SUPPLEMENTARY MATERIALS

Real-World Modifications of Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Hyperkalemia Initiating Sodium Zirconium Cyclosilicate Therapy: The OPTIMIZE I Study

Authors:

Abiy Agiro,[1]* abiy.agiro@astrazeneca.com
Alpesh Amin,[2] anamin@hs.uci.edu
Erin E. Cook,[3] Erin.cook@analysisgroup.com
Fan Mu,[3] fan.mu@analysisgroup.com
Jingyi Chen,[3] Jingyi.chen@analysisgroup.com
Pooja Desai,[1] pooja.desai@astrazeneca.com
Yemmie Oluwatosin,[1] yosolajes@gmail.com
Charles V. Pollack, Jr,[4] cvpollack@gmail.com

Affiliations:

[1]AstraZeneca, 1800 Concord Pike, Wilmington, DE 19850, United States
[2]University of California Irvine, Irvine, CA 92697, United States
[3]Analysis Group, Inc., 111 Huntington Ave, 14th Floor, Boston, MA 02199, United States
[4]University of Mississippi, Jackson, MS 38677, United States

***Corresponding author:**

Abiy Agiro
Astra Zeneca, US Medical Affairs
1800 Concord Pike, Wilmington, DE 19850
Tel: 302-886-1898
abiy.agiro@astrazeneca.com

Supplementary Table 1. RAASi Modifications After SZC Initiation Among Additional Subgroups

		Optimized dose		Non-optimized dose	
Sample	**N**	**Maintained same RAASi dose**	**Increased RAASi dose**	**Discontinued RAASi therapy**	**Decreased RAASi dose**
Stage 3 CKD[1]	171	118 (69.0%)	19 (11.1%)	23 (13.5%)	11 (6.4%)
Stage 4 CKD[1]	174	121 (69.5%)	12 (6.9%)	31 (17.8%)	10 (5.7%)
Stage 5 CKD[1]	33	24 (72.7%)	2 (6.1%)	4 (12.1%)	3 (9.1%)
Stage 5 CKD or ESKD[2]	150	106 (70.7%)	6 (4.0%)	30 (20.0%)	8 (5.3%)
ESKD[3]	117	82 (70.1%)	4 (3.4%)	26 (22.2%)	5 (4.3%)
HF	149	95 (63.8%)	19 (12.8%)	29 (19.5%)	6 (4.0%)
Hypertension	538	376 (69.9%)	40 (7.4%)	92 (17.1%)	30 (5.6%)

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitors; SZC, sodium zirconium cyclosilicate

[1]CKD Stage 3-5 was s assessed using ICD-10 diagnosis codes.

[2]Stage 5 CKD or ESKD includes all patients with either Stage 5 CKD or ESKD.

[3] ESKD was assessed using ICD-10 diagnosis codes for ESKD or an ICD-10 diagnosis code for CKD stage 5 + a code for dialysis.

Supplementary Table 2. Baseline Characteristics of Patients Without ESKD Initiating SZC[1]

	All patients (N=472)	Optimized RAASi[2] (N=370)	Did not optimize RAASi[3] (N=102)	p-value
Demographics				
Age on index date (years), mean ± SD	62.36 ± 12.60	62.03 ± 12.60	63.54 ± 12.58	0.39
Female gender, n (%)	162 (34.3%)	136 (36.8%)	26 (25.5%)	< 0.05*
Claims payer, n (%)				0.14
Commercial or unknown	218 (46.2%)	175 (47.3%)	43 (42.2%)	
Medicaid	102 (21.6%)	84 (22.7%)	18 (17.6%)	
Medicare Advantage	152 (32.2%)	111 (30.0%)	41 (40.2%)	
Region, n (%)				0.78
Midwest	62 (13.1%)	50 (13.5%)	12 (11.8%)	
Northeast	117 (24.8%)	89 (24.1%)	28 (27.5%)	
South	169 (35.8%)	135 (36.5%)	34 (33.3%)	
West	119 (25.2%)	91 (24.6%)	28 (27.5%)	
Other	5 (1.1%)	5 (1.4%)	0 (0.0%)	
HK				
HK diagnosis, n (%)	291 (61.7%)	221 (59.7%)	70 (68.6%)	0.13
Comorbidities, n (%)				
CKD stages 3-5	398 (84.3%)	314 (84.9%)	84 (82.4%)	0.64
Congestive heart failure	101 (21.4%)	80 (21.6%)	21 (20.6%)	0.93
Coronary artery disease	122 (25.8%)	92 (24.9%)	30 (29.4%)	0.42
Diabetes	336 (71.2%)	263 (71.1%)	73 (71.6%)	1.00
Hypertension	427 (90.5%)	336 (90.8%)	91 (89.2%)	0.77
Prior Treatment, n (%)				
HK treatments				
Patiromer	88 (18.6%)	70 (18.9%)	18 (17.6%)	0.88
Sodium polystyrene sulfonate	77 (16.3%)	55 (14.9%)	22 (21.6%)	0.14
Loop diuretics	201 (42.6%)	153 (41.4%)	48 (47.1%)	0.36
Thiazides and thiazide-like diuretics	88 (18.6%)	69 (18.6%)	19 (18.6%)	1.00
Other treatments				
Beta blockers	281 (59.5%)	220 (59.5%)	61 (59.8%)	1.00
NSAIDs	40 (8.5%)	33 (8.9%)	7 (6.9%)	0.65
All-Cause HRU				
Any inpatient stays, n (%)	103 (21.8%)	76 (20.5%)	27 (26.5%)	0.25
Number of inpatient stays, mean ± SD	0.37 ± 0.88	0.33 ± 0.78	0.51 ± 1.16	0.18
Any ED visits, n (%)	128 (27.1%)	91 (24.6%)	37 (36.3%)	< 0.05*
Number of ED visits, mean ± SD	0.41 ± 0.87	0.36 ± 0.84	0.59 ± 0.97	< 0.05*
Any outpatient visits, n (%)	434 (91.9%)	344 (93.0%)	90 (88.2%)	0.18
Number of outpatient visits, mean ± SD	13.38 ± 14.75	12.98 ± 13.59	14.85 ± 18.35	0.53

Abbreviations: CKD, chronic kidney disease; ED, emergency department; ESKD, end-stage kidney disease; HK, hyperkalemia; HRU, healthcare resource utilization; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SZC, sodium zirconium cyclosilicate

[1]Baseline was the 6-month period prior to the initiation of SZC

[2]Optimized RAASi included patients with the same dose or with an up-titration

[3]Non-optimized RAASi included patients who discontinued or with a down-titration

Supplemental Table 3. Baseline Characteristics of Patients With CKD Initiating SZC[1]

	All patients (N=398)	Optimized RAASi[2] (N=314)	Did not optimize RAASi[3] (N=84)	p-value
Demographics				
Age on index date (years), mean ± SD	62.28 ± 12.39	62.05 ± 12.39	63.13 ± 12.42	0.54
Female gender, n (%)	139 (34.9%)	121 (38.5%)	18 (21.4%)	< 0.01*
Claims payer, n (%)				0.41
Commercial or unknown	190 (47.7%)	152 (48.4%)	38 (45.2%)	
Medicaid	84 (21.1%)	69 (22.0%)	15 (17.9%)	
Medicare Advantage	124 (31.2%)	93 (29.6%)	31 (36.9%)	
Region, n (%)				0.95
Midwest	55 (13.8%)	44 (14.0%)	11 (13.1%)	
Northeast	90 (22.6%)	71 (22.6%)	19 (22.6%)	
South	150 (37.7%)	117 (37.3%)	33 (39.3%)	
West	98 (24.6%)	77 (24.5%)	21 (25.0%)	
Other	5 (1.3%)	5 (1.6%)	0 (0.0%)	
HK				
HK diagnosis, n (%)	267 (67.1%)	204 (65.0%)	63 (75.0%)	0.11
Comorbidities, n (%)				
Congestive heart failure	87 (21.9%)	69 (22.0%)	18 (21.4%)	1.00
Coronary artery disease	110 (27.6%)	81 (25.8%)	29 (34.5%)	0.15
Diabetes	311 (78.1%)	243 (77.4%)	68 (81.0%)	0.58
Hypertension	387 (97.2%)	304 (96.8%)	83 (98.8%)	0.47
Prior Treatment, n (%)				
HK treatments				
Patiromer	73 (18.3%)	58 (18.5%)	15 (17.9%)	1.00
Sodium polystyrene sulfonate	67 (16.8%)	50 (15.9%)	17 (20.2%)	0.44
Loop diuretics	176 (44.2%)	134 (42.7%)	42 (50.0%)	0.28
Thiazides and thiazide-like diuretics	78 (19.6%)	61 (19.4%)	17 (20.2%)	0.99
Other treatments				
Beta blockers	239 (60.1%)	185 (58.9%)	54 (64.3%)	0.44
NSAIDs	32 (8.0%)	27 (8.6%)	5 (6.0%)	0.57
All-Cause HRU				
Any inpatient stays, n (%)	94 (23.6%)	69 (22.0%)	25 (29.8%)	0.18
Number of inpatient stays, mean ± SD	0.40 ± 0.92	0.36 ± 0.82	0.56 ± 1.20	0.13
Any ED visits, n (%)	115 (28.9%)	83 (26.4%)	32 (38.1%)	0.05
Number of ED visits, mean ± SD	0.44 ± 0.91	0.40 ± 0.89	0.61 ± 0.98	< 0.05*
Any outpatient visits, n (%)	392 (98.5%)	310 (98.7%)	82 (97.6%)	0.61
Number of outpatient visits, mean ± SD	14.56 ± 15.01	13.89 ± 13.62	17.04 ± 19.23	0.13

Abbreviations: CKD, chronic kidney disease; ED, emergency department; ESKD, end-stage kidney disease; HK, hyperkalemia; HRU, healthcare resource utilization; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SZC, sodium zirconium cyclosilicate

[1]Baseline was the 6-month period prior to the initiation of SZC

[2]Optimized RAASi included patients with the same dose or with an up-titration

[3]Non-optimized RAASi included patients who discontinued or with a down-titration

Supplemental Table 4. Baseline Characteristics of Patients With CKD + Diabetes Initiating SZC[1]

	All patients (N=311)	Optimized RAASi[2] (N=243)	Did not optimize RAASi[3] (N=68)	p-value
Demographics				
Age on index date (years), mean ± SD	62.69 ± 11.77	62.73 ± 11.66	62.54 ± 12.23	0.95
Female gender, n (%)	110 (35.4%)	96 (39.5%)	14 (20.6%)	< 0.01*
Claims payer, n (%)				0.62
Commercial or unknown	139 (44.7%)	109 (44.9%)	30 (44.1%)	
Medicaid	66 (21.2%)	54 (22.2%)	12 (17.6%)	
Medicare Advantage	106 (34.1%)	80 (32.9%)	26 (38.2%)	
Region, n (%)				0.95
Midwest	41 (13.2%)	33 (13.6%)	8 (11.8%)	
Northeast	71 (22.8%)	54 (22.2%)	17 (25.0%)	
South	114 (36.7%)	89 (36.6%)	25 (36.8%)	
West	81 (26.0%)	63 (25.9%)	18 (26.5%)	
Other	4 (1.3%)	4 (1.6%)	0 (0.0%)	
HK				
HK diagnosis, n (%)	210 (67.5%)	161 (66.3%)	49 (72.1%)	0.45
Comorbidities, n (%)				
Congestive heart failure	75 (24.1%)	60 (24.7%)	15 (22.1%)	0.77
Coronary artery disease	94 (30.2%)	70 (28.8%)	24 (35.3%)	0.38
Hypertension	307 (98.7%)	239 (98.4%)	68 (100.0%)	0.58
Prior Treatment, n (%)				
HK treatments				
Patiromer	52 (16.7%)	40 (16.5%)	12 (17.6%)	0.96
Sodium polystyrene sulfonate	50 (16.1%)	37 (15.2%)	13 (19.1%)	0.56
Loop diuretics	150 (48.2%)	114 (46.9%)	36 (52.9%)	0.46
Thiazides and thiazide-like diuretics	69 (22.2%)	55 (22.6%)	14 (20.6%)	0.85
Other treatments				
Beta blockers	197 (63.3%)	151 (62.1%)	46 (67.6%)	0.49
NSAIDs	27 (8.7%)	25 (10.3%)	2 (2.9%)	0.08
All-Cause HRU				
Any inpatient stays, n (%)	81 (26.0%)	61 (25.1%)	20 (29.4%)	0.58
Number of inpatient stays, mean ± SD	0.44 ± 0.95	0.41 ± 0.87	0.56 ± 1.19	0.42
Any ED visits, n (%)	92 (29.6%)	67 (27.6%)	25 (36.8%)	0.19
Number of ED visits, mean ± SD	0.48 ± 0.99	0.44 ± 0.98	0.62 ± 1.04	0.13
Any outpatient visits, n (%)	305 (98.1%)	239 (98.4%)	66 (97.1%)	0.62
Number of outpatient visits, mean ± SD	15.46 ± 16.24	14.94 ± 14.87	17.34 ± 20.44	0.54

Abbreviations: CKD, chronic kidney disease; ED, emergency department; ESKD, end-stage kidney disease; HK, hyperkalemia; HRU, healthcare resource utilization; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SZC, sodium zirconium cyclosilicate

[1]*Baseline was the 6-month period prior to the initiation of SZC*

[2]*Optimized RAASi included patients with the same dose or with an up-titration*

[3]*Non-optimized RAASi included patients who discontinued or with a down-titration*

Supplemental Table 5. RAASi Therapy at Initiation of SZC[1] Among Patients Without ESKD, With CKD, and With CKD + Diabetes

	All patients without ESKD				All patients with stage 3-5 CKD				All patients with stage 3-5 CKD + Diabetes			
	All patients (N=472)	**Optimized RAASi[2] (N=370)**	**Did not optimize RAASi[3] (N=102)**	**p-value**	**All patients (N=398)**	**Optimized RAASi[2] (N=314)**	**Did not optimize RAASi[3] (N=84)**	**p-value**	**All patients (N=311)**	**Optimized RAASi[2] (N=243)**	**Did not optimize RAASi[3] (N=68)**	**p-value**
RAASi	444 (94.1%)	349 (94.3%)	95 (93.1%)	0.83	375 (94.2%)	297 (94.6%)	78 (92.9%)	0.73	293 (94.2%)	228 (93.8%)	65 (95.6%)	0.77
ACEi	245 (51.9%)	192 (51.9%)	53 (52.0%)	1.00	214 (53.8%)	167 (53.2%)	47 (56.0%)	0.74	164 (52.7%)	124 (51.0%)	40 (58.8%)	0.32
ARB	189 (40.0%)	150 (40.5%)	39 (38.2%)	0.76	154 (38.7%)	125 (39.8%)	29 (34.5%)	0.45	123 (39.5%)	100 (41.2%)	23 (33.8%)	0.34
ARNI	19 (4.0%)	15 (4.1%)	4 (3.9%)	1.00	12 (3.0%)	9 (2.9%)	3 (3.6%)	0.72	11 (3.5%)	8 (3.3%)	3 (4.4%)	0.71
DRI	1 (0.2%)	1 (0.3%)	0 (0.0%)	1.00	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
MRA	59 (12.5%)	49 (13.2%)	10 (9.8%)	0.45	46 (11.6%)	38 (12.1%)	8 (9.5%)	0.64	35 (11.3%)	30 (12.3%)	5 (7.4%)	0.35

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CKD, chronic kidney disease; DRI, direct renin inhibitor; ESKD, end-stage kidney disease MRA, mineralocorticoid receptor antagonist, RAASi, renin-angiotensin-aldosterone system inhibitor; RAASi, renin-angiotensin system inhibitor

[1]Patients could be taking monotherapy or combination therapy so the percentages may not add to 100%

[2]Optimized RAASi included patients with the same dose or with an up-titration

[3]Non-optimized RAASi included patients who discontinued or with a down-titration