👩‍🎓Tweetorial Alert 👩‍🎓

1/
Hey #NephTwitter!
Welcome to a 🆕 #tweetorial #xtorial brought to you by @KIReports.

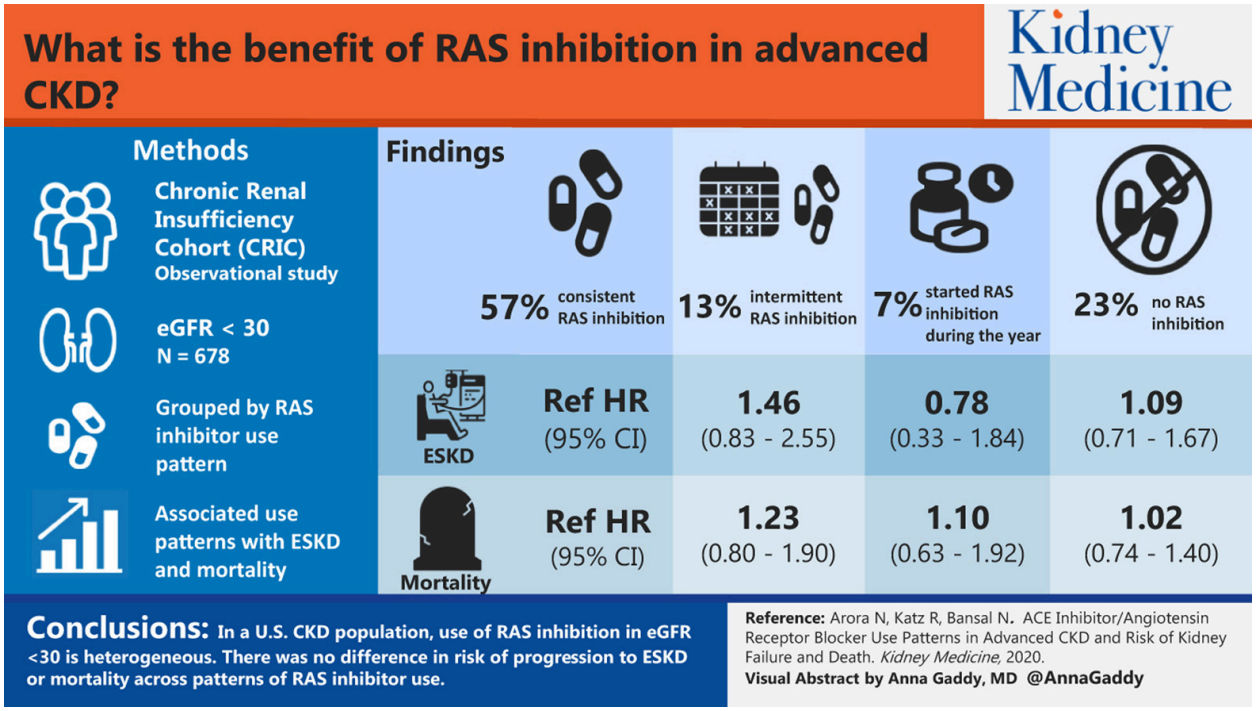
2/
Our author is Melvin @MChanMD (pediatric nephrologist)
Our topic: Impact of Different Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blocker Resumption Timing on Post Acute Kidney Injury Outcomes
#MedTwitter #nephtwitter @ISNkidneycare #XTwitter

3/
There are no conflicts of interest. Please also check out #KIReportsCommunity educational #blogposts lead by @sophia_kidney at https://www.kireportscommunity.org/. FOLLOW US at @KIReports for more expert #MedEd in #kidneydisease. #FOAMed @MedTweetorials

4/
Let's begin with a question: What are the concerns about restarting ACE/ARB after an acute kidney injury (AKI) event?
A. Recurrent AKI
B. Hyperkalemia
C. CKD progression
D. All of the above

5/ The answer is D. All of the above
Does resumption of ACE/ARB even matter? A study by @CaptainChloride seems to suggest no, as beautifully depicted by @AnnaGaddy.

https://www.kidneymedicinejournal.org/article/S2590-0595(20)30034-0/fulltext



6/
Another prior study showed that ACE/ARB resumption or initiation within 6 months after post-discharge with AKI had the following effects:
🔽Mortality
🔼Hospitalization for Renal Cause

https://pubmed.ncbi.nlm.nih.gov/34395482/

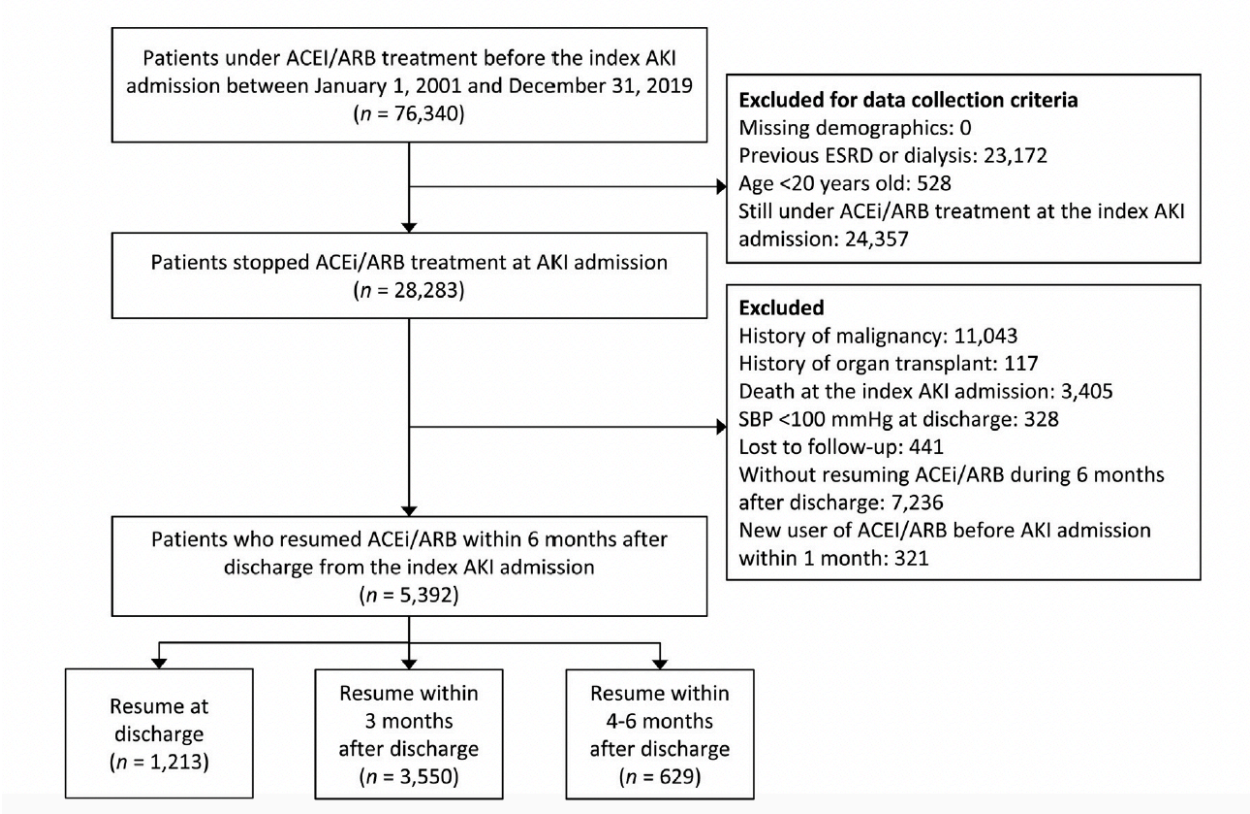
7/
While this study did a great job controlling for multiple confounders to answer this complex question, there were a lot of controversies behind this study, specifically determining the following:
🫘Baseline creatinine
🫘User/Non-user

🫘Outcomes

⏭️http://www.nephjc.com/news/rasafteraki

8/
Our recently published paper by Chen et al attempts to answer this question from a different angle: Does timing of resumption matter?
🖇️: https://www.kireports.org/article/S2468-0249(24)01912-0/fulltext

9/ Population
📢Source: Chang Gung Research Database
📢Taiwan 🇹🇼
📢Includes 🧑>20 years old who stopped ACE/ARB



10/ Definitions
⚡Baseline Creatinine: Lowest level within the last year
⚡AKI: Based on KDIGO criteria
⚡Estimated glomerular renal function: CKD-Epi equation
⚡Baseline proteinuria and lipid profile: Most recent one in the last 2 years

11a/ Time point exposure and outcomes
⌛At discharge, within 3 months, and within 6 months
⏱️Followed from index hospitalization to primary/secondary outcome or 12/31/2019

Primary outcome: All cause ☠️-obtained via death registry

11b/
Secondary outcomes:
👀MACE (Cardiovascular death, non-fatal MI, non-fatal CVA)
👀Onset of dialysis or diagnosis of ESRD
👀Safety: Hyperkalemia (>= 6.5mEq/dL) or AKI hospitalization

12/ Statistics:
👉Baseline covariates were balanced with inverse probability treatment weighting through propensity scoring
👉Missing data was balanced by imputing single expectation maximization, which is a formula for predicting the most likely value
👉Associations between outcomes were evaluated with Cox regression and hazard ratios

13/ Clinical Characteristics
⛳Mean age of 70 years old
⛳50%♂
⛳Delaying resumption of ACE/ARB after discharge was associated with more severe AKI

Table 1. Demographic and clinical characteristics before GBM-IPTW and EM imputation

Variable	Available numbers	Total (n = 5392)	Discharge resumed (n = 1213)	0–3 mo resumed (n = 3550)	4–6 mo resumed (n = 629)	MASD
Age, yr	5392	70.1 ± 13.8	70.2 ± 13.9	70.3 ± 13.6	69.2 ± 14.6	0.08
Age group	5392					0.02
20–65 yrs		1751 (32.5)	402 (33.1)	1146 (32.3)	203 (32.3)	
> 65 yrs		3641 (67.5)	811 (66.9)	2404 (67.7)	426 (67.7)	
Male	5392	2703 (50.1)	589 (48.6)	1775 (50.0)	339 (53.9)	0.11
Smoking	5392	1144 (21.2)	262 (21.6)	750 (21.1)	132 (21.0)	0.02
BMI, kg/m^2	5136	24.8 ± 5.1	25.0 ± 4.8	24.8 ± 5.3	24.2 ± 4.9	0.14
Baseline laboratory data						
eGFR, ml/min per 1.73 m^2	5149	76.5 ± 32.6	77.0 ± 32.0	76.2 ± 32.3	77.5 ± 35.3	0.02
Proteinuria	5392					0.02
Negative		1600 (29.7)	360 (29.7)	1059 (29.8)	181 (28.8)	
Trace		546 (10.1)	107 (8.8)	366 (10.3)	73 (11.6)	
1+		653 (12.1)	118 (9.7)	450 (12.7)	85 (13.5)	
2+		727 (13.5)	167 (13.8)	485 (13.7)	75 (11.9)	
3+		594 (11.0)	141 (11.6)	367 (10.3)	86 (13.7)	
4+		179 (3.3)	53 (4.4)	100 (2.8)	26 (4.1)	
Unknown		1093 (20.3)	267 (22.0)	723 (20.4)	103 (16.4)	
LDL, mg/dl	3955	103.0 ± 46.6	104.1 ± 48.1	102.4 ± 45.7	103.6 ± 48.2	0.04
HDL, mg/dl	3869	44.2 ± 14.3	43.4 ± 13.7	44.6 ± 14.5	43.3 ± 14.7	0.07
Total cholesterol, mg/dl	4236	175.7 ± 50.4	176.0 ± 50.2	175.2 ± 49.7	178.0 ± 54.8	0.05
Mean of baseline hemoglobin, g/dl	4843	11.5 ± 2.0	11.5 ± 2.0	11.6 ± 2.0	11.4 ± 2.0	0.09
Comorbidity						
Hypertension	5392	4848 (89.9)	1099 (90.6)	3195 (90.0)	554 (88.1)	0.08
Diabetes mellitus	5392	3355 (62.2)	786 (64.8)	2188 (61.6)	381 (60.6)	0.09
Coronary artery disease	5392	1864 (34.6)	445 (36.7)	1,212 (34.1)	207 (32.9)	0.08
Peripheral arterial disease	5392	580 (10.8)	140 (11.5)	368 (10.4)	72 (11.4)	0.04
Cerebrovascular disease	5392	1,155 (21.4)	258 (21.3)	761 (21.4)	136 (21.6)	0.01
Heart failure	5392	935 (17.3)	234 (19.3)	603 (17.0)	98 (15.6)	0.10
Chronic obstructive pulmonary disease	5392	1,254 (23.3)	262 (21.6)	853 (24.0)	139 (22.1)	0.06
Atrial fibrillation	5392	804 (14.9)	191 (15.7)	527 (14.8)	86 (13.7)	0.06
Liver cirrhosis	5392	311 (5.8)	60 (4.9)	227 (6.4)	24 (3.8)	0.11
Prior admission times 1 yr before AKI	5392	1.06 ± 1.27	1.02 ± 1.21	1.04 ± 1.25	1.26 ± 1.44	0.19
Prior OPD times 1 yr before AKI	5392	14.0 ± 10.0	13.6 ± 9.7	14.1 ± 10.0	14.6 ± 10.7	0.11
Baseline medication						
MRAs/spironolactone	5392	835 (15.5)	179 (14.8)	540 (15.2)	116 (18.4)	0.10
Loop diuretics	5392	2376 (44.1)	540 (44.5)	1527 (43.0)	309 (49.1)	0.12
Thiazide	5392	746 (13.8)	153 (12.6)	485 (13.7)	108 (17.2)	0.13
Statin	5392	2285 (42.4)	507 (41.8)	1537 (43.3)	241 (38.3)	0.10
Beta-blockers	5392	1848 (34.3)	440 (36.3)	1200 (33.8)	208 (33.1)	0.07
CCBs	5392	3041 (56.4)	687 (56.6)	1967 (55.4)	387 (61.5)	0.12
Aspirin	5392	2420 (44.9)	554 (45.7)	1595 (44.9)	271 (43.1)	0.05
Clopidogrel	5392	1006 (18.7)	234 (19.3)	663 (18.7)	109 (17.3)	0.05
Severity of index AKI admission						
AKI stage	5392					0.25
1		2619 (48.6)	668 (55.1)	1683 (47.4)	268 (42.6)	
2		1384 (25.7)	284 (23.4)	923 (26.0)	177 (28.1)	
3		819 (15.2)	160 (13.2)	561 (15.8)	98 (15.6)	
D-AKI		570 (10.6)	101 (8.3)	383 (10.8)	86 (13.7)	
Sodium, mg/dl	5195	135.9 ± 6.5	136.1 ± 6.2	135.8 ± 6.7	136.1 ± 6.5	0.05
Potassium, mg/dl	5224	4.3 ± 0.9	4.2 ± 0.9	4.3 ± 0.9	4.2 ± 0.9	0.09
Albumin, g/dl	2923	3.2 ± 0.7	3.2 ± 0.7	3.2 ± 0.7	3.1 ± 0.7	0.18
Hemoglobin, g/dl	5199	11.1 ± 2.5	11.1 ± 2.5	11.1 ± 2.5	11.0 ± 2.6	0.03
Hospitalization days	5392	12 (8, 19)	10 (7, 15)	12 (8, 20)	15 (9, 26)	0.56
ICU admission	5392	1007 (18.7)	200 (16.5)	669 (18.8)	138 (21.9)	0.14
Ventilator	5392	629 (11.7)	107 (8.8)	426 (12.0)	96 (15.3)	0.20
Inotropic agents	5392	636 (11.8)	108 (8.9)	454 (12.8)	74 (11.8)	0.12

(Continued on following page)

Table 1. (Continued) Demographic and clinical characteristics before GBM-IPTW and EM imputation

Variable	Available numbers	Total (n = 5392)	Discharge resumed (n = 1213)	0–3 mo resumed (n = 3550)	4–6 mo resumed (n = 629)	MASD
Vital sign						
SBP before AKI, mm Hg	4045	138.0 ± 24.9	138.7 ± 24.2	137.3 ± 24.7	140.7 ± 27.4	0.12
DBP before AKI, mm Hg	4044	74.7 ± 13.9	74.4 ± 13.9	74.4 ± 13.6	77.1 ± 15.1	0.20
SBP at AKI discharge, mm Hg	5090	135.7 ± 19.1	137.3 ± 20.4	135.3 ± 18.6	135.2 ± 18.9	0.11
DBP at AKI discharge, mm Hg	5090	75.8 ± 12.0	75.4 ± 12.2	75.8 ± 12.0	76.1 ± 11.6	0.06
Pre-discharge SCr, mg/dl[a]	4976	1.11 (0.78–1.74)	1.10 (0.80–1.71)	1.11 (0.78–1.71)	1.10 (0.72–2.00)	0.13
Pre-discharge eGFR, ml/min per 1.73 m^{2}[a]	4976	66.4 (38.4–92.3)	67.0 (39.9–91.3)	65.9 (39.1–92.2)	67.7 (33.1–94.2)	0.04
Primary diagnosis of index AKI admission	5392					0.11
Cardiac surgery (1)		94 (1.7)	13 (1.1)	65 (1.8)	16 (2.5)	
Major noncardiac surgery (2)		738 (13.7)	135 (11.1)	507 (14.3)	96 (15.3)	
Coronary artery disease (3)		184 (3.4)	50 (4.1)	101 (2.8)	33 (5.2)	
Cerebrovascular accident (4)		112 (2.1)	30 (2.5)	70 (2.0)	12 (1.9)	
Congestive heart failure (5)		224 (4.2)	83 (6.8)	114 (3.2)	27 (4.3)	
Cardiac arrhythmia (6)		90 (1.7)	39 (3.2)	44 (1.2)	7 (1.1)	
Acute pulmonary edema (7)		27 (0.5)	8 (0.7)	16 (0.5)	3 (0.5)	
Sepsis or severe infection (8)		1512 (28.0)	311 (25.6)	1045 (29.4)	156 (24.8)	
Gastrointestinal bleeding (9)		189 (3.5)	43 (3.5)	129 (3.6)	17 (2.7)	
Cirrhosis and related complication (10)		45 (0.8)	9 (0.7)	32 (0.9)	4 (0.6)	
Renal (CKD, AKI or electrolyte imbalance) (11)		619 (11.5)	128 (10.6)	427 (12.0)	64 (10.2)	
Diabetes mellitus and related complication (12)		309 (5.7)	72 (5.9)	192 (5.4)	45 (7.2)	
Respiratory failure (13)		133 (2.5)	20 (1.6)	98 (2.8)	15 (2.4)	
Others (14)		1116 (20.7)	272 (22.4)	710 (20.0)	134 (21.3)	
SCr at resumed ACEI/ARB, mg/dl[b]	2063	1.38 (0.90–2.56)	1.40 (1.00–2.22)	1.39 (0.90–2.52)	1.30 (0.80–3.20)	0.19
eGFR at resumed ACEI/ARB, mL/min/1.73m^{b}	2063	50.9 (24.9–84.7)	50.5 (28.7–78.4)	50.5 (24.9–84.0)	52.4 (19.6–90.8)	0.06
Mean follow up yrs	5392	2.5 (0.9–5.3)	2.8 (1.1–5.5)	2.4 (0.9–5.4)	3.3 (2.2–0.8)	0.12

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BMI, body mass index; CCBs, calcium channel blockers; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; GBM, generalized boosted modeling; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; LDL, low-density lipoprotein; MASD, maximum absolute standardized difference; MRAs, mineralocorticoid receptor antagonists; OPD, outpatient department; SBP, systolic blood pressure; SCr, serum creatinine.
[a]Did not include patients who were still under dialysis treatment at discharge.
[b]Did not include patients who were under dialysis treatment at resumed ACEI/ARBs point.
Data were presented as frequency (percentage), mean ± SD or median (25th–75th percentiles).

14a/ Associations

💡Resumption of ACE/ARB at discharge or within 3 months was associated with ⬇️likelihood of mortality, new dialysis/ESRD, MACE, CV death

💡Timing or resumption was not associated with hyperkalemia or recurrent AKI

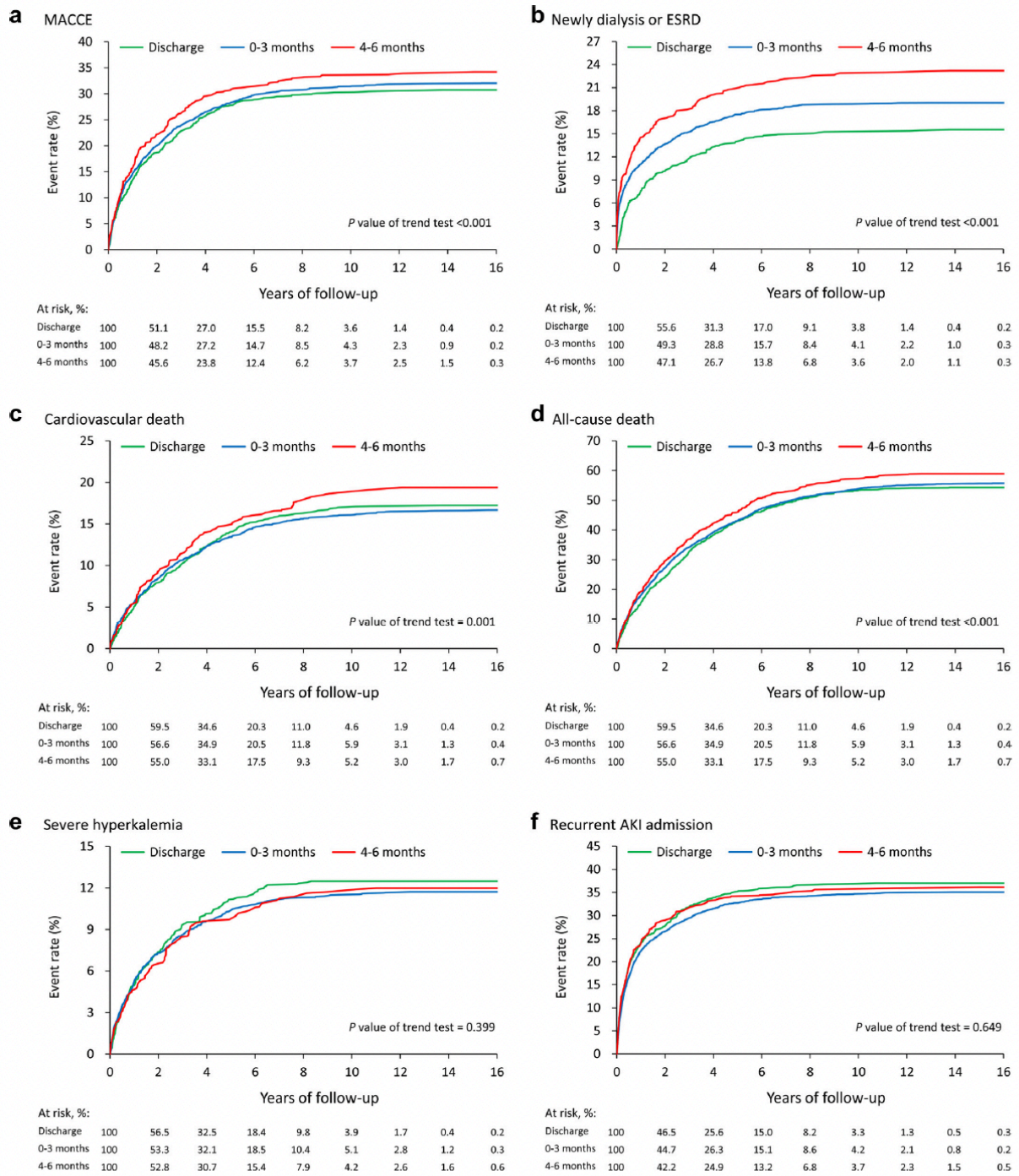


Figure 2. Cumulative event rates by timing of ACEI/ARB resumption: (a) MACCE, (b) new dialysis/ESRD, (c) cardiovascular death, (d) all-cause mortality, (e) severe hyperkalemia, (f) recurrent AKI admission. ACEI, angiotensin- converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiac and cerebrovascular events.

14b/ Associations

💡There was an average reduction of 10-20% risk for mortality, new dialysis/ESRD, MACE, CV death in those who resumed ACE/ARB at discharge or within 3 months of discharge as compared to those at4-6 months

Table 2. Follow-up outcomes after resumption of ACEI/ARB

Outcomes	Event and event rate before GBM-IPTW[a]			Event rate after GBM-IPTW			Hazard ratio (95% CI) after GBM-IPTW		
	Discharge resumed (n = 1213)	0–3 mo resumed (n = 3550)	4–6 mo resumed (n = 629)	Discharge resumed (n = 4567.0)	0–3 mo resumed (n = 5214.2)	4–6 mo resumed (n = 4410.8)	Discharge vs. 4–6 mo	0–3 mo vs. 4–6 mo	P value of trend test
MACCE[b]	397 (32.7)	1,122 (31.6)	212 (33.7)	30.7%	32.0%	34.2%	0.84 (0.78–0.90)	0.88 (0.82–0.94)	<0.001
Newly dialysis or ESRD[c]	174 (15.4)	655 (18.8)	159 (26.1)	15.5%	19.0%	23.2%	0.63 (0.57–0.70)	0.80 (0.74–0.88)	<0.001
Cardiovascular death	227 (18.7)	586 (16.5)	121 (19.2)	17.2%	16.7%	19.4%	0.85 (0.77–0.94)	0.81 (0.74–0.90)	0.001
All-cause death	659 (54.3)	1,980 (55.8)	386 (61.4)	54.3%	55.8%	58.9%	0.88 (0.83–0.93)	0.89 (0.85–0.94)	<0.001
Severe hyperkalemia[d]	143 (11.8)	417 (11.7)	88 (14.0)	12.5%	11.7%	12.0%	1.05 (0.94–1.18)	0.98 (0.87–1.10)	0.399
Re-AKI admission[c]	418 (36.9)	1,225 (35.2)	226 (37.0)	36.9%	35.1%	36.1%	1.02 (0.95–1.09)	0.95 (0.89–1.02)	0.649

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CI, confidence interval; ESRD, end-stage renal disease; GBM, generalized boosted modeling; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiac and cerebrovascular events.
[a]Data are presented as frequency (percentage).
[b]Any out of cardiovascular related death, acute myocardial infarction, and stroke.
[c]Patients who did not under dialysis when resumed ACEI/ARB were eligible for analysis.
[d]Potassium levels higher than 6.5 mg/dl.

15/ Subgroup Analysis

🧩Those with an eGFR < 30mL/min/1.73m2 had decreased risk of being on dialysis or diagnosis of ESRD with earlier resumption

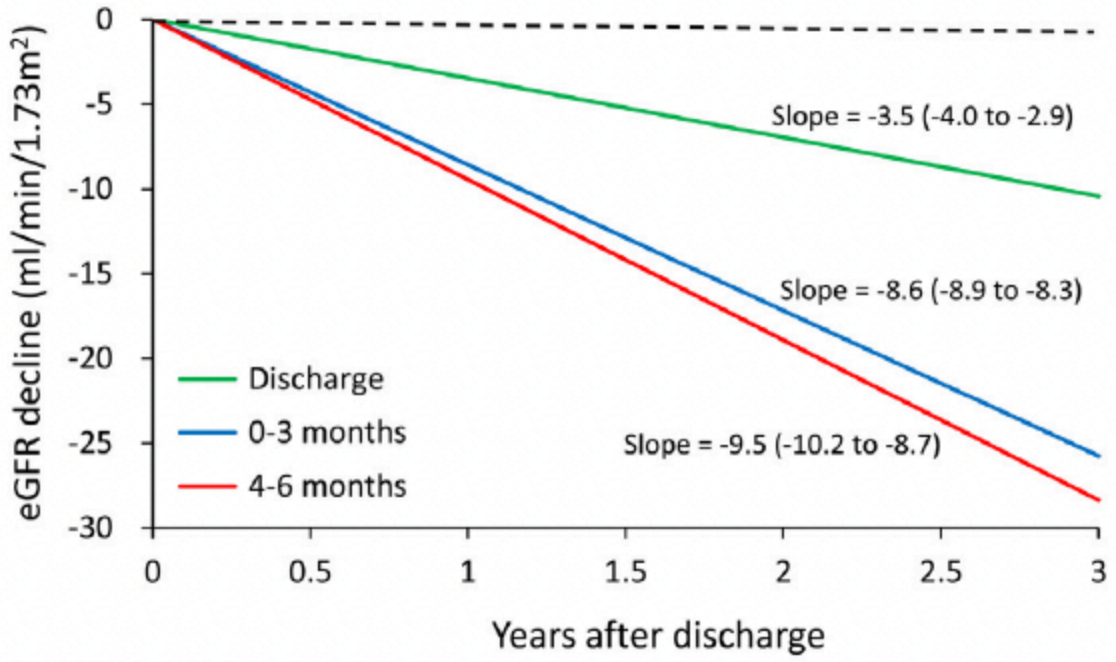
🧩No other reductions in all-cause mortality, MACE, or CV death were found with earlier resumption in those with eGFR < 30mL/min/1.73m2

Supplementary Table S9. Subgroup analysis of renal related outcomes stratified by eGFR when ACEI/ARB resumption

Outcomes/Subgroup	Event rate after GBM-IPTW§			Hazard ratio (95% CI) after GBM-IPTW		P value of trend test
	Discharge resumed (n = 1047.6)	0-3 months resumed (n = 2,179.6)	4-6 months resumed (n = 2,666.6)	Discharge vs 4-6 months	0-3 months vs 4-6 months	
MACCE†						
$eGFR_{resumed}$						
≥30	33.1%	33.4%	35.2%	0.92 (0.79 - 1.07)	0.92 (0.82 - 1.03)	0.168
<30	40.6%	35.6%	31.3%	1.07 (0.87 - 1.32)	1.09 (0.92 - 1.29)	0.433
Newly dialysis or ESRD#						
$eGFR_{resumed}$						
≥30	9.0%	9.9%	11.1%	0.85 (0.65 - 1.13)	0.92 (0.74 - 1.14)	0.225
<30	60.7%	61.5%	61.0%	0.80 (0.68 - 0.94)	1.02 (0.89 - 1.18)	0.032
Cardiovascular death						
$eGFR_{resumed}$						
≥30	19.6%	17.9%	19.7%	0.95 (0.79 - 1.15)	0.89 (0.75 - 1.04)	0.397
<30	22.7%	16.4%	16.8%	1.09 (0.82 - 1.44)	0.89 (0.69 - 1.13)	0.756
All-cause death						
$eGFR_{resumed}$						
≥30	51.1%	57.2%	63.7%	0.77 (0.69 - 0.86)*	0.87 (0.80 - 0.96)*	<0.001
<30	68.4%	64.9%	60.4%	0.91 (0.78 - 1.07)	0.98 (0.87 - 1.11)	0.277

16/ eGFR Slope based on Timing of Resumption

⚡Those resuming earlier had a less steep slope in eGFR decline



Available number

Discharge	1126	599	487	427	365	339	301
0-3 months	3263	768	1688	1390	1199	1029	865
4-6 months	564	229	278	215	174	159	123

Figure 3. eGFR decline and slope after ACEI/ARB resumption in the IPTW-adjusted cohort. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IPTW, inverse probability of treatment weighting. The slope of eGFR decline during 3-year follow-up after discharge day from the index AKI admission in each study group were estimated using the linear mixed model which treated participants as random effect.

17a/ Learning Points

📋Earlier resumption of ACE/ARB decrease the risk of all-cause mortality, MACE, CV death, and new onset ESRD/dialysis initiation, including those with eGFR < 30mL/min/1.73m2

17b/ Learning Points

📋No increased risk for hyperkalemia or hospitalization for recurrent AKI

📋Rate of eGFR decline was lower in those who restarted earlier

18/ Strengths

🦾Large sample

🦾1st study looking at timing of resumption and outcomes
🦾Sub-group analysis of those with eGFR < 30mL/min/1.73m2

Limitations
🥲Retrospective with mainly older pts
🥲Later resumption may indicate that the pt is sicker at baseline and confound result

19/ Future Directions
🔮Randomized clinical trial that matches patients based on frailty
🔮Observational study that does propensity scored based on frailty score

20a/ Now, let's see if you learned something!

What does earlier resumption of ACE/ARB show?

A. Hyperkalemia
B. AKI
C. Decreased mortality
D. All of the above

20b/ The answer is C. Decreased mortality

Does this study change your practice?

A. Yes
B. No
C. Need more studies

21/ There are no right answers! Please share this #tweetorial with your followers and friends! Thanks to @MChanMD for authoring & @sophia_kidney, @Brian_Rifkin, @nephron1310 for great feedbacks!
#FOAMed #nephtwitter @ISNkidneycare @KIReports