Supplementary Materials

Renin-angiotensin-aldosterone system inhibitor dosing after initiation of outpatient sodium zirconium cyclosilicate therapy: The GALVANIZE RAASi real-world evidence study

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Supplementary Table S1. RAASi dose guidelines

	Target dose[a]
Angiotensin-converting enzyme inhibitor (ACEi)	
Benazepril HCl	40 mg
Captopril	150 mg
Enalapril Maleate	40 mg
Fosinopril Sodium	40 mg
Lisinopril	40 mg
Moexipril HCl	30 mg
Perindopril Erbumine	16 mg
Quinapril HCl	20 mg
Ramipril	10 mg
Trandolapril	4 mg
Angiotensin-receptor blocker (ARB)	
Amlodipine[b]	10 mg
Azilsartan Medoxomil	80 mg
Candesartan Cilexetil	Heart failure: 32 mg No heart failure: 16 mg
Eprosartan Mesylate	800 mg
Irbesartan	300 mg
Losartan Potassium	150 mg
Olmesartan Medoxomil	40 mg
Nebivolol[b]	40 mg
Telmisartan	80 mg
Valsartan	320 mg
Angiotensin-receptor neprilysin inhibitor (ARNI)	
Sacubitril-Valsartan	194 mg (sacubitril)
Direct renin inhibitor (DRI)	
Aliskiren Fumarate	300 mg
Mineralocorticoid receptor antagonist (MRA)/aldosterone-receptor antagonist (ARA)	
Eplerenone	50 mg
Spironolactone	50 mg

Abbreviation: RAASi, renin-angiotensin-aldosterone system inhibitor.

Notes:

[a] The target dose per heart failure guidelines was used as the target dose when available; otherwise, the target dose for hypertension was used for each RAASi. If a range of target doses were recommended the highest dose was used as the target dose for this study.

[b] The following target doses were used for combination ARBs: Amlodipine-Valsartan, 10 mg; Nebivolol-Valsartan, 40 mg.

Supplementary Table S2. Baseline characteristics of hyperkalemia, CKD or HF, HF and no CKD, and resistant hypertension sub-studies

	Hyperkalemia N = 1,893	CKD or HF N = 2,668	HF and no CKD N = 119	Resistant Hypertension N = 903
Demographics				
Age on index date (years), mean ± SD	66.2 ± 14.1	66.3 ± 14.2	66.4 ± 13.4	66.8 ± 13.3
Female sex, n (%)	783 (41.4)	1,101 (41.3)	44 (37.0)	380 (42.1)
Region, n (%)				
Northeast	493 (26.0)	765 (28.7)	72 (60.5)	281 (31.1)
Midwest	266 (14.1)	373 (14.0)	22 (18.5)	130 (14.4)
South	625 (33.0)	849 (31.8)	20 (16.8)	299 (33.1)
West	473 (25.0)	632 (23.7)	5 (4.2)	178 (19.7)
Other/Unknown	36 (1.9)	49 (1.8)	0 (0.0)	15 (1.7)
Pharmacy insurance type, n (%)				
Commercial	383 (20.2)	529 (19.8)	23 (19.3)	165 (18.3)
Medicaid	437 (23.1)	579 (21.7)	17 (14.3)	198 (21.9)
Medicare Advantage	927 (49.0)	1,346 (50.4)	70 (58.8)	482 (53.4)
Unknown	146 (7.7)	214 (8.0)	9 (7.6)	58 (6.4)
Index year, n (%)				
2019	204 (10.8)	293 (11.0)	7 (5.9)	87 (9.6)
2020	449 (23.7)	598 (22.4)	25 (21.0)	218 (24.1)
2021	735 (38.8)	1,018 (38.2)	59 (49.6)	381 (42.2)
2022	505 (26.7)	759 (28.4)	28 (23.5)	217 (24.0)
CCI, mean ± SD	3.2 ± 1.9	3.2 ± 1.9	3.7 ± 2.0	3.6 ± 2.0
Comorbidities, n (%)				
Acute kidney injury	661 (34.9)	809 (30.3)	28 (23.5)	364 (40.3)
Arrythmia	38 (2.0)	64 (2.4)	19 (16.0)	41 (4.5)
Any CKD[b]	1,727 (91.2)	2,549 (95.5)	0 (0.0)	820 (90.8)
Unspecified	47 (2.5)	94 (3.5)	0 (0.0)	36 (4.0)
Stage 1	8 (0.4)	12 (0.4)	0 (0.0)	4 (0.4)
Stage 2	47 (2.5)	87 (3.3)	0 (0.0)	25 (2.8)
Stage 3	936 (49.4)	1,375 (51.5)	0 (0.0)	392 (43.4)
Stage 4	689 (36.4)	981 (36.8)	0 (0.0)	363 (40.2)
Coronary artery disease	576 (30.4)	823 (30.8)	71 (59.7)	371 (41.1)

COVID-19 (diagnosis)	116 (6.1)	161 (6.0)	11 (9.2)	60 (6.6)
Diabetes	1,509 (79.7)	2,093 (78.4)	79 (66.4)	745 (82.5)
HF	591 (31.2)	879 (32.9)	119 (100.0)	448 (49.6)
Hyperkalemia diagnosis	1,893 (100.0)	1,784 (66.9)	57 (47.9)	647 (71.7)
Hypertension	1,762 (93.1)	2,458 (92.1)	108 (90.8)	903 (100.0)
Resistant hypertension[c]	647 (34.2)	867 (32.5)	47 (39.5)	903 (100.0)
Liver disease	178 (9.4)	247 (9.3)	18 (15.1)	94 (10.4)
Peripheral vascular disease	556 (29.4%)	795 (29.8%)	68 (57.1%)	339 (37.5%)
Proteinuria	729 (38.5)	981 (36.8)	6 (5.0)	324 (35.9)
Stroke	191 (10.1)	258 (9.7)	20 (16.8)	107 (11.8)
Hyperkalemia treatments, n (%)				
SPS	241 (12.7)	276 (10.3)	12 (10.1)	105 (11.6)
Patiromer	125 (6.6)	160 (6.0)	5 (4.2)	60 (6.6)
Prior SZC use	180 (9.5)	206 (7.7)	11 (9.2)	50 (5.5)
SZC duration[d]				
Short-term	439 (23.2)	635 (23.8)	42 (35.3)	232 (25.7)
Medium-term	527 (27.8)	706 (26.5)	35 (29.4)	230 (25.5)
Long-term	927 (49.0)	1327 (49.7)	42 (35.3)	441 (48.8)
Number of potassium binders used				
0	1,540 (81.4)	2,248 (84.3)	103 (86.6)	744 (82.4)
1	340 (18.0)	404 (15.1)	15 (12.6)	153 (16.9)
2	13 (0.7)	16 (0.6)	1 (0.8)	6 (0.7)
Any temporizing agent	93 (4.9)	118 (4.4)	1 (0.8)	42 (4.7)
Any diuretic	1,194 (63.1)	1,640 (61.5)	83 (69.7)	903 (100.0)
Any RAASi during baseline, n (%)	1,633 (86.3)	2,278 (85.4)	100 (84.0)	874 (96.8)
Baseline RAASi dose				
Suboptimal (<50% of target dose)	604 (31.9)	865 (32.4)	38 (31.9)	252 (27.9)
Optimal (≥50% of target dose)	1,029 (54.4)	1,413 (53.0)	62 (52.1)	622 (68.9)
Sub-maximized (<100% of target dose)	1,193 (63.0)	1,690 (63.3)	77 (64.7)	591 (65.4)
Maximized (≥100% of target dose)	440 (23.2)	588 (22.0)	23 (19.3)	283 (31.3)
RAASi use at index, n (%)				
ACEi	911 (48.1)	1,255 (47.0)	42 (35.3)	324 (35.9)
ARB	833 (44.0)	1,210 (45.4)	59 (49.6)	436 (48.3)
DRI	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
ARNI	82 (4.3)	140 (5.2)	45 (37.8)	87 (9.6)

MRA	203 (10.7)	283 (10.6)	28 (23.5)	205 (22.7)
Index RAASi dose				
Suboptimal (<50% of target dose)	763 (40.3)	1,075 (40.3)	48 (40.3)	283 (31.3)
Optimal (≥50% of target dose)	1,130 (59.7)	1,593 (59.7)	71 (59.7)	620 (68.7)
Sub-maximized (<100% of target dose)	1,436 (75.9)	2,039 (76.4)	93 (78.2)	634 (70.2)
Maximized (≥100% of target dose)	457 (24.1)	629 (23.6)	26 (21.8)	269 (29.8)
Other medication use, n (%)				
Beta blockers	1,126 (59.5)	1,593 (59.7)	102 (85.7)	802 (88.8)
NSAIDs	225 (11.9)	312 (11.7)	18 (15.1)	117 (13.0)
SGLT2i	220 (11.6)	359 (13.5)	36 (30.3)	125 (13.8)
Vasodilators	324 (17.1)	455 (17.1)	13 (10.9)	313 (34.7)
Central alpha-2 receptor agonists	139 (7.3)	186 (7.0)	2 (1.7)	127 (14.1)
Calcium channel blockers	978 (51.7)	1,354 (50.7)	31 (26.1)	631 (69.9)
All-cause HRU, n (%)				
Any all-cause hospitalizations	587 (31.0)	710 (26.6)	43 (36.1)	337 (37.3)
Any all-cause emergency department visits	547 (28.9)	706 (26.5)	37 (31.1)	271 (30.0)
Any all-cause outpatient visits	1,678 (88.6)	2,355 (88.3)	108 (90.8)	794 (87.9)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin-receptor neprilysin inhibitor; CCI, Charlson comorbidity index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; DRI, direct renin inhibitor; ESKD, end-stage kidney disease; HF, heart failure; HRU, healthcare resource utilization; MRA, mineralocorticoid receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SPS, sodium polystyrene sulfonate; SZC, sodium zirconium cyclosilicate.

Notes:

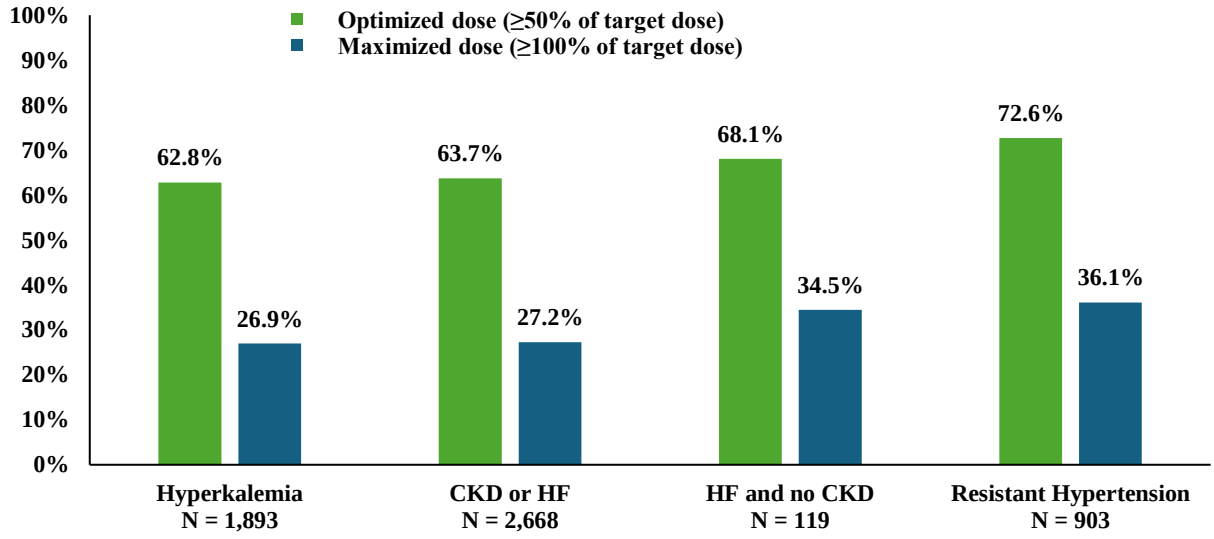
[a] Baseline characteristics were assessed during the 6-month baseline period prior to the index date.

[b] Patients flagged with more than one CKD stage or ESKD were assigned to the most severe disease flag based on the following ranking: ESKD > CKD stage 5 > CKD stage 5 or ESKD > CKD stage 4 > CKD stage 3 > CKD stage 2 > CKD stage 1 > CKD unspecified.

[c] Resistant hypertension was defined as the presence of a hypertension diagnosis code and the use of three or more classes of anti-hypertensive medications, including a diuretic.

[d] Patients were classified by the total duration of observed SZC use as short-term SZC (≤30 days supply), intermediate-term SZC (31-90 days supply) or long-term SZC (>90 days supply) users.

Supplementary Figure S1. Proportion of patients with an optimized or maximized RAASi dose during the follow-up period among the hyperkalemia, CKD or HF, HF and no CKD, and resistant hypertension sub-studies



Abbreviations: CKD, chronic kidney disease; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitor.