuria were missing, any eGFR ≥60 ml/min/1.73 m^2 could not define CKD stage 1 or 2. Thus, we referred to the categories as eGFR strata. The Swedish Renal Registry (22) was used to identify individuals undergoing dialysis treatment and having a functioning kidney transplant.

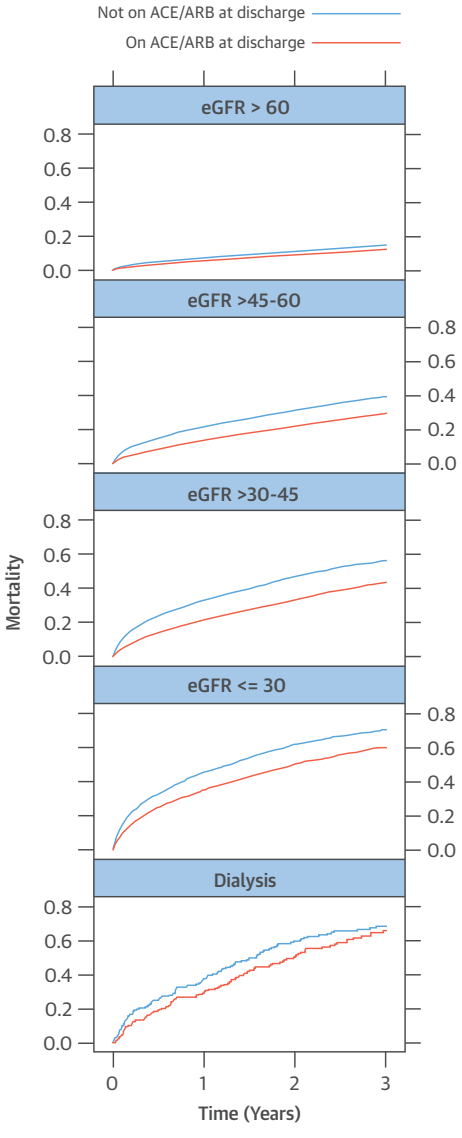
ASCERTAINMENT OF EXPOSURES. ACEI or ARB use was recorded in the SWEDEHEART protocol and in the Registry of Dispensed Drugs, the latter of which contains all pharmacy-drug dispensations in the country linked to each citizen's unique personal

identifier (18). ACEI and ARB on admission was defined as a registered use in SWEDEHEART or pharmacy dispensation of an ACEI or ARB <6 months prior to the admission date. The main exposure, ACEI or ARB at hospital discharge, was defined as a registered use in SWEDEHEART or pharmacy dispensation within 7 days from discharge (Online Appendix). After discharge, we assumed that the patients were treated as intended for 3 months on the basis of in-hospital-provided medication. Thereafter, continuous medication use was estimated from drug refill patterns as captured by the Registry of Dispensed Drugs. Briefly, each drug dispensation was assumed to keep the patient exposed for a subsequent 6 months. A gap of more than 6 months from the previous drug dispensation was considered drug discontinuation, which was defined separately for ACEI, ARB, and ACEI or ARB. Conversely, unexposed patients at discharge were regarded as unexposed until a dispensation of an ACEI or ARB occurred, after which they were censored from follow-up.

OUTCOMES. Study outcomes were defined a priori to the data analyses. The primary outcome was all-cause mortality after 1 and 3 years. Secondary outcomes were MI (fatal and nonfatal), any fatal or nonfatal stroke (transient ischemic, ischemic, or hemorrhagic), renal damage (AKI or start in renal replacement therapy), and the composite of death and renal damage. The AKI outcome was defined as a hospitalization episode with a code for AKI or start of renal replacement therapy. (For complete outcome definitions and International Classification of Diseases codes, please see the Online Appendix.) Occurrence of MI, stroke, and AKI was obtained from the National Inpatient Registry, whereas the date for start of renal replacement therapy was obtained from linkage to the Swedish Renal Registry. For MI, we applied a 30-day grace period after discharge to avoid misclassification of reinfarction according to the Patient Registry. Censoring occurred after 3 years of follow-up or at the end of the study date. Dialysis patients were also censored if they received a renal transplant.

STATISTICAL ANALYSES. All analyses were performed using R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). We analyzed ACEI, ARB, and the combination of either ACEI or ARB use as time-fixed variables throughout the 2 defined follow-up periods: 1 and 3 years. The association between drug exposure and outcomes were studied in Cox proportional hazards models adjusting for the potential confounders at baseline. Two different models were used; in our main analysis, we performed an analysis according to intended use at discharge, censoring at end of follow-up (after 3 years), new renal transplantation (only dialysis patients), or December 31, 2010, whichever came first. Second, we performed an analysis for time "on treatment" where censoring occurred also at drug discontinuation as assessed by dispensation dates. If a patient was switched from ACEI to ARB or vice versa, it was regarded as a drug discontinuation in the ACEI analysis but not in the combined ACEI/ARB

FIGURE 1 3-Year Mortality



The Kaplan-Meier survival curves demonstrate improved survival in acute myocardial infarction patients using angiotensin-converting enzyme (ACE) inhibition and angiotensin receptor blockers (ARBs) stratified according to their renal function. eGFR = estimated glomerular filtration rate.

TABLE 1 Baseline Characteristics

	No ACEI/ARB at Discharge (n = 18,745; 29.1%)	ACEI/ARB at Discharge (n = 45,697; 70.9%)
Demographics		
Age, yrs	74 (62–83)	71 (62–80)
Men	11,351 (60.6)	29,950 (65.5)
Smoking (n = 58,987)	3,917 (24.8) [1,903]	9,623 (23.0) [3,552]
Discharge year*		
2006	5,608 (29.9)	10,904 (23.9)
2007	5,066 (27.0)	11,883 (26.0)
2008	4,323 (23.1)	11,643 (25.5)
2009	3,748 (20.0)	11,267 (24.7)
Creatinine, μmol/l	84 (70–106)	84 (71–102)
eGFR, ml/min/1.73 m^2	73 (51–89)	74 (56–89)
eGFR strata, ml/min/1.73 m^2		
>60	12,366 (66.0)	32,124 (70.3)
>45–60	2,715 (14.5)	7,386 (16.2)
>30–45	2,028 (10.8)	4,319 (9.5)
≤30 (nondialysis)	1,464 (7.8)	1,687 (3.7)
Dialysis	173 (0.9)	181 (0.4)
Renal transplantation on admission	46 (0.2)	69 (0.2)
Comorbidity at admission		
Diabetes mellitus	3,084 (16.5)	12,368 (27.1)
Hypertension	7,677 (41.0)	27,648 (60.5)
Previous MI	4,383 (23.4)	12,078 (26.4)
HF	3,255 (17.4)	10,750 (23.5)
Peripheral vascular disease	1,019 (5.4)	2630 (5.8)
Previous stroke (any)	2,601 (13.9)	6,240 (13.7)
COPD	1,921 (10.2)	4,364 (9.5)
Cancer diagnosis within the past 3 yrs	576 (3.1)	1,072 (2.3)
Previous PCI	1,636 (8.7)	5,460 (11.9)
Previous CABG	1,337 (7.1)	4,196 (9.2)
Atrial fibrillation	2,187 (11.7)	5,147 (11.3)
Hospital course		
Decompensated HF (Killip ≥2)	2,439 (13.5)	6,271 (14.4)
STEMI	4,233 (22.8)	1,4526 (32.0)
NSTEMI (n = 63,913)	14,350 (77.2) [162]	30,804 (68.0) [367]
PCI	7,991 (42.6)	26,262 (57.5)
CABG	523 (2.8)	847 (1.9)
LVEF <50% (n = 44,502)	3,137 (28.3) [7,666]	17,414 (52.1) [12,274]
Intravenous inotrope	330 (1.8)	1095 (2.4)
Intravenous diuretic agent	3,713 (19.9)	11,024 (24.2)

Continued on the next page

analysis. Similarly, unexposed patients initiating treatment with ACEI/ARB were censored at the first dispensation date. In the analysis of AKI, MI, and stroke, we additionally censored for death unless it was part of the event (e.g., fatal MI and stroke).

In the final model we included our a priori-decided confounders at baseline, during hospital course, and at discharge. Possible confounders at baseline were age (in 3 knot-restricted cubic splines), sex, diabetes mellitus, hypertension, previous MI, congestive heart failure (CHF), peripheral arterial disease, ischemic stroke, chronic obstructive pulmonary disease, cancer within 3 years, any previous stroke, renal transplantation, eGFR, ST-segment elevation MI on admission, Killip score >1 on admission, and atrial fibrillation on admission. During hospital course, we further adjusted for percutaneous coronary intervention, coronary arterial bypass graft surgery, use of intravenous diuretic agents, inotrope drug use, and hospital (random effects). Finally, we included therapy confounders at discharge: antiplatelet therapy (none, mono, or dual), warfarin, beta-blockers, calcium antagonists, diuretic agents, digoxin, statins, and atrial fibrillation. The decision to include eGFR in the model was made to reduce the variability of renal function within each of the investigated eGFR categories. Missing data were handled by multiple imputation with chained equations by generating 5 imputed datasets using all applicable adjustment variables and all outcome variables as predictors. To investigate the hazard rates associated with specific subgroups of interest (patients with and without diabetes, with and without hypertension, and with and without LVSD), we performed subgroup analyses for each outcome (primary and secondary). Kaplan-Meier curves were plotted by treatment and eGFR category. Finally, 2 sensitivity analyses were performed. First, we assessed the final model using the complete-case data (n = 58,939 or 91.5% of total cohort) and then we performed a propensity-score matched analysis for the main outcomes to study effects of confounding by indication. In the propensity score, we used the same imputed datasets as in the final analysis. Propensity scores were then estimated within each eGFR category using random effects logistic regression models with all variables from the fully adjusted model. Patients were matched on estimated propensity scores using full matching via R-package optmatch. For further details about the propensity-score matched analysis, please see the Online Appendix.

RESULTS

There were 78,003 admissions to Swedish hospitals because of AMI between 2006 and 2009. Of these, 2,368 events were excluded due to missing creatinine concentration, 7 because the patient's age was <18 years, and 60 because of registration duplicates. Because we only included 1 AMI event per patient in our baseline cohort, we further excluded 7,725 events because the patient had already been included previously. Finally, we excluded 3,401 patients who died during the hospitalization (Online Figure 1).

The final study population included 64,442 patients with a median age of 72 years, of whom 64% were men. Characteristics of the cohort as stratified by use of

ACEI/ARB at discharge are described in **Table 1**. The median eGFR was 74 ml/min/1.73 m^2. About 30% of patients had an eGFR <60 ml/min/1.73 m^2, and thus were defined as having CKD. At discharge, 70.9% of the patients used either ACEIs (58.4%) or ARBs (13.6%). The proportion of patients treated with either an ACEI or ARB decreased from 72% of those with eGFR >60 ml/min/1.73 m^2 to 51% of those on dialysis. The characteristics in relation to eGFR and probability of treatment with either ACEI or ARB are shown in Online Tables 1 and 2. By 3 months post-discharge, 16.7% of the unexposed patients had initiated ACEI or ARB, whereas the number of patients who started de novo ACEI or ARB after 1, 2, and 3 years were 26%, 31%, and 33%, respectively. Of the patients treated with either ACEI or ARB at discharge, 2.1% discontinued their use after 3 months, whereas 14%, 24%, and 30% had stopped their use after 1, 2, and 3 years, respectively. In total, 13.6% of the ACEI users switched to ARB use and 5.8% of the ARB users changed to an ACEI during follow-up.

TABLE 1 Continued

	No ACEI/ARB at Discharge (n = 18,745; 29.1%)	ACEI/ARB at Discharge (n = 45,697; 70.9%)
Medication at discharge		
Aspirin	16,931 (90.6)	42,438 (92.9)
Mono antiplatelet therapy	5,727 (30.6)	9,776 (21.4)
Dual antiplatelet therapy	11,739 (62.8)	34,027 (74.5)
Warfarin	925 (5.0)	3,242 (7.1)
Beta-blocker	15,879 (85.0)	41,454 (90.7)
Calcium antagonist	2,621 (14.0)	7,205 (15.8)
Digoxin	735 (3.9)	1,735 (3.8)
Diuretic agent	58,05 (31.1)	17,146 (37.5)
Statin	13,522 (72.4)	39,425 (86.3)
No ACEI on admission	17,440 (93.0)	31,385 (68.7)
No ARB on admission	17,831 (95.1)	36,704 (80.3)

Values are median (interquartile range) or n (%) [missing number of patients], unless otherwise indicated. *Values are n (% of patients included).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

MORTALITY. A total of 12,745 (19.8%) patients had died after 3 years of follow-up: 4,772 (25.4%) of those not receiving ACEI/ARB and 7,973 (17.4%) of those with ACEI/ARB use. Across worsening renal function strata, the mortality rate increased for all patients. The crude 3-year mortality was lower for patients treated with either ACEI or ARB as compared with nontreated patients (17.4% for ACEI/ARB-treated vs. 25.5% for nontreated). The Kaplan-Meier survival curves associated with ACEI/ARB use within each renal function strata are displayed in **Figure 1**. In fully adjusted analyses, significantly better survival was observed in patients receiving ACEI or ARB compared with patients not receiving the medication. This survival benefit was consistent through all renal function strata, including dialysis patients (**Central Illustration**). Results were similar after 3 years in both "intention-to-treat analysis" and "on-treatment" analyses (Online Figure 2).

Sensitivity analysis was carried out on individuals naïve to ACEI or ARB on admission (n = 40,560), observing again an association with survival for ACEI/ARB users (3-year hazard ratio [HR] with ACEI/ARB: 0.76; 95% confidence interval [CI]: 0.72 to 0.81; p value for trend across eGFR strata = 0.01). The associations observed for ACEI and ARB were statistically significant and of a similar magnitude for all eGFR categories considered. In the subpopulation of dialysis patients, however, the CI broadened, rendering a nonsignificant association (Online Table 3). The propensity-score matched analyses had results similar to the main analysis, and the same was true for the complete case analysis. Neither did the results differ substantially between use of ACEI or ARB in any of the analyses (Online Table 4).

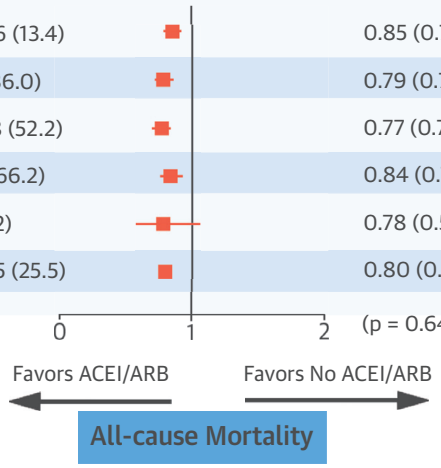
Finally, we studied our primary endpoint across several subgroups: patients with and without diabetes, with and without hypertension, diagnosed with CHF before admission, with no LVSD, and with LVSD (LV ejection fraction <50%) (**Figure 2**). Results were consistent throughout all subgroups, showing, in general, lower hazards associated with ACEI/ARB use, irrespective of renal function stratum.

MI, STROKE, AND RENAL OUTCOMES. There were 10,030 (15.6%) patients admitted with a new fatal or nonfatal MI and 3,697 (5.7%) with stroke within 3 years of follow-up. The number and event rates increased across worsening renal function strata. In the overall, fully adjusted model, there was a lower risk of MI after 3 years with ACEI (**Figure 3**). The association between ACEI/ARB and MI was similar across renal function strata, with slightly lower estimates (although mostly nonsignificant) for the lower renal function strata. The propensity-score matched and "on-treatment" analyses produced results very close to the main analyses. Restricting to patients with de novo ACEI/ARB, we observed an even lower risk of MI in all renal function strata, but especially in patients with eGFR 30 to 45 ml/min/1.73 m^2 (Online Table 3).

We did not observe a lower risk of stroke in ACEI/ARB-treated patients, overall or in any of the renal function strata (**Figure 4**). The results were also

CENTRAL ILLUSTRATION **ACEI and ARB After MI in Renal Dysfunction: All-Cause Mortality**

eGFR	Event Rates (n/N)		3-year HR (95% CI)	3-year PS Matched
	ACEI/ARB	No ACEI/ARB		HR (95% CI)
>60	3,387/33,124 (10.5)	1,656/12,366 (13.4)	0.85 (0.79-0.90)	0.83 (0.78-0.88)
45-60	1,901/7,386 (25.7)	978/2,715 (36.0)	0.79 (0.72-0.86)	0.69 (0.64-0.75)
30-45	1,658/4,319 (38.4)	1,058/2,028 (52.2)	0.77 (0.70-0.83)	0.69 (0.63-0.75)
<30	923/1,687 (54.7)	969/1,463 (66.2)	0.84 (0.76-0.93)	0.79 (0.71-0.87)
Dialysis	104/181 (57.5)	111/173 (64.2)	0.78 (0.58-1.06)	0.85 (0.64-1.12)
Total	7,973/45,697 (17.4)	4,772/18,745 (25.5)	0.80 (0.77-0.83)	0.81 (0.78-0.85)
			(p = 0.64) Trend	(p =0.55) Trend
				I^2 0.79 (0.51, 0.91)



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At 3 years in the intention-to-treat population, use of angiotensin-converting enzyme inhibition (ACEI) and angiotensin receptor blockade (ARB) produced more favorable outcomes regarding all-cause mortality in acute myocardial infarction (MI) patients at all strata of renal function. CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; I^2 = test for homogeneity over the renal function categories; PS = propensity score.

consistent in the propensity-matched and "on-treatment" analyses (Online Figure 2).

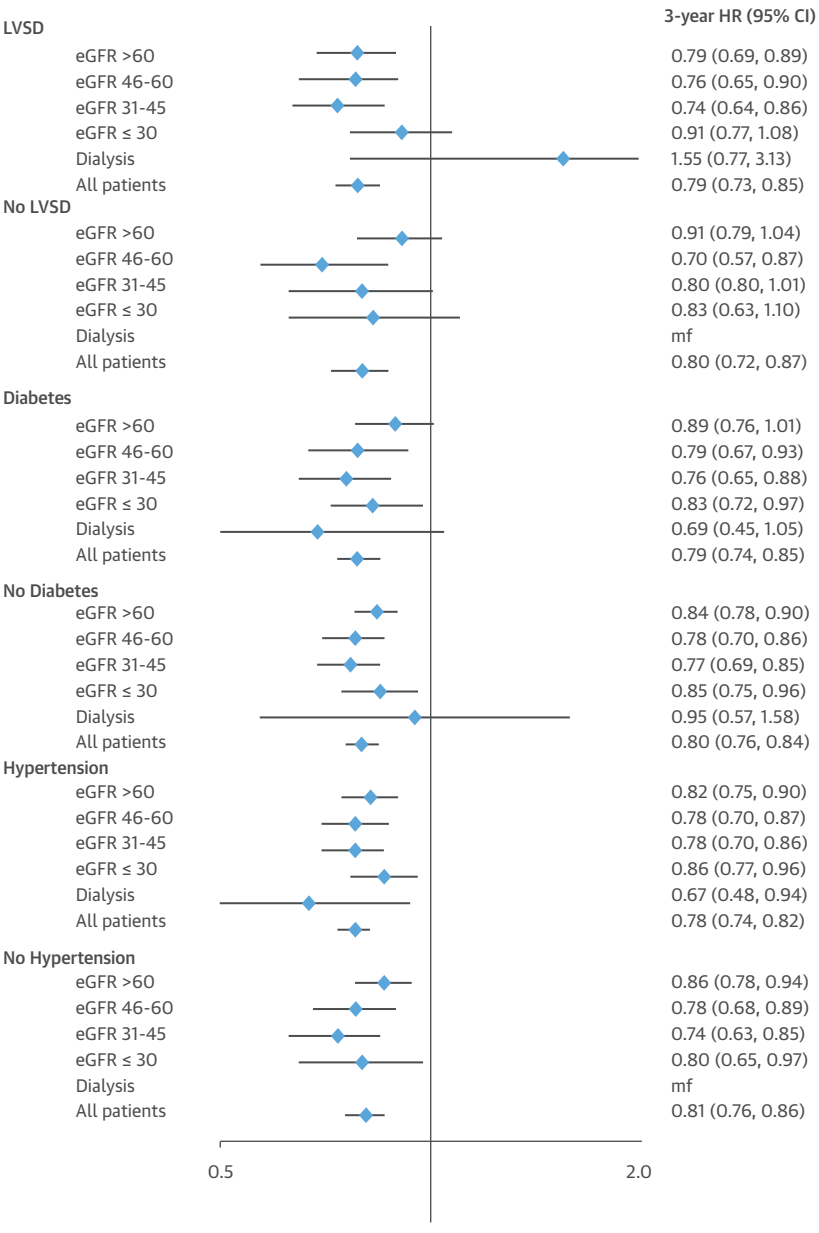
The number of patients admitted because of AKI or who started renal replacement therapy (dialysis or kidney transplantation) during 3-year follow-up was overall low (n = 1,528 [2.4%]), but the incidence was borderline significantly associated with ACEI/ARB use (adjusted HR: 1.12; 95% CI: 0.99 to 1.27) (**Figure 5**). In subgroup analysis, the risk for AKI was highest for patients with an eGFR >30 ml/min/1.73 m^2, but corresponded to an overall very low absolute risk (2.6 cases/100 patient-years for patients with eGFR 30 to 45 ml/min/1.73 m^2). The combined endpoint of death/AKI/renal replacement therapy was, due to the low number of AKI events, still in favor of ACEI/ARB use across all renal function strata (3-year HR: 0.80; 95% CI: 0.74 to 0.87 for eGFR <60 to 45 ml/min/1.73 m^2; HR: 0.78; 95% CI: 0.72 to 0.85 for eGFR <45 to 30 ml/min/1.73 m^2; HR: 0.86; 95% CI: 0.78 to 0.94 for eGFR <30 ml/min/1.73 m^2).

We then analyzed the secondary outcomes in the pre-defined subgroups. There was a lower 3-year risk of MI among patients treated with ACEI/ARB in almost all subgroups, but the risk reduction was more significant for patients in risk groups such as those with hypertension, LVSD, or previous CHF (Online Figure 3).

DISCUSSION

In a large, contemporary, nationwide cohort of MI patients, we showed that treatment with either ACEI or ARB was associated with better survival as compared with no treatment. This association was consistent across all renal function strata considered, regardless of the presence of LVSD, HF, diabetes, or hypertension. Results did not differ materially between ACEI and ARB use. In general, our results are similar in direction and magnitude to previous randomized trials and meta-analyses of trials including both AMI patients with evidence of LVSD (4,5) and coronary artery disease patients without evidence of LVSD (23,24). We observed a lower 3-year risk of fatal and nonfatal MI, with a stronger association across the traditional high-risk populations (patients with hypertension, LVSD, and HF) and across the different

FIGURE 2 **3-Year Mortality: Subgroup Analysis**

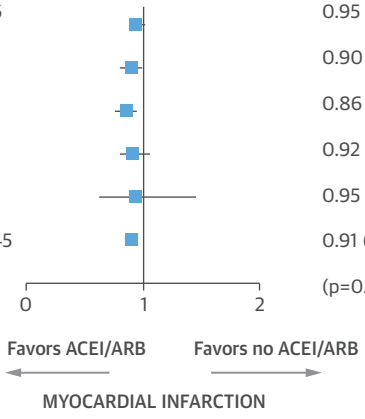


In an analysis of subgroups comparing presence or absence of left ventricular systolic dysfunction (LVSD), diabetes, and hypertension, use of angiotensin-converting enzyme inhibitors (ACEI)/ARB generally produced lower hazards in regard to 3-year mortality at all strata of renal function. CI = confidence interval; HR = hazard ratio; mf = model failed; other abbreviations as in Figure 1.

renal function strata considered. Although the estimated risk failed to reach statistical significance in some of the renal function groups, ACEI/ARB was associated with a consistently lower risk of MI in most subgroups as well as the overall analysis and propensity-score matched analysis. One reason for the larger risk reduction in overall mortality as compared with MI in our study could be due to ACEI/ARB-related reduction in other cardiovascular mortality, such as sudden death or death from CHF.

FIGURE 3 3-Year Myocardial Infarction

eGFR	Event rates (n/N) ACEI/ARB	Event rates (n/N) No ACEI/ARB	3-year HR (95% CI)	3-year PS matched HR (95% CI)
> 60	(10.4) 3336/33124	(9.9) 1219/12366	0.95 (0.89, 1.01)	1.04 (0.97, 1.11)
45-60	(17.8) 1314/7386	(18.7) 509/2715	0.90 (0.81, 0.99)	0.85 (0.77, 0.93)
30-45	(24.0) 1035/4319	(24.1) 488/2028	0.86 (0.77, 0.95)	0.81 (0.73, 0.90)
< 30	(29.2) 492/1687	(27.9) 404/1463	0.92 (0.81, 1.05)	0.88 (0.78, 1.00)
Dialysis	(32.0) 58/181	(27.2) 47/173	0.95 (0.63, 1.45)*	1.02 (0.68, 1.53)
Total	(13.6) 6235/45697	(14.2) 2667/18745	0.91 (0.87, 0.95)	0.96 (0.91, 1.00)
			(p=0.35) trend	(p=0.21) trend
				I^2 0.82 (0.59, 0.92)



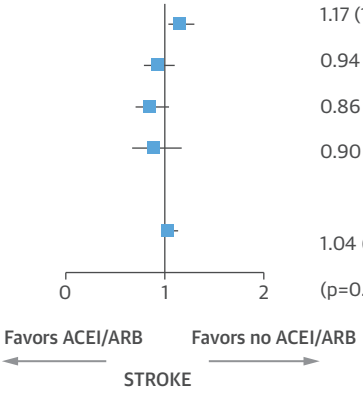
Use of ACEI/ARB reduced the risk of myocardial infarction at 3-year follow-up. *Some confounders were removed due to lack of contrast. I^2 = test for homogeneity over the renal function categories; PS = propensity score; other abbreviations as in Figures 1 and 2.

Also, the competing risk of death in this generally old population could contribute to a lower risk reduction.

In contrast to some previous studies (15,25), our cohort did not show any significant association between ACEI/ARB use and the secondary endpoints of fatal and nonfatal stroke. However, there are important differences between patients from routine clinical practice as compared with those participating in trials: our patients were older (about 5 to 10 years) and more often had a history of previous stroke and a higher readmission rate for MI. Although the mean eGFR was 74 ml/min/1.73 m^2, more than 30% of the patients had a renal function in the CKD range (<60 ml/min/1.73 m^2) and more than 15% had an eGFR that was considered an exclusion criterion in previous trials (4,5,14). In a recent combined analysis of 3 trials (23), a stroke-protective effect for ACEI was reported, which was, however, largely driven by the HOPE (Heart Outcomes Prevention Evaluation) study (15) including high-risk patients with coronary artery

FIGURE 4 3-Year Stroke

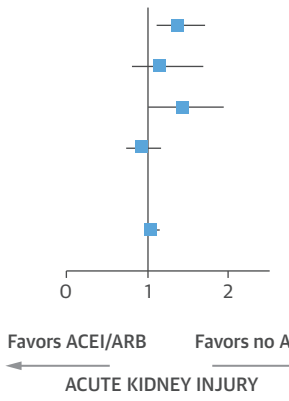
eGFR	Event rates (n/N) ACEI/ARB	Event rates (n/N) No ACEI/ARB	3-year HR (95% CI)	3-year PS matched HR (95% CI)
> 60	(4.7) 1504/33124	(4.1) 512/12366	1.17 (1.05, 1.30)	1.18 (1.06, 1.31)
45-60	(8.0) 593/7386	(8.7) 235/2715	0.94 (0.80, 1.10)	0.89 (0.76, 1.04)
30-45	(8.8) 378/4319	(9.7) 197/2028	0.86 (0.72, 1.04)	0.80 (0.67, 0.96)
< 30	(7.8) 131/1687	(8.1) 118/1463	0.90 (0.69, 1.17)	0.90 (0.69, 1.18)
Dialysis	(7.7) 14/181	(8.7) 15/173		0.83 (0.38, 1.84)
Total	(5.7) 2620/45697	(5.7) 1077/18745	1.04 (0.97, 1.13)	1.03 (0.95, 1.12)
			(p=0.10) trend	(p=0.14) trend
				I^2 0.78 (0.46, 0.91)



There was no observed reduction in stroke risk at 3 years with use of ACEI/ARB. Abbreviations as in Figures 1 to 3.

FIGURE 5 3-Year AKI

eGFR	Event rates (n/N) ACEI/ARB	Event rates (n/N) No ACEI/ARB	3-year HR (95% CI)	3-year PS matched HR (95% CI)
> 60	(1.7) 541/33124	(0.9) 112/12366	1.38 (1.11, 1.71)	1.87 (1.52, 2.31)
45-60	(2.2) 164/7386	(1.5) 41/2715	1.16 (0.81, 1.68)	1.36 (0.96, 1.92)
30-45	(4.9) 210/4319	(2.9) 58/2028	1.43 (1.05, 1.94)	1.48 (1.10, 2.00)
< 30	(14.0) 236/1687	(11.3) 166/1463	0.93 (0.75, 1.15)	1.02 (0.82, 1.27)
Dialysis	n.a	n.a	n.a	n.a
Total	(2.5) 1151/45697	(2.0) 377/18745	1.12 (0.99, 1.27)	1.26 (1.11, 1.44)
			(p=0.21) trend	(p=0.05) trend
				I^2 0.81 (0.50, 0.93)



Use of ACEI/ARB was associated with a slightly significantly increased incidence of admittance for acute kidney injury (AKI) or dialysis/kidney transplantation. n.a. = not applicable; other abbreviations as in Figures 1 to 3.

disease. Our results found no association between ACEI users and stroke risk prevention, which is nevertheless more in line with previous estimates from ACEI trials after MI (4,5).

Some previous smaller observational studies have tried to address outcomes associated with ACEI/ARB use after MI. Our observations align with those from a German registry (26) but contrast somewhat from an Australian report (27). Our results further diverged from 1 Japanese registry study (28), which showed that patients had worse survival when prescribed ARBs compared with ACEIs.

Despite the lack of evidence from randomized controlled trials, a large proportion of CKD patients in our study were treated with ACEIs/ARBs (53.6% of the patients with eGFR <30 ml/min/1.73 m^2, of whom 16.5% were treated de novo). Our results suggested that patients with reduced renal function benefit just as much from ACEI/ARB treatment after AMI as patients with normal renal function. However, ACEI/ARB treatment also resulted in a higher risk of AKI in patients with an eGFR >30 ml/min/1.73 m^2. In our study, the risk of AKI associated with ACEI/ARB use did not increase with declining renal function, and the composite outcome of death/AKI was still in favor of treatment, because of the low number of absolute AKI events (overall 2.4% after 3 years). The reason for the low number of AKI events may have been under-reporting, because we only registered events in need of hospitalization, but overall the frequency of events was close to that reported in previous trials (4,15). Our study suggests that even though adverse events such as AKI may develop with the use of ACEI/ARB, and close monitoring and dose adjustment are therefore needed, the overall benefit of using these drugs in patients with lower renal function may still outweigh the risks. Also, in studies targeting renal outcomes, both ACEIs and ARBs are well documented for their renoprotective effects, reducing albuminuria and slowing the renal deterioration rate and the incidence of renal replacement therapy (29,30).

STUDY LIMITATIONS. The strengths of our analysis were the larger sample size with national representation and extensive clinical characteristics registered both at admission and at discharge. The personal identity number unique to all Swedish citizens and the possibility to enrich data with other national registries made the number of patients lost to follow-up virtually nonexistent. Moreover, we updated information on drug dispensations during 3 years. Because both inpatient and outpatient health care (including medication use to some extent) in Sweden is tax financed, we believe that confounding related to socioeconomic status affecting the probability to adhere to treatment was lower than in other countries. However, as with all observational studies, the allocation of treatment could have been influenced by confounding by indication. This resulted in differences between treated and nontreated patients at baseline that should be considered when interpreting

the unadjusted results. Although we were able to use advanced statistical models and rich sets of adjustment variables, unmeasured or residual confounding could have influenced the results. We did not, for example, have information on discharge blood pressure. Individual tolerability for antihypertensive agents could have allocated patients to treatment or nontreatment. Residual confounding by magnitude of hypertension could explain the significantly higher risk of stroke in the normal renal function strata, because patients with severe hypertension would be more likely to receive ACEIs/ARBs and also to develop stroke. Furthermore, eGFR was estimated from serum creatinine on admission. All creatinine-based equations might result in misclassification, especially in those with deviating body composition or muscle mass. Also, we lacked information on reasons for drug discontinuation or frequency of hyperkalemia in the registry.

CONCLUSIONS

In a large, nationwide cohort study, treatment with either ACEI or ARB after MI was associated with significantly improved survival after 1 and 3 years. Better survival associated with ACEI/ARB use also was observed in patients with decreased renal function and was accompanied by low rates of adverse renal events.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: ACEIs or ARBs reduce cardiovascular morbidity and mortality after MI in patients with impaired renal function. This benefit generally outweighs the risk of AKI.

TRANSLATIONAL OUTLOOK: Clinical studies of large cohorts are needed to evaluate the long-term effect of angiotensin inhibitor therapy on the incidence of end-stage renal disease in survivors of MI.

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KEY WORDS chronic kidney disease, mortality, risk profile, survival analysis

APPENDIX For supplemental Methods, figures, and tables, please see the online version of this article.