

SUPPLEMENTARY MATERIAL

Hyperkalemia Recurrence Following Medical Nutrition Therapy in Patients with Stage 3–4 Chronic Kidney Disease: The REVOLUTIONIZE I Real- World Study

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Supplementary Table S1 Patient disposition

| Step | Study cohort | N |
|---|---|-------------|
| 0 | Total number of patients in the TriNetX Dataworks USA Network | 90,924,420 |
| 1 | MNT during the study period (01 January 2019 to 31 October 2022) | 399,254 |
| 2 | Age \geq 18 years at the time of MNT | 289,451 |
| 3 | Serum K^+ $>$ 5.0 mmol/L within 30 days prior to MNT | 24,357 |
| 4 | HK diagnosis within 2 years pre-index ^a | 10,584 |
| 5 | CKD diagnosis within 2 years pre-index ^a | 6473 |
| 6 | CKD stage 3–4 (eGFR \geq 15 and $<$ 60 mL/min/1.73 m ²) within 12 months pre-index ^a | 2870 |
| 7 | \geq 1 healthcare encounter between 12–24 months pre-index ^a | 2246 |
| 8 | No outpatient record for a potassium binder within 182 days pre-index ^a | 2048 |
| Total number of patients in the study cohort | | 2048 |

^aThe index date is the date of first MNT plus 7 days.

CKD chronic kidney disease, eGFR estimated glomerular filtration rate, HK hyperkalemia, K^+ potassium, MNT medical nutrition therapy

Supplementary Table S2 Patient attrition

| | Total study cohort (N = 2048) |
|---|-------------------------------|
| Time to first censoring event, days | |
| Mean \pm SD | 148.3 (59.9) |
| Median (IQR) | 180 (159–180) |
| Patients censored at each post-index ^a analysis interval (cumulative), n (%) | |
| 1 month | 258 (12.6) |
| 2 months | 321 (15.7) |
| 3 months | 377 (18.4) |
| 4 months | 425 (20.8) |
| 5 months | 488 (23.8) |
| 6 months | 545 (26.6) |
| Reason for censoring, n (%) | |
| Index period end date (October 31, 2022) | 116 (5.7) |
| Death | 287 (14.0) |
| Outpatient K ⁺ binder use | 142 (6.9) |
| End of 6-month follow-up period | 1503 (73.4) |
| Total | 2048 (100.0) |

^aThe index date is the date of first MNT plus 7 days.

IQR interquartile range, *K⁺* potassium, *MNT* medical nutrition therapy, *SD* standard deviation

Supplementary Table S3 Baseline patient demographics, clinical characteristics, treatments, and healthcare resource utilization in additional patient subgroups

| | Patient subgroup | | | | | |
|--|----------------------------|---------------------------|--|-------------------------------------|-------------------------------|---|
| | Hypertension (n = 1968) | CKD stage 3a (n = 532) | HF and stage 3a/3b CKD (n = 665) | HF and stage 3a CKD (n = 294) | Type 2 diabetes (n = 1334) | Moderate-to- severe HK ^a (n = 839) |
| Age at index, years | | | | | | |
| Mean ± SD | 66.1 ± 14.0 | 66.6 ± 13.6 | 68.1 ± 13.0 | 67.9 ± 12.9 | 66.6 ± 12.8 | 64.9 ± 14.7 |
| Median (IQR) | 68 (59, 76) | 68 (59, 76) | 69 (60, 78) | 69 (59, 77) | 68 (59, 76) | 67 (57, 75) |
| Sex, n (%) | | | | | | |
| Female | 787 (40.0) | 189 (35.5) | 252 (37.9) | 100 (34.0) | 546 (40.9) | 329 (39.2) |
| Male | 1181 (60.0) | 343 (64.5) | 413 (62.1) | 194 (66.0) | 788 (59.1) | 510 (60.8) |
| Race, n (%) | | | | | | |
| Asian | 65 (3.3) | 16 (3.0) | 10 (1.5) | 3 (1.0) | 47 (3.5) | 30 (3.6) |
| Black or African American | 574 (29.2) | 156 (29.3) | 197 (29.6) | 95 (32.3) | 413 (31.0) | 260 (31.0) |
| Other | 10 (0.5) | 2 (0.4) | 3 (0.5) | 2 (0.7) | 10 (0.7) | 5 (0.6) |
| Unknown | 118 (6.0) | 28 (5.3) | 36 (5.4) | 19 (6.5) | 81 (6.1) | 64 (7.6) |
| White | 1201 (61.0) | 330 (62.0) | 419 (63.0) | 175 (59.5) | 783 (58.7) | 480 (57.2) |
| Ethnicity, n (%) | | | | | | |
| Hispanic or Latino | 77 (3.9) | 22 (4.1) | 29 (4.4) | 18 (6.1) | 62 (4.6) | 35 (4.2) |
| Not Hispanic or Latino | 1783 (90.6) | 482 (90.6) | 609 (91.6) | 265 (90.1) | 1193 (89.4) | 765 (91.2) |
| Unknown | 108 (5.5) | 28 (5.3) | 27 (4.1) | 11 (3.7) | 79 (5.9) | 39 (4.6) |
| US Census region, n (%) | | | | | | |
| Midwest | 66 (3.4) | 21 (3.9) | 16 (2.4) | 12 (4.1) | 62 (4.6) | 23 (2.7) |
| Northeast | 1756 (89.2) | 477 (89.7) | 605 (91.0) | 265 (90.1) | 1161 (87.0) | 755 (90.0) |
| South | 120 (6.1) | 27 (5.1) | 34 (5.1) | 12 (4.1) | 90 (6.7) | 50 (6.0) |
| West | 26 (1.3) | 7 (1.3) | 10 (1.5) | 5 (1.7) | 21 (1.6) | 11 (1.3) |
| Serum K⁺ (mmol/L), n (%) | | | | | | |
| Mean ± SD | 5.5 ± 0.5 | 5.5 ± 0.5 | 5.5 ± 0.6 | 5.5 ± 0.6 | 5.5 ± 0.5 | 5.9 ± 0.6 |
| Median (IQR) | 5.4 (5.2, 5.7) | 5.4 (5.2, 5.7) | 5.3 (5.2, 5.6) | 5.4 (5.2, 5.6) | 5.4 (5.2, 5.7) | 5.7 (5.6, 6.0) |
| >5.0 to < 5.5 (mild HK) | 1156 (58.7) | 314 (59.0) | 400 (60.2) | 179 (60.9) | 794 (59.5) | 0 (0.0) |
| 5.5 to < 6.0 (moderate HK) | 559 (28.4) | 157 (29.5) | 182 (27.4) | 81 (27.6) | 372 (27.9) | 580 (69.1) |

| | | | | | | |
|--|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| 6.0 to < 6.5 (severe HK) | 166 (8.4) | 37 (7.0) | 51 (7.7) | 19 (6.5) | 109 (8.2) | 170 (20.3) |
| ≥6.5 (very severe HK) | 87 (4.4) | 24 (4.5) | 32 (4.8) | 15 (5.1) | 59 (4.4) | 89 (10.6) |
| eGFR (mL/min/1.73 m²)^a, n (%) | | | | | | |
| Mean ± SD | 34.6 ± 12.8 | 51.8 ± 4.3 | 43.5 ± 8.4 | 51.6 ± 4.3 | 34.7 ± 12.9 | 34.4 ± 13.0 |
| Median (IQR) | 33.4 (23.5, 45.5) | 51.5 (48.0, 55.6) | 43.2 (36.4, 50.2) | 51.0 (47.7, 55.6) | 33.8 (23.4, 45.6) | 33.0 (22.6, 45.6) |
| 15–29 (stage 4 CKD) | 826 (42.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 557 (41.8) | 357 (42.6) |
| 30–44 (stage 3b CKD) | 628 (31.9) | 0 (0.0) | 371 (55.8) | 0 (0.0) | 430 (32.2) | 264 (31.5) |
| 45–59 (stage 3a CKD) | 514 (26.1) | 532 (100.0) | 294 (44.2) | 294 (100.0) | 347 (26.0) | 218 (26.0) |
| Comorbidities, n (%) | | | | | | |
| CCI score, mean ± SD | 9.40 ± 3.87 | 9.52 ± 3.83 | 10.48 ± 3.78 | 10.4 ± 3.58 | 10.4 ± 3.5 | 9.09 ± 3.91 |
| Hypertension | 1968 (100.0) | 514 (96.6) | 649 (97.6) | 290 (98.6) | 1306 (97.9) | 812 (96.8) |
| HF | 1151 (58.5) | 294 (55.3) | 665 (100.0) | 294 (100.0) | 815 (61.1) | 469 (55.9) |
| Type 2 diabetes | 1306 (66.4) | 347 (65.2) | 464 (69.8) | 205 (69.7) | 1334 (100.0) | 540 (64.4) |
| Pharmacotherapy, n (%) | | | | | | |
| RAASi | 881 (44.8) | 258 (48.5) | 340 (51.1) | 165 (56.1) | 642 (48.1) | 351 (41.8) |
| MRA | 262 (13.3) | 80 (15.0) | 139 (20.9) | 63 (21.4) | 189 (14.2) | 109 (13.0) |
| ACEI | 475 (24.1) | 134 (25.2) | 167 (25.1) | 81 (27.6) | 365 (27.4) | 192 (22.9) |
| ARB | 460 (23.4) | 138 (25.9) | 200 (30.1) | 97 (33.0) | 319 (23.9) | 179 (21.3) |
| ARNI | 143 (7.3) | 50 (9.4) | 84 (12.6) | 44 (15.0) | 99 (7.4) | 58 (6.9) |
| Loop diuretic | 1413 (71.8) | 364 (68.4) | 561 (84.4) | 244 (83.0) | 958 (71.8) | 612 (72.9) |
| Thiazide diuretic | 507 (25.8) | 119 (22.4) | 187 (28.1) | 76 (25.9) | 352 (26.4) | 217 (25.9) |
| HRU within 12 months pre-index, n (%) | | | | | | |
| Outpatient healthcare visit | 1920 (97.6) | 518 (97.4) | 650 (97.7) | 288 (98.0) | 1293 (96.9) | 818 (97.5) |
| ED visit | 509 (25.9) | 141 (26.5) | 202 (30.4) | 89 (30.3) | 385 (28.9) | 208 (24.8) |
| Inpatient hospitalization | 1713 (87.0) | 451 (84.8) | 596 (89.6) | 264 (89.8) | 1135 (85.1) | 743 (88.6) |

^aSerum K⁺ ≥5.5 mmol/L for the index HK episode.

^bBased on the last serum creatinine measured pre-index and calculated using the Mayo Clinic quadratic equation.

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *CCI* Charlson Comorbidity Index, *CKD* chronic kidney disease, *ED* emergency department, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *HK* hyperkalemia, *HRU* healthcare resource utilization, *IQR* interquartile range, *K⁺* potassium, *MRA* mineralocorticoid receptor antagonist, *RAASi* renin-angiotensin-aldosterone system inhibitor, *SD* standard deviation, *US* United States.

Supplementary Table S4 Hyperkalemia recurrence and healthcare resource utilization following medical nutrition therapy in additional patient subgroups

| | Patient subgroup | | | | | |
|--|------------------------------------|-----------------------------------|---------------------------------------|---|--|---|
| | Hypertension (<i>n</i> = 1968) | Stage 3a CKD (<i>n</i> = 532) | Type 2 diabetes (<i>n</i> = 1334) | Heart failure and stage 3a/3b CKD (<i>n</i> = 665) | Heart failure and stage 3a CKD (<i>n</i> = 294) | Moderate-to- severe HK ^a (<i>n</i> = 839) |
| Patients with ≥6 months of follow-up | 1444 | 417 | 978 | 496 | 236 | 628 |
| HK recurrence by analysis interval^b, <i>n</i> (%) | | | | | | |
| 0–1 month | 642/1722 (37.3) | 160/485 (33.0) | 430/1171 (36.7) | 224/596 (37.6) | 90/271 (33.2) | 286/738 (38.8) |
| 0–2 months | 726/1661 (43.7) | 188/470 (40.0) | 484/1130 (42.8) | 244/569 (42.9) | 104/258 (40.3) | 327/716 (45.7) |
| 0–3 months | 766/1608 (47.6) | 202/456 (44.3) | 516/1100 (46.9) | 253/549 (46.1) | 111/251 (44.2) | 332/691 (48.0) |
| 0–4 months | 798/1561 (51.1) | 217/443 (49.0) | 538/1067 (50.4) | 266/530 (50.2) | 123/247 (49.8) | 350/675 (51.9) |
| 0–5 months | 807/1500 (53.8) | 219/431 (50.8) | 545/1021 (53.4) | 268/517 (51.8) | 124/242 (51.2) | 354/648 (54.6) |
| 0–6 months | 810/1444 (56.1) | 221/417 (53.0) | 549/978 (56.1) | 266/496 (53.6) | 124/236 (52.5) | 359/628 (57.2) |
| Number of HK recurrences^c, <i>n</i> (%) | | | | | | |
| 0 | 634 (43.9) | 196 (47.0) | 429 (43.9) | 230 (46.4) | 112 (47.5) | 269 (42.8) |
| 1 | 341 (23.6) | 107 (25.7) | 237 (24.2) | 119 (24.0) | 63 (26.7) | 162 (25.8) |
| 2 | 191 (13.2) | 47 (11.3) | 117 (12.0) | 50 (10.1) | 22 (9.3) | 81 (12.9) |
| 3 | 85 (5.9) | 19 (4.6) | 61 (6.2) | 35 (7.1) | 14 (5.9) | 30 (4.8) |
| 4 | 78 (5.4) | 19 (4.6) | 56 (5.7) | 28 (5.6) | 10 (4.2) | 35 (5.6) |
| 5 | 47 (3.3) | 11 (2.6) | 34 (3.5) | 13 (2.6) | 5 (2.1) | 15 (2.4) |
| ≥6 | 68 (4.7) | 18 (4.3) | 44 (4.5) | 21 (4.2) | 10 (4.2) | 36 (5.7) |
| Change in serum K⁺ from baseline to first HK recurrence (mmol/L) | | | | | | |
| Mean ± SD | −0.1 ± 0.6 | −0.1 ± 0.5 | −0.1 ± 0.6 | −0.1 ± 0.6 | −0.1 ± 0.6 | −0.5 ± 0.6 |
| Serum K⁺ at recurrence (mmol/L)^d, mean ± SD | | | | | | |
| First | 5.4 ± 0.4 | 5.4 ± 0.3 | 5.4 ± 0.4 | 5.4 ± 0.4 | 5.3 ± 0.3 | 5.4 ± 0.4 |
| Second | 5.4 ± 0.4 | 5.3 ± 0.3 | 5.4 ± 0.4 | 5.3 ± 0.3 | 5.3 ± 0.2 | 5.4 ± 0.4 |
| Third | 5.5 ± 0.5 | 5.4 ± 0.4 | 5.5 ± 0.6 | 5.4 ± 0.4 | 5.5 ± 0.4 | 5.6 ± 0.6 |
| Fourth | 5.5 ± 0.4 | 5.4 ± 0.4 | 5.4 ± 0.4 | 5.5 ± 0.5 | 5.4 ± 0.2 | 5.5 ± 0.4 |
| Fifth | 5.4 ± 0.3 | 5.4 ± 0.3 | 5.4 ± 0.4 | 5.4 ± 0.3 | 5.4 ± 0.3 | 5.4 ± 0.4 |
| Sixth | 5.4 ± 0.3 | 5.4 ± 0.4 | 5.4 ± 0.4 | 5.4 ± 0.3 | 5.5 ± 0.4 | 5.4 ± 0.4 |

Time to each HK recurrence (days)^d, mean ± SD

| | | | | | | |
|--|------------|------------|------------|------------|------------|------------|
| First | 45 ± 46 | 48 ± 47 | 48 ± 48 | 42 ± 44 | 45 ± 45 | 45 ± 47 |
| Second | 35 ± 37 | 38 ± 37 | 34 ± 35 | 37 ± 39 | 38 ± 40 | 35 ± 35 |
| Third | 29 ± 29 | 25 ± 24 | 30 ± 29 | 27 ± 27 | 25 ± 25 | 28 ± 25 |
| Fourth | 27 ± 26 | 22 ± 19 | 30 ± 28 | 25 ± 22 | 24 ± 23 | 25 ± 24 |
| Fifth | 24 ± 22 | 27 ± 29 | 27 ± 25 | 21 ± 23 | 21 ± 30 | 21 ± 21 |
| Sixth | 20 ± 19 | 23 ± 27 | 19 ± 22 | 20 ± 25 | 24 ± 34 | 20 ± 21 |
| HK-related HRU^c, n (%) | | | | | | |
| Hospitalization | 196 (13.6) | 45 (10.8) | 141 (14.4) | 61 (12.3) | 26 (11.0) | 94 (15.0) |
| ED visit | 21 (1.5) | 6 (1.4) | 15 (1.5) | 2 (0.4) | 1 (0.4) | 7 (1.1) |
| All-cause HRU^c, n (%) | | | | | | |
| Hospitalization | 919 (63.6) | 256 (61.4) | 623 (63.7) | 340 (68.5) | 167 (70.8) | 398 (63.4) |
| ED visit | 321 (22.2) | 83 (19.9) | 228 (23.3) | 117 (23.6) | 42 (17.8) | 140 (22.3) |
| Mortality ^e | 313 (15.9) | 67 (12.6) | 199 (14.9) | 112 (16.8) | 41 (13.9) | 130 (15.5) |

^aSerum K⁺ ≥5.5 mmol/L for the index HK episode.

^bAnalyses included patients who remained uncensored for the entire duration of each analysis interval.

^cAnalyses included patients with ≥6 months of follow-up.

^dAnalyses included patients with ≥6 months of follow-up and sufficient number of HK recurrences.

^eMortality analyses included all patients in each cohort without censoring.

CKD chronic kidney disease, *ED* emergency department, *HK* hyperkalemia, *HRU* healthcare resource utilization, *K*⁺ potassium, *SD* standard deviation

Supplementary Table S5 Hyperkalemia recurrence following medical nutrition therapy by analysis interval, sensitivity analysis with serum $K^+ \geq 5.5$ mmol/L as the recurrence threshold

| | Analysis interval ^a | | | | | |
|--|--------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | 0–1 month | 0–2 months | 0–3 months | 0–4 months | 0–5 months | 0–6 months |
| HK recurrence in overall population, <i>n</i> (%) | | | | | | |
| | 353/1790 (19.7) | 432/1727 (25.0) | 458/1671 (27.4) | 478/1623 (29.5) | 494/1560 (31.7) | 502/1503 (33.4) |
| HK recurrence in patient subgroups, <i>n</i> (%) | | | | | | |
| Stage 3b CKD | 112/571 (19.6) | 135/549 (24.6) | 145/530 (27.4) | 151/512 (29.5) | 157/494 (31.8) | 161/472 (34.1) |
| Stage 4 CKD | 165/734 (22.5) | 205/708 (29.0) | 215/685 (31.4) | 221/668 (33.1) | 228/635 (35.9) | 230/614 (37.5) |
| HF | 198/1036 (19.1) | 254/996 (25.5) | 271/964 (28.1) | 282/930 (30.3) | 293/895 (32.7) | 295/861 (34.3) |
| Baseline RAASi | 147/794 (18.5) | 179/776 (23.1) | 193/753 (25.6) | 207/731 (28.3) | 214/702 (30.5) | 221/681 (32.5) |
| Hypertension | 336/1722 (19.5) | 413/1661 (24.9) | 438/1608 (27.2) | 458/1561 (29.3) | 475/1500 (31.7) | 482/1444 (33.4) |
| Stage 3a CKD | 76/485 (15.7) | 92/470 (19.6) | 98/456 (21.5) | 106/443 (23.9) | 109/431 (25.3) | 111/417 (26.6) |
| Type 2 diabetes | 234/1171 (20.0) | 280/1130 (24.8) | 299/1100 (27.2) | 314/1067 (29.4) | 325/1021 (31.8) | 332/978 (33.9) |
| HF and stage 3a/3b CKD | 106/596 (17.8) | 133/569 (23.4) | 142/549 (25.9) | 150/530 (28.3) | 156/517 (30.2) | 157/496 (31.7) |
| HF and stage 3a CKD | 41/271 (15.1) | 52/258 (20.2) | 53/251 (21.1) | 60/247 (24.3) | 63/242 (26.0) | 64/236 (27.1) |
| Moderate-to-severe HK ^b | 146/738 (19.8) | 187/716 (26.1) | 195/691 (28.2) | 205/675 (30.4) | 212/648 (32.7) | 215/628 (34.2) |

^aAnalyses included patients who remained uncensored for the entire duration of each analysis interval.

^bSerum $K^+ \geq 5.5$ mmol/L for the index HK episode.

CKD chronic kidney disease, HF heart failure, HK hyperkalemia, K^+ potassium, RAASi renin-angiotensin-aldosterone system inhibitor