Risk of acute kidney injury among older adults with heart failure and with reduced ejection fraction treated with angiotensin-neprilysin inhibitor vs renin-angiotensin system inhibitor in routine clinical care

Bhatt, A.S.; Vaduganathan, M.; Zhuo, M.; Fu, E.L.; Solomon, S.D.; Desai, R.J.

Risk of Acute Kidney Injury Among Older Adults With Heart Failure and With Reduced Ejection Fraction Treated With Angiotensin-Neprilysin Inhibitor vs Renin-Angiotensin System Inhibitor in Routine Clinical Care

ANKEET S. BHATT, MD, MBA,[1,*] MUTHIAH VADUGANATHAN, MD, MPh,[1,*] MIN ZHUO, MD, MPh,[2,3] EDOUARD L. FU, PhD,[3] SCOTT D. SOLOMON, MD,[1] AND RISHI J. DESAI, PhD[3,*]
Boston, Massachusetts

ABSTRACT

Background: The acute hemodynamic effects of sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNI), may result in early changes in kidney function, raising concerns about acute kidney injury (AKI), particularly in those who are naïve to renin-angiotensin system inhibitors (RASis).

Methods: We conducted a cohort study using U.S. Medicare fee-for-service claims data (2014−2017). Patients with HFrEF $\geq$ 65 years newly initiating ARNI or RASi, with no prior use of either drug class, were included. The primary outcome was hospitalization due to AKI as the primary discharge diagnosis, and the secondary outcome included AKI as a primary or secondary discharge diagnosis. AKI risks were described under an as-treated follow-up approach, with censoring on treatment discontinuation, switch, insurance disenrollment, death, or administrative censoring as well as an intent-to-treat approach. Propensity-score−based fine-stratification weighting was used to account for potential confounding by 81 pre-exposure characteristics. Cumulative incidence functions were used to report absolute risks, and Cox proportional hazards models were used to provide hazard ratios (HR) and 95% confidence intervals (CI).

Results: We included 27,166 patients with a mean (SD) age of 73 (7.3) years, and 4155 (15.3%) were initiating ARNI. After propensity score weighting, the 180-day cumulative incidence was 2.7% (2.4%−3.1%) among RASi initiators and 2.7% (2.2%−3.5%) among ARNI initiators for the primary outcome, and it was 6.5% (6.0%−7.1%) and 6.1% (5.2%−7.1%), respectively, for the secondary outcome under as-treated follow-up. HR (95% CI) comparing ARNI with RASi were 0.91 (95% CI: 0.72−1.16) for the primary outcome and 0.92 (95% CI: 0.79−1.08) for the secondary outcome. Similar results were observed in the intent-to-treat analysis.

Conclusions: Among a large cohort of U.S. Medicare beneficiaries with HFrEF, ARNI treatment was not associated with higher rates of AKI than RASi treatment. These results provide reassurance for providers considering ARNI initiation in older patients who are RASi-naïve. (*J Cardiac Fail 2023;29:138−146*)

Key Words: acute kidney injury, heart failure, sacubitril/valsartan.

From the [1]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [2]Division of Renal Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts and [3]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts..

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Reprint requests: Rishi J Desai, PhD, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont Street, Suite 3030-R, Boston, MA 02120. Tel: + 1: 617 278 0932; Fax: + 1 617 232 8602. E-mail: rdesai@bwh.harvard.edu

*Contributed equally as co-first authors.

See page 145 for disclosure information.

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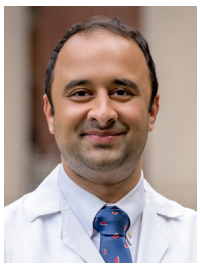
Take Home Points:

1. In this population-based cohort study of > 25,000 Medicare beneficiaries with HFrEF, hospitalization rates for AKI were similar among patients newly initiating ARNI vs RASi.
2. Similar results were observed when expanding hospitalization to those with either a primary or a secondary diagnosis of AKI and when using an intention-to-treat approach.
3. These results may provide reassurance to clinicians concerned about early changes in renal function when considering initiation of ARNI in older adults without prior demonstrated tolerance to RASi.

Lay Summary

Sacubitril/valsartan, which is a medication in a class called angiotensin receptor neprilysin inhibitors (ARNIs), is a newer medication for the treatment for heart failure that can be used in place of older medications. This drug may affect kidney function, particularly in patients who have not tried previous treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. In this large dataset of > 25,000 patients enrolled in Medicare, we found that the risk of hospitalization for kidney injury was no different in patients with heart failure starting an ARNI vs those starting 1 of the older medications. This reassuring finding, combined with the established effectiveness profile, supports the potential use of this newer therapy in patients who are older and in those who have not tried older treatments.



Proposed Social Media Text

Concern about AKI might stall effective HFrEF therapeutic implementation. Now out in @JCardFail #simpub w/ @HFSAASM 2022, in > 25,000 highly comorbid Medicare beneficiaries with HFrEF, hospitalization for AKI was no different in those with de novo ARNI initiation vs RASi initiation. Implementation efforts supporting de novo ARNI initiation in eligible patients are needed. @ankeetbhatt @mvaduganathan @Rishidesai11 @scottdsolomon @gcfmd

The angiotensin receptor neprilysin inhibitor (ARNI), sacubitril/valsartan, has been shown to reduce cardiovascular death and hospitalizations due to heart failure (HF) in patients with chronic HF with reduced ejection fraction (HFrEF).[1] Despite guideline recommendations supporting its use, the broad implementation of this therapy in practice has remained suboptimal and has included frequent lack of treatment persistence and early discontinuation.[2,3] Renin-angiotensin-system inhibition (RASi) has intraglomerular effects, which routinely lead to short-term declines in estimated glomerular filtration rates (eGFRs). In addition, neprilysin inhibition may augment circulating vasoactive peptides, resulting in acute hemodynamic effects and hypotension in some. Alternatively, neprilysin inhibition may also counteract eGFR declines by RAS inhibitors via improvement in renal blood flow. Collectively, the risk of acute kidney injury (AKI) after initiation of ARNI vs RASi remains unclear, particularly in patients without prior tolerance to RASi and in older patients with additional risk factors for renal dysfunction. Randomized controlled trials using run-in phases are not ideally suited to answer this question because they include only patients who tolerate RASis and ARNIs. To address this knowledge gap, we used the data of a large cohort of Medicare beneficiaries to evaluate the risk of AKI following initiation of ARNI vs RASi in routine clinical care.

Methods

Data Sources

We used nationwide Medicare fee-for-service claims data from July 2014−2017. Medicare Part A (hospitalizations), Part B (medical services) and Part D (prescription medications) claims contain comprehensive longitudinal patient information concerning routine care. A signed data-use agreement with the Centers for Medicare and Medicaid Services was available, and the Brigham and Women's Hospital Institutional Review Board approved this study.

Study Design

A new-user active-comparator cohort study was conducted[4]; it included patients newly starting ARNI or RASi, including angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs). New initiation was defined as no prior prescription for either of these drug classes within the preceding 12 months of continuous Medicare enrollment (parts A, B, D). Inclusion of patients naïve to both therapies minimizes potential confounding due to varying treatment history with RASis. The date of the first dispensing of the study drug of

interest (ARNI or RASi) was defined as the cohort entry date. We excluded patients < 65 years of age on the cohort entry date, nursing-home stay within 12 months prior to cohort entry, history of heart or kidney transplant, history of end-stage renal disease, and incomplete recording of gender. We also required that patients have an HF diagnosis within 6 months prior to the cohort entry date. Use of ARNI was assumed to be an indicator of HFrEF in the exposure group because it was indicated only for HFrEF during the study period. To restrict the cohort to HFrEF in the RASi group, we implemented a Medicare-claims–based probabilistic phenotyping algorithm with a reported positive predicted value of 73% in a previous validation study.[5]

Follow-up and Outcome of Interest

Patients were followed from the cohort entry date until the first occurrence of hospitalization for AKI, Medicare disenrollment, death, or December 31, 2017. In the primary analysis, we used an as-treated follow-up approach in which follow-up was censored at the time of treatment switch (RASI to ARNI or vice versa) or discontinuation of RASI or ARNI (defined as ≥ 30 days of no prescription refills after the most recent prescription supply ended) to minimize the impact of exposure misclassification. In other words, patients contributed time for as long as they were on the study drug in this follow-up scheme. However, such treatment-based censoring could lead to bias if it is informative with respect to changing renal function. To evaluate this possibility, we also implemented an intention-to- treat analysis where we followed patients in their assigned exposure group for a maximum of 1 year without censoring at treatment switch or discontinuation.

The primary outcome of interest was hospitalization for AKI, when AKI was listed as the primary discharge diagnosis. As a secondary outcome, we evaluated all hospitalizations in which AKI was listed as a discharge diagnosis in either the primary or the secondary position. Diagnosis codes for AKI are reported to have a positive predicted value of 80.2% in a prior validation study.[6]

Statistical Analysis

Propensity score (PS)-based fine stratification and weighting were used for confounding adjustment for a large number of covariates, including demographics, HF treatments and histories of hospitalizations, AKI risk factors, including history of AKI, chronic kidney disease, comorbid conditions, medication use, and markers of healthy behavior and health care use.[7] A complete list of variables is included in Table 1. The PS was derived as the conditional probability of initiating ARNI on the basis of the covariates listed above by using a logistic regression model. Based on the distribution of the PS in the ARNI group, 50 strata were created after trimming nonoverlapping regions to focus on comparable patients. RASi initiators were assigned to the created strata based on their PS and were weighted according to the distribution of ARNI patients in their respective stratum. Balance achieved in patients' characteristics after PS weighting was evaluated by using standardized differences. Weighted Cox proportional hazards models were used to estimate hazard ratios (HRs), and 95% confidence intervals (CIs) were calculated by using robust variance estimators to account for weighting. We estimated the cumulative incidence for AKI on the basis of cumulative incidence functions accounting for competing risk by death.[8] The number of events and median follow-up were descriptively reported, stratified by the treatment in the overall sample before and after PS weighting. We used SAS 9.4 (SAS Institute, Cary, NC) to conduct the propensity scores' fine stratification and weighting and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) for cumulative incidence.

Results

Of 9.2 million patients with ≥ 1 filled prescription for sacubitril/valsartan or RASi, based on Medicare claims data from 2014–2017, 27,166 patients met all our inclusion criteria and were included (Fig. 1). The study cohort contained 4155 (15.3%) patients initiating ARNI and 23,011 (84.7%) initiating RASi. The mean age (SD) was 73 (7.3) years, and most patients were male and white. Patients' characteristics were well balanced after propensity weighting (Table 1).

Over a median follow-up of approximately 4 months in the as-treated follow-up approach for ARNI initiators, there were a total of 90 primary outcome events and 214 secondary outcome events (Table 2). Under the as-treated follow-up scheme, the estimated 180-day cumulative incidence was 2.7% (2.4%–3.1%) among RASi initiators and 2.7% (2.2%–3.5%) among ARNI initiators for the primary outcome, and it was 6.5% (6.0%–7.1%) and 6.1% (5.2%–7.1%), respectively, for the secondary outcome after PS-weighting (Table 2) (Fig. 2). Hazard ratios comparing ARNI to RASi were 0.91 (95% CI: 0.72–1.16) for the primary outcome and 0.92 (95% CI: 0.79–1.08) for the secondary outcome (Fig. 3). Similar results were observed in the intention-to-treat follow-up scheme.

Discussion

In this population-based cohort study of Medicare beneficiaries with HF, hospitalization rates for AKI were similar among patients newly initiating ARNI

Table 1. Baseline Characteristics Among ACEi/ARB and ARNI Initiators Before and After Propensity Score Weighting (2014−2017)

Variable	Unweighted-ARNI (n = 4155)	Unweighted-ACEi/ARB (n = 23,168)	Unweighted standardized difference	PS-weighted: ARNI (n = 4155)	PS-weighted: ACEi/ARB	PS-weighted standardized difference
Total sample size	4155	23168		4155	23011	
Demographics						
Mean age (SD), years	77.3 (7.3)	76.4 (7.3)	13.1	77.3 (7.3)	77.3 (7.3)	0.2
Male, n (%)	2820 (67.9)	15225 (65.7)	4.6	2820 (67.9)	15559 (67.6)	0.5
White, n (%)	3524 (84.8)	19581 (84.5)	0.8	3524 (84.8)	19561 (85)	-0.5
Black race, n (%)	399 (9.6)	2425 (10.5)	-2.9	399 (9.6)	2206 (9.6)	0.1
Low-income subsidy recipients, n (%)	957 (23)	5811 (25.1)	-4.8	957 (23)	5216 (22.7)	0.9
Socioeconomic status (SES) index	57 (7.5)	57 (7.3)	-0.1	57 (7.5)	57 (7.3)	0.1
Baseline HF therapy, n (%)						
MRA	1418 (34.1)	6887 (29.7)	9.5	1418 (34.1)	7879 (34.2)	-0.2
Beta-blockers	3670 (88.3)	21203 (91.5)	-10.6	3670 (88.3)	20303 (88.2)	0.3
Digoxin	819 (19.7)	4430 (19.1)	1.5	819 (19.7)	4622 (20.1)	-0.9
Loop diuretics	3352 (80.7)	17209 (74.3)	15.4	3352 (80.7)	18512 (80.4)	0.6
Thiazide diuretics	616 (14.8)	2293 (9.9)	15.0	616 (14.8)	3344 (14.5)	0.8
Hydralazine	379 (9.1)	1452 (6.3)	10.7	379 (9.1)	2122 (9.2)	-0.3
Nitrates	1318 (31.7)	6279 (27.1)	10.1	1318 (31.7)	7287 (31.7)	0.1
SGLT2i	51 (1.2)	152 (0.7)	5.9	51 (1.2)	277 (1.2)	0.2
Ivabradine	36 (0.9)	20 (0.1)	11.3	36 (0.9)	117 (0.5)	4.4
Cardiac resynchronization therapy	76 (1.8)	579 (2.5)	-4.6	76 (1.8)	428 (1.9)	-0.2
Implantable cardiac defibrillator	1879 (45.2)	7634 (33)	25.4	1879 (45.2)	10606 (46.1)	-1.7
Number of prior HF hospital visits in past 365 days, n (%)						
0	3111 (74.9)	14846 (64.1)	23.6	3111 (74.9)	17137 (74.5)	0.9
1	727 (17.5)	5844 (25.2)	-18.9	727 (17.5)	4029 (17.5)	0.0
2	207 (5)	1560 (6.7)	-7.5	207 (5)	1208 (5.3)	-1.2
≥3	110 (2.6)	918 (4)	-7.4	110 (2.6)	637 (2.8)	-.7
Number of non-HF hospital visits, n (%)						
0	2652 (63.8)	10643 (45.9)	36.5	2652 (63.8)	14687 (63.8)	0.0
1	932 (22.4)	7560 (32.6)	-23.0	932 (22.4)	5107 (22.2)	0.6
2	355 (8.5)	3038 (13.1)	-14.7	355 (8.5)	1978 (8.6)	-0.2
≥3	216 (5.2)	1927 (8.3)	-12.4	216 (5.2)	1238 (5.4)	-0.8
History of baseline renal disease, n (%)						
History acute kidney injury in past 365 days	971 (23.4)	5958 (25.7)	-5.5	971 (23.4)	5412 (23.5)	-0.4
Chronic kidney disease, stages 1−2	359 (8.6)	1510 (6.5)	8.0	359 (8.6)	2058 (8.9)	-1.1
Chronic kidney disease, stages ≥ 3	1605 (38.6)	6232 (26.9)	25.2	1605 (38.6)	8906 (38.7)	-0.2
Diabetic nephropathy	113 (2.7)	811 (3.5)	-4.5	113 (2.7)	636 (2.8)	-0.3
Hypertensive nephropathy	1495 (36)	6634 (28.6)	15.8	1495 (36)	8293 (36)	-0.1
Other renal disease	1225 (29.5)	5896 (25.4)	9.0	1225 (29.5)	6797 (29.5)	-0.1
Comorbidity burden, n (%)						
Diabetes	2342 (56.4)	11154 (48.1)	16.5	2342 (56.4)	13001 (56.5)	-0.3
Hypertension	3867 (93.1)	20757 (89.6)	12.4	3867 (93.1)	21438 (93.2)	-0.4
Smoking	1767 (42.5)	11659 (50.3)	-15.7	1767 (42.5)	9760 (42.4)	0.2
Obesity	1130 (27.2)	4998 (21.6)	13.1	1130 (27.2)	6219 (27)	0.4
Myocardial infarction	526 (12.7)	6808 (29.4)	-41.9	526 (12.7)	2822 (12.3)	1.2
Coronary artery bypass surgery	1305 (31.4)	5370 (23.2)	18.6	1305 (31.4)	7206 (31.3)	0.2
Unstable angina	385 (9.3)	3107 (13.4)	-13.1	385 (9.3)	2119 (9.2)	0.2
Stable angina	986 (23.7)	3852 (16.6)	17.8	986 (23.7)	5499 (23.9)	-0.4
Stroke or TIA	544 (13.1)	3187 (13.8)	-1.9	544 (13.1)	3015 (13.1)	0.0
Valve disorders	1009 (24.3)	5763 (24.9)	-1.4	1009 (24.3)	5577 (24.2)	0.1
Peripheral vascular disease	1674 (40.3)	8718 (37.6)	5.5	1674 (40.3)	9229 (40.1)	0.4
Atrial fibrillation	2334 (56.2)	11930 (51.5)	9.4	2334 (56.2)	12941 (56.2)	-0.1

(*continued*)

Table 1 (*Continued*)

Variable	Unweighted-ARNI (n = 4155)	Unweighted-ACEi/ARB (n = 23,168)	Unweighted standardized difference	PS-weighted: ARNI (n = 4155)	PS-weighted: ACEi/ARB	PS-weighted standardized difference
Other dysrhythmias	2374 (57.1)	14604 (63)	-12.1	2374 (57.1)	13173 (57.2)	-0.2
Endocarditis	20 (0.5)	87 (0.4)	1.6	20 (0.5)	110 (0.5)	0.0
Anemia	1800 (43.3)	9157 (39.5)	7.7	1800 (43.3)	9925 (43.1)	0.4
Chronic obstructive pulmonary disease	1641 (39.5)	9414 (40.6)	-2.3	1641 (39.5)	9096 (39.5)	-0.1
Pulmonary hypertension	263 (6.3)	3008 (13)	-22.7	263 (6.3)	1431 (6.2)	0.5
Sleep apnea	994 (23.9)	4345 (18.8)	12.6	994 (23.9)	5492 (23.9)	0.1
Alzheimer disease	114 (2.7)	1031 (4.5)	-9.2	114 (2.7)	614 (2.7)	0.5
Other dementia	260 (6.3)	1880 (8.1)	-7.2	260 (6.3)	1411 (6.1)	0.5
Depression	751 (18.1)	4506 (19.4)	-3.5	751 (18.1)	4201 (18.3)	-0.5
History of hyperkalemia	433 (10.4)	1970 (8.5)	6.6	433 (10.4)	2351 (10.2)	0.7
History of angioedema	9 (0.2)	42 (0.2)	0.8	9 (0.2)	53 (0.2)	-0.3
History of hypotension	756 (18.2)	4501 (19.4)	-3.2	756 (18.2)	4188 (18.2)	0.0
Frailty score, mean (SD)	0.2 (0)	0.2 (0.1)	-11.5	0.2 (0)	0.2 (0)	0.6
Combined comorbidity score, mean (SD)	6.4 (2.8)	6.1 (2.9)	11.8	6.4 (2.8)	6.4 (3)	0.1
Baseline medications, n (%)						
Antiplatelet	1077 (25.9)	5552 (24)	4.5	1077 (25.9)	5971 (25.9)	-0.1
Anticoagulant	1613 (38.8)	7937 (34.3)	9.5	1613 (38.8)	8952 (38.9)	-0.2
Insulin	684 (16.5)	2923 (12.6)	10.9	684 (16.5)	3754 (16.3)	0.4
Non-insulin hyperglycemic agents	1166 (28.1)	5705 (24.6)	7.8	1166 (28.1)	6496 (28.2)	-0.4
Uric acid-lowering treatments	690 (16.6)	2426 (10.5)	18.0	690 (16.6)	3755 (16.3)	0.8
Statin	2814 (67.7)	15222 (65.7)	4.3	2814 (67.7)	15479 (67.3)	1.0
Treatment for COPD						
Short-acting bronchodilators	507 (12.2)	2696 (11.6)	1.7	507 (12.2)	2798 (12.2)	0.1
Long-acting bronchodilators	94 (2.3)	411 (1.8)	3.5	94 (2.3)	502 (2.2)	0.5
Dual therapy for COPD	309 (7.4)	1608 (6.9)	1.9	309 (7.4)	1688 (7.3)	0.4
Triple therapy for COPD	293 (7.1)	2019 (8.7)	-6.2	293 (7.1)	1599 (6.9)	0.4
Total distinct medications	15.2 (6.6)	14.1 (6.4)	17.2	15.2 (6.6)	15.2 (6.6)	0.1
Health care use markers						
Physician office visits	19 (11)	15.2 (11)	34.0	19 (11)	19.1 (12.2)	-0.7
Distinct prescribing physicians	5 (3)	5 (3.6)	0.7	5 (3)	5.1 (3.4)	-1.4
Emergency room visits, mean (SD)	1.2 (2)	1.3 (2.6)	-5.9	1.2 (2)	1.2 (2.1)	-1.0
≥1 Cardiologist visit, n (%)	3442 (82.8)	15505 (66.9)	37.3	3442 (82.8)	19271 (83.7)	-2.4
≥1 Nephrologist visit, n (%)	865 (20.8)	3483 (15)	15.1	865 (20.8)	4788 (20.8)	0.0
Markers of healthy behavior, n (%)						
Colonoscopy	344 (8.3)	1956 (8.4)	-0.6	344 (8.3)	1948 (8.5)	-0.7
Fecal occult blood test	281 (6.8)	1360 (5.9)	3.7	281 (6.8)	1566 (6.8)	-0.2
Flu vaccination	2739 (65.9)	13807 (59.6)	13.1	2739 (65.9)	15281 (66.4)	-1.0
Mammography	327 (7.9)	1932 (8.3)	-1.7	327 (7.9)	1838 (8)	-0.4
Pap smear test	53 (1.3)	277 (1.2)	0.7	53 (1.3)	295 (1.3)	-0.1
Pneumococcal vaccine	859 (20.7)	4690 (20.2)	1.1	859 (20.7)	4788 (20.8)	-0.3
Prostate-specific antigen test	1194 (28.7)	5805 (25.1)	8.3	1194 (28.7)	6522 (28.3)	0.9

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor Neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; PS, propensity score; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SD, standard deviation; TIA, transient ischemic attack.

vs RASi. We found similar results when expanding hospitalization to those with either a primary or a secondary diagnosis of AKI and when using an intention-to-treat follow-up scheme.

ARNI improved outcomes of HF better than enalapril in ambulatory patients with HfrEF in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[1] In PARADIGM-HF, rates of AKI were low and infrequently led to discontinuation of the study drug. However, the design of this trial included sequential run-in phases, which may have excluded patients from randomization due to kidney-function changes or other

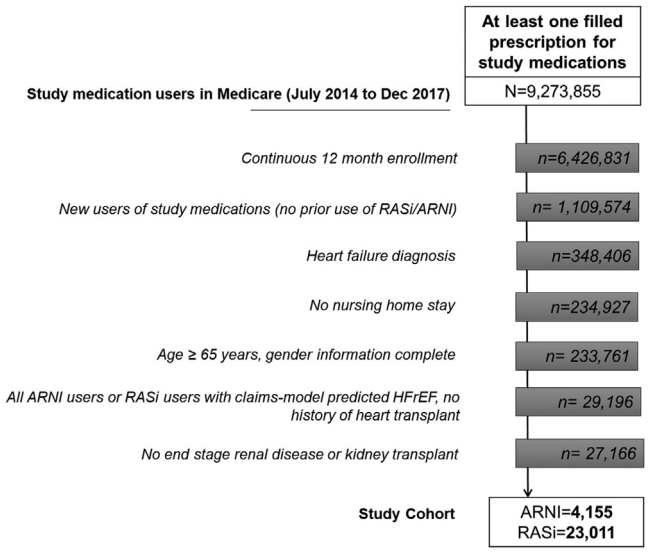


Fig. 1. Patient attrition flow chart. ARNI, angiotensin receptor neprilysin inhibitor; HfrEF, heart failure with reduced ejection fraction; RASi, renin angiotensin system inhibitor.

causes (ie, hypotension) after exposure to target doses of RASi or ARNI in sequential run-ins. In addition, patients at high risk of AKI may have been preferentially excluded from randomization at screening. The Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial assessed the efficacy of ARNI vs enalapril in stabilized patients with acute HF in the absence of run-in, and it included patients without prior history of RASi exposure; rates of AKI were similar in the 2 groups, but this trial was modest in size and had relatively short follow-up; therefore, it was not ideally suited to assess the risk of adverse kidney events.[9] Given the known association between RASi initiation and short-term declines in eGFR, combined with a greater risk of hypotension with ARNI, concerns about the risk of worsening kidney function may prevent clinicians from implementing ARNI in RASi-naïve patients in routine practice.

In this analysis of a large, older contemporary U.S. population, the initiation of ARNI in patients previously naïve to RASi was reassuringly not associated with greater hospitalization rates for AKI compared to new initiation of RASi. Similar results were observed in another claim-based analysis, which included patients previously treated with RASi as well as RASi-naïve patients.[10] Importantly, the patients included in our study were generally older and had high burdens of comorbid conditions, including more than 1 in 3 with documented chronic kidney disease stage 3 or greater at baseline. In addition, approximately a quarter of the patients had histories of AKI, a powerful predictor of

Table 2. Kidney Event Rates Among ACEi/ARB and ARNI Initiators Before and After Propensity Score Weighting (2014–2017)

	Unweighted- ARNI	Unweighted-ACEi/ARB	PS weighted- ARNI	PS-weighted ACEi/ARB
Sample size	4155	23,168	4155	23,011
Primary outcome, as-treated follow-up				
Number of events	90	582	90	614
Follow-up time in days (median, IQR)	121 (61–227)	145 (61–339)	121 (61–227)	135 (61–315)
% Cumulative incidence at 180 days (95% CI)	2.7 (2.2–3.5)	2.5 (2.2–2.7)	2.7 (2.2–3.5)	2.7 (2.4–3.1)
Primary outcome, intent-to-treat follow-up				
Number of events	141	794	141	827
Follow-up time (median, IQR)	244 (117–365)	365 (181-365)	244 (117-365)	365 (167-365)
% Cumulative incidence at 180 days (95% CI)	2.9 (2.4-3.5)	2.5 (2.3–2.7)	2.9 (2.4–3.5)	2.8 (2.5–3.1)
Secondary outcome, as-treated follow-up				
Number of events	214	1410	214	1451
Follow-up time (median, IQR)	118 (61–222)	141 (61–328)	118 (61–222)	128 (61–305)
% Cumulative incidence at 180 days (95% CI)	6.1 (5.2–7.1)	6.0 (5.7–6.4)	6.1 (5.2–7.1)	6.5 (6.0–7.1)
Secondary outcome, intent-to-treat follow-up				
Number of events	319	1973	319	2048
Follow-up time (median, IQR)	234 (109–365)	365 (160–365)	234 (109–365)	349 (146–365)
% Cumulative incidence at 180 days (95% CI)	6.0 (5.3–6.8)	6.2 (5.9–6.6)	6.0 (5.3–6.8)	6.9 (6.4–7.5)

Hospitalizations due to AKI as primary discharge diagnosis was the primary outcome; hospitalizations due to AKI as primary or secondary discharge diagnosis was the secondary outcome.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor Neprilysin inhibitor; PS, propensity score; TIA, transient ischemic attack.

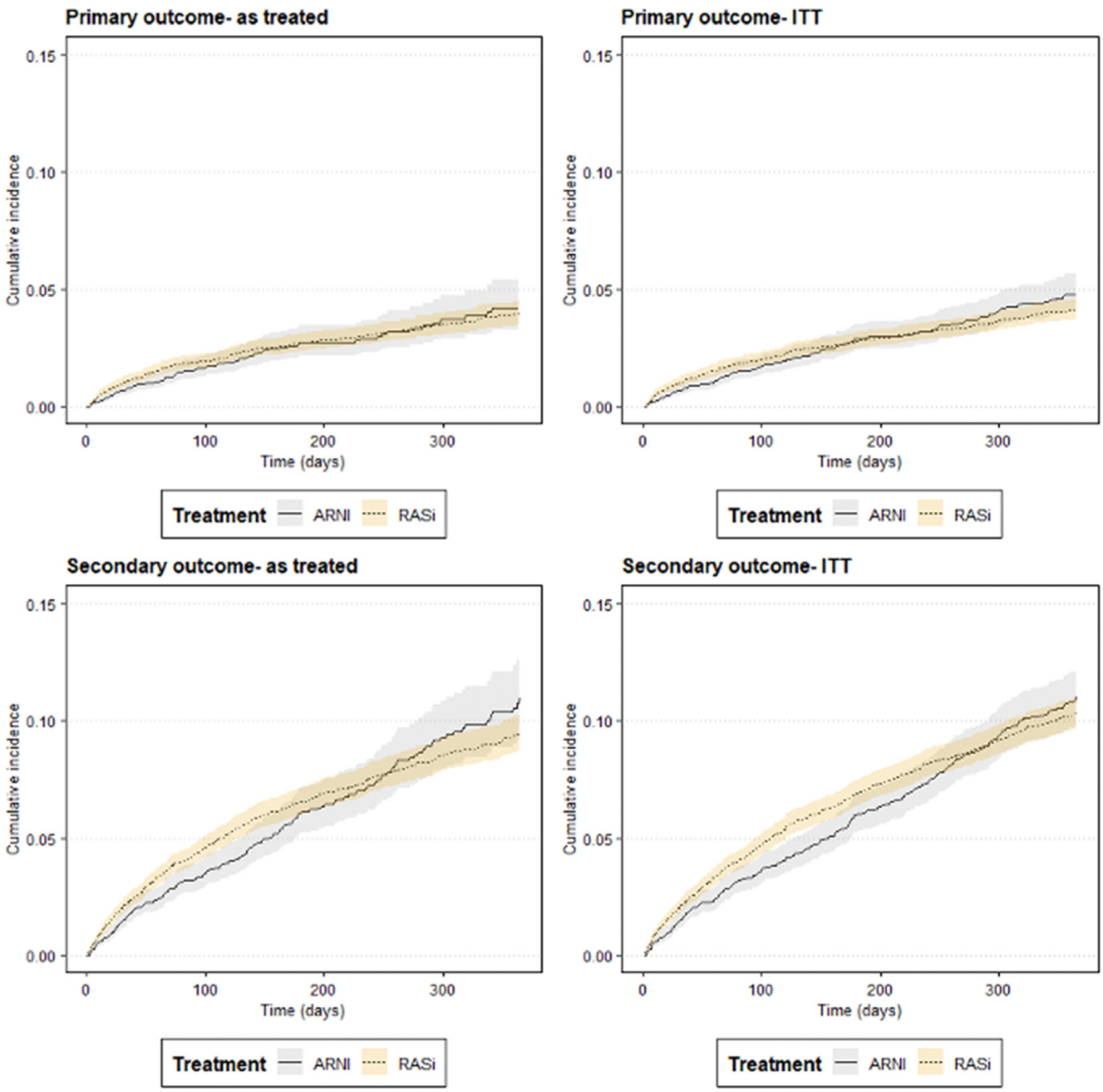


Fig. 2. Cumulative incidence plots for AKI after new initiation of RASi or ARNI in the propensity score weighted cohort. *Primary outcome, hospitalization for AKI as a primary discharge diagnosis; secondary outcome, hospitalization for AKI as a primary or secondary discharge diagnosis. AKI, acute kidney injury; ARNI, angiotensin receptor neprilysin inhibitor; RASi, renin angiotensin system inhibitor; ITT, intent-to-treat.

recurrent adverse kidney events. Our findings provide reassurance to clinicians who may be concerned about potential untoward kidney effects when considering the new initiation of ARNI in a high-risk population without prior exposure to RASi. Declines in eGFR early after initiation may be more reflective of the hemodynamic effects of ARNI on intraglomerular pressures rather than reflecting true AKI. Over time, ARNI continuation has been demonstrated to slow the decline in glomerular filtration rate compared with RASi in HfrEF, as seen in the PARADIGM-HF trial.[11]

Limitations

This study has several limitations. First, misclassification of HFrEF and AKI is possible because we relied on International Classification of Diseases codes to identify these diagnoses. To increase the specificity of AKI, we limited AKI outcomes to patients hospitalized for AKI who had AKI listed as a discharge diagnosis in the primary and secondary positions. Patients with mild AKI who were managed as outpatients were not captured in this study, nor were patients who had AKI coded in an alternative

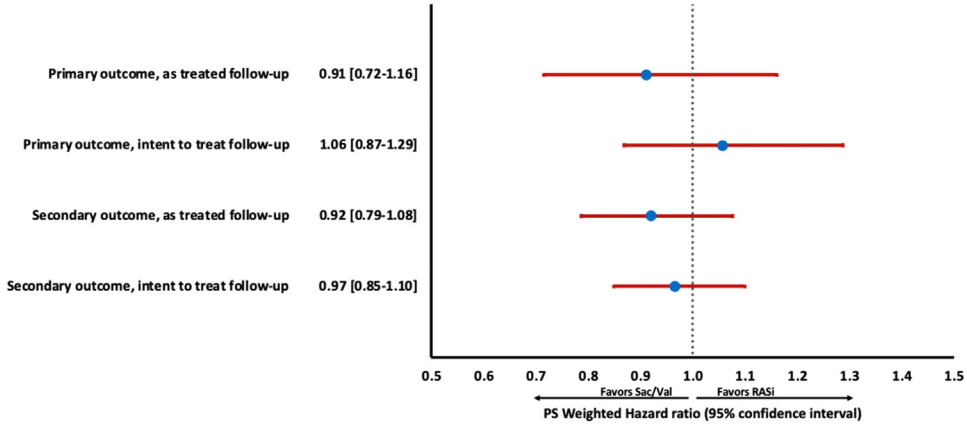


Fig. 3. Forest plot of comparative risks of developing AKI after initiation of RASi or ARNI in the propensity score weighted cohort. *Primary outcome, hospitalization for AKI as a primary discharge diagnosis; secondary outcome, hospitalization for AKI as a primary or secondary discharge diagnosis. AKI, acute kidney injury; ARNI, angiotensin receptor neprilysin inhibitor; RASi, renin angiotensin system inhibitor; sac/val, sacubitril/valsartan.

position. Medicare claims do not contain ejection fraction results, so we used a previously validated probabilistic phenotyping algorithm to restrict the cohort to patients suspected of having HfrEF, and that could lead to misclassification. Specifically, this algorithm compromises sensitivity to achieve higher predicted positive value for HFrEF, which could lower the generalizability of the findings. However, patients with HFrEF who were identified based on this probabilistic phenotyping approach based on Medicare claims are reported to resemble outcome trajectories closely, including HF worsening as well as cause-specific mortality rates reported in patients with HFrEF who were included in seminal epidemiologic studies that had more definitive phenotyping of HF.[12] Second, residual confounding due to factors not measured in administrative claims may exist. Specifically, we did not have access to granular information about serial blood pressure measurement or blood or urine markers of kidney function or injury around the time of ARNI or RASi initiation. Finally, our findings may not apply to patient populations not well represented in Medicare or to patients from more recent time periods after revised Food and Drug Administration labeling of ARNI to include patients with higher ejection- fraction ranges.

Conclusions

Among a large cohort of Medicare beneficiaries with HFrEF in the U.S., new initiation of ARNI in RASi-naïve patients was not associated with a greater risk of hospitalization due to AKI as compared to those newly initiating RASi. These results may reassure clinicians concerned about early changes in renal function when considering initiation of ARNI without prior demonstrated tolerance to RASi.

Disclosures

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