Supplementary Material

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Supplementary Figure 1. Sample selection criteria

Supplementary Table 1. List of confounders by multivariable-adjusted regression models for baseline time-averaged K exposure

Model	Confounders
Model 1	Unadjusted
Model 2	Model 1 + age, sex, race, marital status, region of residence, and income
Model 3	Model 2 + smoking status, comorbidities (diabetes mellitus, congestive heart failure, hypertension, hyperlipidemia, ischemic stroke/TIA, ischemic heart disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, peptic ulcer disease, para-/hemiplegia, anemia, atrial fibrillation, liver disease, and malignancies), CCI, outpatient, hospital, emergency and nephrology visits recorded during the baseline period
Model 4 (fully-adjusted)	Model 3 + baseline medications (RAASi, SPS, loop diuretics, K sparing diuretics, thiazide diuretics, NSAID, antiplatelet agents, aspirin, anticoagulants, lipid lowering medications, antiarrhythmics, digoxin, beta blockers, calcium channel blockers, insulin, oral hypoglycemics, calcineurin inhibitors, trimethoprim, azole antifungals, beta-2 agonist, laxatives), index eGFR, baseline averaged levels of bicarbonate, sodium, BMI, LDL, HDL, total cholesterol, and triglycerides and number of K measurements and occurrence of at least one hypokalemia (K <3.5 mEq/L), hyperkalemia (K >5.5 mEq/L), and both (those who experienced both hyper- and hypokalemia) event in the baseline
Model 5 (additional)	Model 4 + SBP, DBP

BMI: body mass index; CCI: Charlson comorbidity index; DBP: diastolic blood pressure; eGFR; estimated glomerular filtration rate; HDL: high density lipoprotein; K: serum potassium; LDL: low density lipoprotein; NSAID: non-steroidal anti-inflammatory drugs; RAASi: renin-angiotensin-aldosterone system inhibitors; SBP: systolic blood pressure; SPS: sodium polystyrene sulphonate

Supplementary Table 2. Crude event rates, follow-up time and number of events overall and by baseline time-averaged potassium categories (n=21,357)

	Overall (n=21,357)	Hypokalemia (K<3.5 mEq/L) (N=402)	Referent (K 3.5-5.5 mEq/L) (N=20,287)	Hyperkalemia (K>5.5 mEq/L) (N=668)
Follow-up time in years, median (Q1-Q3)	2.56 (1.59-3.89)	2.18 (1.42-3.43)	2.57 (1.61-3.90)	2.64 (1.67-3.87)
N (%) ischemic stroke events	2,638 (12.4%)	61 (15.2)	2,489 (12.3)	88 (13.2)
Crude event rate per 1,000 patient years (95% CI)	41.9 (40.4-43.6)	57.9 (45.1-74.5)	41.6 (39.9-43.2)	44.4 (36.0-54.7)

CI: confidence interval; K: potassium; N: number

Supplementary Table 3. Association of baseline time-averaged granular potassium categories with time to ischemic stroke (n=21,357)

Model	K <3.5 mEq/L (N=402)	3.5-<4.0 mEq/L (N=2,617)	4.0-<4.5 mEq/L (N=6,602)	4.5-<5.0 mEq/L (N=7,369)	5.0-5.5 mEq/L (N=3,534)	5.5-<6.0 mEq/L (N=738)	≥6.0 mEq/L (N=95)
N (%) ischemic stroke events	61 (15.2)	328 (12.5)	867 (13.1)	876 (11.9)	403 (11.4)	90 (12.2)	13 (13.7)
1	1.25 (0.97-1.62)	1.00 (0.88-1.14)	1[Reference]	0.86 (0.78-0.95)	0.83 (0.74-0.93)	0.90 (0.73-1.12)	1.02 (0.59-1.77)
2	1.24 (0.95-1.60)	0.99 (0.87-1.13)	1[Reference]	0.87 (0.79-0.96)	0.84 (0.75-0.95)	0.90 (0.73-1.12)	1.04 (0.60-1.80)
3	1.24 (0.96-1.61)	0.98 (0.86-1.11)	1[Reference]	0.89 (0.82-0.98)	0.88 (0.79-0.99)	0.99 (0.79-1.23)	1.27 (0.73-2.20)
4 (fully-adjusted)	1.33 (0.98-1.82)	0.99 (0.86-1.14)	1[Reference]	0.87 (0.79-0.96)	0.84 (0.73-0.96)	0.92 (0.72-1.19)	1.18 (0.67-2.09)
5 (additional model)	1.32 (0.97-1.79)	0.99 (0.86-1.14)	1[Reference]	0.88 (0.79-0.97)	0.85 (0.74-0.97)	0.93 (0.72-1.20)	1.18 (0.67-2.08)

Data reported as hazard ratio (95% CI)
Models conducted as described in Supplementary Table 1

Supplementary Table 4. Association of baseline time-averaged potassium categories with time to ischemic stroke by subgroups (n=21,357)

Subgroup	Hypokalemia (K<3.5 mEq/L) (N=402)	Referent (K 3.5-5.5 mEq/L) (N=20,287)	Hyperkalemia (K>5.5 mEq/L) (N=668)	p-value for interaction
N (%) ischemic stroke events	61 (15.2)	2,489 (12.3)	88 (13.2)	
Age <65 years (n=7,930)	1.55 (1.00-2.38)	1[Reference]	0.88 (0.51-1.52)	0.31
Age ≥65 years (n=13,427)	1.25 (0.84-1.88)	1[Reference]	1.32 (1.00-1.75)	
White (n=14,712)	1.33 (0.87-2.04)	1[Reference]	1.23 (0.93-1.62)	0.63
Black (n=6,044)	1.35 (0.89-2.04)	1[Reference]	1.06 (0.59-1.92)	
Residence in US South (n=9,650)	1.38 (0.94-2.04)	1[Reference]	1.32 (0.93-1.89)	0.75
Residence in other US regions (n=11,707)	1.31 (0.93-1.84)	1[Reference]	1.24 (0.94-1.63)	
Diabetes (n=14,752)	1.31 (0.93-1.84)	1[Reference]	1.24 (0.94-1.63)	0.77
No Diabetes (n=6,605)	1.51 (0.83-2.75)	1[Reference]	1.22 (0.74-2.02)	
Congestive heart failure (n=7,466)	1.01 (0.64-1.62)	1[Reference]	1.34 (0.92-1.98)	0.22
No congestive heart failure (n=13,891)	1.79 (1.22-2.62)	1[Reference]	1.25 (0.91-1.71)	
Ischemic heart disease (n=10,573)	1.29 (0.85-1.96)	1[Reference]	1.12 (0.82-1.53)	0.36
No ischemic heart disease (n=10,784)	1.59 (1.04-2.41)	1[Reference]	1.52 (1.02-2.25)	
Stroke/TIA (n=3,261)	1.18 (0.76-1.82)	1[Reference]	1.26 (0.86-1.86)	0.95
No stroke/TIA (n=18,096)	1.63 (1.09-2.43)	1[Reference]	1.23 (0.90-1.69)	
RAASi (n=15,982)	1.43 (1.02-2.01)	1[Reference]	1.29 (0.97-1.69)	0.99
No RAASi (n=5,465)	1.13 (0.63-2.03)	1[Reference]	1.05 (0.63-1.74)	
SPS (n=1,684)	N/A	1[Reference]	1.34 (0.83-2.18)	0.61
No SPS (n=19,673)	1.41 (1.05-1.89)	1[Reference]	1.18 (0.88-1.57)	
Loop diuretics (n=11,986)	1.19 (0.81-1.74)	1[Reference]	0.97 (0.66-1.43)	0.22
No loop diuretics (n=9,371)	1.69 (1.05-2.69)	1[Reference]	1.53 (1.10-2.13)	
Antiplatelet agents (n=3,300)	1.12 (0.59-2.15)	1[Reference]	0.75 (0.45-1.26)	0.63
No Antiplatelet agents (n=18,057)	1.43 (1.02-1.99)	1[Reference]	1.49 (1.13-1.97)	
BMI <30 kg/m^2 (n=12,102)	1.13 (0.75-1.70)	1[Reference]	1.32 (0.98-1.79)	0.90
BMI ≥30 kg/m^2 (n=9,255)	1.65 (1.07-2.53)	1[Reference]	1.13 (0.75-1.71)	
eGFR <20 ml/min/1.73m^2 (n=4,373)	0.86 (0.42-1.79)	1[Reference]	1.39 (0.82-2.38)	0.22
eGFR ≥20 ml/min/1.73m^2 (n=16,984)	1.50 (1.09-2.07)	1[Reference]	1.20 (0.91-1.59)	

Data reported as hazard ratio (95% CI)
Model adjusted for confounders listed in Supplementary Table 1

Supplementary Table 5. Association of baseline time-averaged potassium categories with time to ischemic stroke amongst those without baseline history of stroke (n=18,096)

Model	Hypokalemia (K<3.5 mEq/L) (N=338)	Referent (K 3.5-5.5 mEq/L) (N=17,178)	Hyperkalemia (K>5.5 mEq/L) (N=580)
N (%) ischemic stroke events	34 (10.1)	1,424 (8.3)	54 (9.3)
1	1.36 (0.97-1.91)	1[Reference]	1.12 (0.85-1.46)
2	1.36 (0.96-1.91)	1[Reference]	1.11 (0.85-1.46)
3	1.40 (0.99-1.97)	1[Reference]	1.09 (0.83-1.44)
4 (fully-adjusted)	1.63 (1.09-2.43)	1[Reference]	1.23 (0.90-1.69)
5 (additional model)	1.65 (1.10-2.45)	1[Reference]	1.22 (0.89-1.67)

Data reported as hazard ratio (95% CI)

Models conducted as described in Supplementary Table 1

Supplementary Table 6. Distribution of potassium categories using the last time-updated potassium level prior to ischemic stroke by baseline time-averaged potassium categories amongst those experiencing ischemic stroke (n=2,368)

		Baseline time-averaged K		
		Hypokalemia (K<3.5 mEq/L) (N=61)	Referent (K 3.5-5.5 mEq/L) (N=2,489)	Hyperkalemia (K>5.5 mEq/L) (N=88)
Time-updated K	Hypokalemia (K<3.5 mEq/L)	14 (22.9)	63 (2.5)	0
	Referent (K 3.5-5.5 mEq/L)	47 (77.1)	2,324 (93.4)	64 (72.7)
	Hyperkalemia (K>5.5 mEq/L)	0	102 (4.1)	24 (27.3)

Data reported as n (%).
K: potassium; N: number

Supplementary Table 7. Distribution of time-updated potassium categories by baseline time-averaged potassium categories (n=21,357)

		Time-updated K			
		N of time-updated K measure-ments[*]	Hypokalemia (K <3.5 mEq/L)	Referent (K 3.5-5.5 mEq/L)	Hyperkalemia (K>5.5 mEq/L)	At least 1 event belonging to other two K categories[†]
Baseline time-averaged K	Hypokalemia (K<3.5 mEq/L) (N=402)	8,452	5.4	90.5	4.1	11.9
	Referent (K 3.5-5.5 mEq/L) (N=20,287)	470,354	26.8	72.3	0.9	10.2
	Hyperkalemia (K>5.5 mEq/L) (N=668)	10,680	1.1	80.8	18.1	8.9

Data presented as row percentages unless otherwise noted
* Number of time-updated K measurements by baseline time-averaged K levels
† Row percentages reporting percentage of patients in each baseline time-averaged K category who had at least one event belonging to each of the K categories (using time-updated K levels) other than for which data is reported
K: potassium; N: number

Supplementary Table 8. Association of time-updated granular potassium categories with time to ischemic stroke (n=21,357).

Model	K <3.5 mEq/L	3.5-<4.0 mEq/L	4.0-<4.5 mEq/L	4.5-<5.0 mEq/L	5.0-5.5 mEq/L	5.5-<6.0 mEq/L	≥6.0 mEq/L
N (row %) of repeated K measurements	21,832 (4.5)	75,727 (15.5)	139,112 (28.4)	139,898 (28.6)	77,528 (15.8)	26,798 (5.5)	8,391 (1.7)
1	0.92 (0.73-1.16)	1.05 (0.92-1.19)	1[Reference]	0.95 (0.86-1.05)	0.87 (0.78-0.98)	0.73 (0.60-0.88)	0.71 (0.51-0.98)
2	0.92 (0.73-1.16)	1.04 (0.92-1.18)	1[Reference]	0.95 (0.86-1.05)	0.88 (0.78-0.98)	0.73 (0.61-0.89)	0.72 (0.52-0.99)
3	0.86 (0.68-1.09)	1.02 (0.89-1.16)	1[Reference]	0.98 (0.89-1.08)	0.89 (0.79-1.01)	0.77 (0.64-0.93)	0.73 (0.64-0.93)
4 (fully-adjusted)	0.84 (0.66-1.06)	1.01 (0.89-1.15)	1[Reference]	1.01 (0.91-1.12)	0.95 (0.84-1.07)	0.81 (0.67-0.98)	0.78 (0.55-1.08)
5 (additional model)	0.84 (0.66-1.07)	1.01 (0.89-1.15)	1[Reference]	1.01 (0.91-1.11)	0.95 (0.84-1.07)	0.81 (0.67-0.98)	0.77 (0.55-1.08)

Data reported as hazard ratio (95% CI)

Models conducted as described in Supplementary Table 1 with further accounting for baseline averaged potassium levels and time-varying medications, estimated glomerular filtration rate and sodium levels in model 4 and 5

Supplementary Table 9. Association of time-updated potassium categories with time to ischemic stroke by subgroups (n=21,357).

Subgroup	Hypokalemia (K<3.5 mEq/L) (N=402)	Referent (K 3.5-5.5 mEq/L) (N=20,287)	Hyperkalemia (K>5.5 mEq/L) (N=668)	p-value for interaction
N (row %) of repeated K measurements	21,832 (4.5)	440,336 (89.9)	27,318 (5.6)	
Age <65 years (n=7,930)	0.84 (0.59-1.18)	1[Reference]	0.65 (0.43-0.94)	0.09
Age ≥65 years (n=13,427)	0.76 (0.55-1.06)	1[Reference]	0.89 (0.72-1.11)	
White (n=14,712)	0.78 (0.56-1.09)	1[Reference]	0.85 (0.68-1.09)	0.67
Black (n=6,044)	0.88 (0.63-1.23)	1[Reference]	0.77 (0.54-1.08)	
Residence in US South (n=9,650)	1.05 (0.78-1.41)	1[Reference]	0.97 (0.75-1.26)	0.04
Residence in other US regions (n=11,707)	0.63 (0.43-0.92)	1[Reference]	0.72 (0.55-0.93)	
Diabetes (n=14,752)	0.80 (0.61-1.05)	1[Reference]	0.81 (0.65-1.00)	0.75
No Diabetes (n=6,605)	0.94 (0.59-1.49)	1[Reference]	0.84 (0.58-1.22)	
Congestive heart failure (n=7,466)	0.67 (0.46-0.98)	1[Reference]	0.84 (0.62-1.14)	0.15
No congestive heart failure (n=13,891)	0.98 (0.73-1.34)	1[Reference]	0.79 (0.63-1.01)	
Ischemic heart disease (n=10,573)	0.81 (0.59-1.12)	1[Reference]	0.85 (0.67-1.19)	0.55
No ischemic heart disease (n=10,784)	0.85 (0.60-1.19)	1[Reference]	0.76 (0.57-1.02)	
Stroke/TIA (n=3,261)	0.74 (0.52-1.06)	1[Reference]	0.76 (0.57-1.03)	0.83
No stroke/TIA (n=18,096)	0.92 (0.68-1.25)	1[Reference]	0.86 (0.68-1.09)	
RAASi (n=15,982)	0.92 (0.71-1.19)	1[Reference]	0.84 (0.68-1.04)	0.33
No RAASi (n=5,465)	0.56 (0.31-1.00)	1[Reference]	0.74 (0.51-1.08)	
SPS (n=1,684)	0.78 (0.24-2.56)	1[Reference]	0.73 (0.46-1.17)	0.96
No SPS (n=19,673)	0.83 (0.66-1.06)	1[Reference]	0.84 (0.69-1.03)	
Loop diuretics (n=11,986)	0.87 (0.65-1.16)	1[Reference]	0.76 (0.58-0.99)	0.39
No loop diuretics (n=9,371)	0.75 (0.49-1.13)	1[Reference]	0.88 (0.68-1.13)	
Antiplatelet agents (n=3,300)	0.67 (0.41-1.09)	1[Reference]	0.66 (0.44-0.99)	0.44
No Antiplatelet agents (n=18,057)	0.91 (0.69-1.19)	1[Reference]	0.88 (0.72-1.09)	
BMI <30 kg/m^2 (n=12,102)	0.70 (0.49-0.98)	1[Reference]	0.89 (0.71-1.11)	0.18
BMI ≥30 kg/m^2 (n=9,255)	0.99 (0.72-1.38)	1[Reference]	0.69 (0.49-0.96)	
eGFR <20 ml/min/1.73m^2 (n=4,373)	0.78 (0.43-1.41)	1[Reference]	0.95 (0.64-1.39)	0.19

eGFR ≥20 ml/min/1.73m^2 (n=16,984)	0.85 (0.66-1.10)	1[Reference]	0.78 (0.63-0.96)

Data reported as hazard ratio (95% CI)

Models conducted as described in Supplementary Table 1 with further accounting for baseline averaged potassium levels and time-varying medications, estimated glomerular filtration rate and sodium levels in model 4 and 5

Supplementary Table 10. Association of time-updated potassium categories with time to ischemic stroke amongst those without baseline history of stroke (n=18,096).

Model	Hypokalemia (K<3.5 mEq/L)	Referent (K 3.5-5.5 mEq/L)	Hyperkalemia (K>5.5 mEq/L)
N (row %) of repeated K measurements	19,144 (4.4)	390,973 (89.9)	24,489 (5.6)
1	0.97 (0.72-1.32)	1[Reference]	0.79 (0.63-1.00)
2	0.98 (0.73-1.33)	1[Reference]	0.81 (0.64-1.01)
3	0.95 (0.70-1.29)	1[Reference]	0.82 (0.65-1.03)
4 (fully-adjusted)	0.92 (0.68-1.25)	1[Reference]	0.86 (0.68-1.09)
5 (additional model)	0.92 (0.68-1.26)	1[Reference]	0.85 (0.67-1.08)

Data reported as hazard ratio (95% CI)

Models conducted as described in Supplementary Table 1 with further accounting for baseline averaged potassium levels and time-varying medications, estimated glomerular filtration rate and sodium levels in model 4 and 5
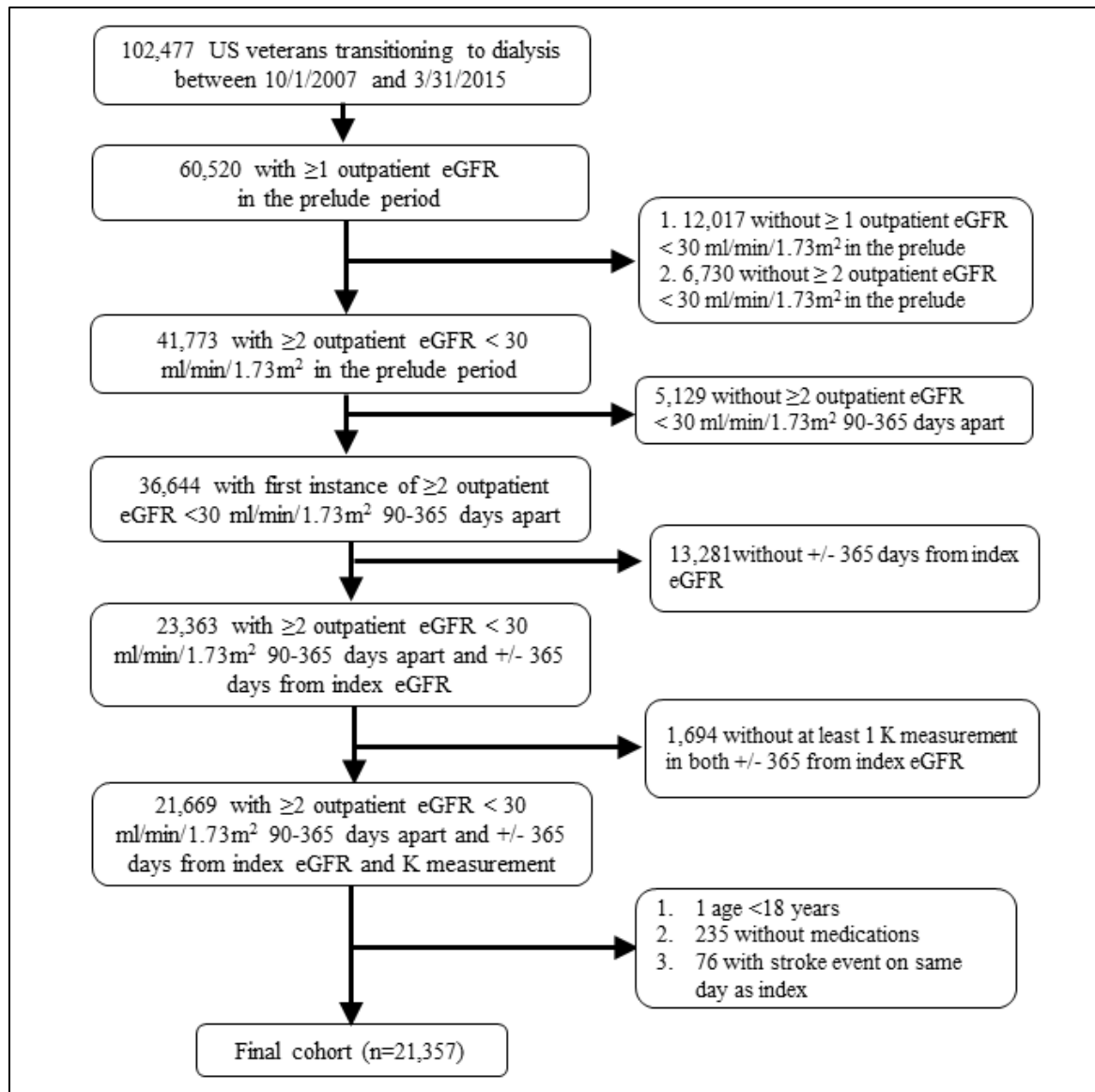
Supplementary Figure 1. Sample selection criteria.


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┌─────────────────────────────────────────┐
│ 102,477 US veterans transitioning to     │
│ dialysis between 10/1/2007 and 3/31/2015 │
└─────────────────────────────────────────┘
                    ↓
┌─────────────────────────────────────────┐           ┌──────────────────────────────────────┐
│ 60,520 with ≥1 outpatient eGFR           │           │ 1. 12,017 without ≥ 1 outpatient eGFR │
│ in the prelude period                    │──────────→│    < 30 ml/min/1.73m² in the prelude  │
└─────────────────────────────────────────┘           │ 2. 6,730 without ≥ 2 outpatient eGFR  │
                    ↓                                   │    < 30 ml/min/1.73m² in the prelude  │
                                                        └──────────────────────────────────────┘
┌─────────────────────────────────────────┐           ┌──────────────────────────────────────┐
│ 41,773 with ≥2 outpatient eGFR < 30      │──────────→│ 5,129 without ≥2 outpatient eGFR      │
│ ml/min/1.73m² in the prelude period      │           │ < 30 ml/min/1.73m² 90-365 days apart  │
└─────────────────────────────────────────┘           └──────────────────────────────────────┘
                    ↓
┌─────────────────────────────────────────┐           ┌──────────────────────────────────────┐
│ 36,644 with first instance of ≥2         │──────────→│ 13,281 without +/- 365 days from index │
│ outpatient eGFR <30 ml/min/1.73m²        │           │ eGFR                                   │
│ 90-365 days apart                        │           └──────────────────────────────────────┘
└─────────────────────────────────────────┘
                    ↓
┌─────────────────────────────────────────┐           ┌──────────────────────────────────────┐
│ 23,363 with ≥2 outpatient eGFR < 30      │──────────→│ 1,694 without at least 1 K measurement │
│ ml/min/1.73m² 90-365 days apart and      │           │ in both +/- 365 from index eGFR        │
│ +/- 365 days from index eGFR             │           └──────────────────────────────────────┘
└─────────────────────────────────────────┘
                    ↓
┌─────────────────────────────────────────┐           ┌──────────────────────────────────────┐
│ 21,669 with ≥2 outpatient eGFR < 30      │           │ 1.  1 age <18 years                    │
│ ml/min/1.73m² 90-365 days apart and      │──────────→│ 2.  235 without medications            │
│ +/- 365 days from index eGFR and K       │           │ 3.  76 with stroke event on same       │
│ measurement                              │           │     day as index                       │
└─────────────────────────────────────────┘           └──────────────────────────────────────┘
                    ↓
           ┌──────────────────────┐
           │ Final cohort (n=21,357) │
           └──────────────────────┘
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eGFR: estimated glomerular filtration rate; K potassium; US: United States