Lab monitoring and acute care utilization during initiation of renin angiotensin aldosterone inhibitors or diuretics in chronic kidney disease

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Abstract

Renin angiotensin aldosterone system inhibitors (RAASi) and diuretics are among the most frequently prescribed anti-hypertensives. Individuals with chronic kidney disease (CKD) are particularly at risk for electrolyte disturbances and kidney injury but the appropriate use of lab monitoring following RAASi or diuretic initiation is uncertain in CKD.

We describe the frequency and time interval of lab monitoring during initiation of RAASi and diuretics in CKD and assess whether close lab monitoring associates with one-year risk of emergency department (ED) visit or hospitalization.

We evaluated an observational cohort of 8,217 individuals with stage 3–5 non-dialysis CKD newly prescribed a RAASi (52.3%) or diuretic (47.7%) from thirty-six primary care offices affiliated with Brigham and Women's Hospital and Massachusetts General Hospital between 2009 and 2011.

Overall, 3306 (40.2%) individuals did not have pre-prescription labs done within 2 weeks, and 5957 (72.5%) did not have post-prescription labs done within 2 weeks which includes 524 (6.4%) individuals without post-prescription within 1 year. Close monitoring occurred in only 1547 (20.1%) and was more likely in individuals prescribed diuretics compared to RAASi (adjusted OR 1.39; 95%CI 1.20–1.62), with CKD stage 4,5 compared with stage 3 (adjusted OR 1.47; 95%CI 1.16–1.86) and with cardiovascular disease (adjusted OR 1.42; 95%CI 1.21–1.66). Close monitoring was not associated with decreased risk of ED visit or hospitalization.

Close lab monitoring during initiation of RAASi or diuretics was more common in participants with cardiovascular disease and advanced CKD suggesting physicians selected high-risk individuals for close monitoring. As nearly 80% of individuals did not receive close lab monitoring there may be value in future research on electronic physician decision tools targeted at lab monitoring.

Abbreviations: ACEi = angiotensin converting enzyme inhibitors, ARBs = angiotensin receptor blockers, CI = confidence Interval, CKD = chronic kidney disease, ED = emergency department, EHR = electronic health record, MCRA = mineralocorticoid receptor antagonists, MDRD = modification of diet in renal disease, OR = odds ratio, RAASi = renin angiotensin aldosterone system inhibitors.

Keywords: angiotensin receptor blockers, chronic kidney disease, diuretics, emergency department visits, hospitalization, renin angiotensin converting enzymes

1. Introduction

Approximately 72% of individuals with chronic kidney disease (CKD) and diabetes receive renin angiotensin aldosterone inhibitors (RAASi). They are the second most utilized anti-hypertensive class in the United States and are prescribed to 22% to 33% of the general population.[1] Healthy People 2020, launched by the Office of Disease Prevention and Health Promotion to achieve high-quality care in the United States,[2] recognizes the widespread benefits of RAASi in blood pressure control, cardiovascular disease prevention, and protection of chronic kidney disease.[3] This program aims to increase RAASi

prescription by nearly 10%.[2] Diuretics also represent a critical component of anti-hypertensive therapy, particularly in combination with other agents, and prescribed to patients with similar comorbidities.[4,5] Despite the benefits of these agents, their use is complicated by potential safety concerns related to electrolyte disturbances and kidney impairment. CKD patients, especially those with diabetes or heart disease, derive the greatest benefit from these medications however they are also the patients at highest risk of electrolyte disturbances and kidney impairment due to changes in renal hemodynamics. These asymptomatic abnormalities can be readily identified on lab testing and is subject to the frequency of monitoring. Nevertheless, there is limited evidence regarding the appropriate timing and frequency of lab monitoring during the initiation of RAASi or diuretic therapy in patients with CKD. Partially due to this lack of evidence, the standard of care for lab monitoring in this population remains poorly defined.

We assessed three objectives in this study:

1) the timing and frequency of lab monitoring before and after initiation of RAASi or diuretics in individuals with CKD managed in primary care practices;
2) associations of patient characteristics with close lab monitoring; and
3) associations of lab monitoring with acute care utilization with emergency department (ED) visits or hospitalization. We hypothesized that close lab monitoring would facilitate early recognition of metabolic abnormalities thereby reducing acute care utilization.

2. Methods

2.1. Study design and patient population

The cohort included participants with pre-dialysis CKD stage 3–5 and incident prescription of RAASi or diuretics at outpatient primary care offices in the Partners Healthcare (Boston, MA) between January 2009 and December 2011 with a one year follow up through December 2012. The data source included 36 primary care practices with 1,718 prescribers as previously described.[6,9,10] RAASi and diuretics were selected given their prevalent use in CKD and known disturbances in serum electrolytes and creatinine for which lab monitoring is frequently utilized.[7]

De-identified laboratory values for creatinine and potassium were extracted from the Electronic Health Record (EHR) as previously described.[6,9,10] Pre-exsiting CKD stage was abstracted directly from the estimated glomerular filtration rate (eGFR) automatically calculated by the Modification of Diet in Renal Disease (MDRD) Study[7] equation and reported to clinicians in the EHR and did not require use of diagnostic codes. The three most recent measurements of serum creatinine and eGFR each ≥90 days apart and no more than 1 year prior to the prescription date were averaged. End stage renal disease was assumed to be present in participants with baseline creatinine ≥6 mg/dL or eGFR ≤10 ml/min/1.73 m,[2] and these individuals were excluded from further analysis. CKD was staged according to standard definitions (stage 3 eGFR 31–59, stage 4 eGFR ≥15-<30, and stage 5 eGFR <15 ml/min/1.73 m^2).[8] The most recent potassium concentration within 90 days of the prescription date was used as the baseline potassium value.

Drug exposure was captured through EHR prescriptions written between January 2009 and December 2011. The absence of prescriptions for RAASi and diuretics for ≥ 6 months prior to the prescription date was required to identify a new prescription. Angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MCRA) were included in the RAASi group. Loop, thiazide, beta blockers/thiazide, and alpha blocker/thiazide were included in the diuretic group. MCRA and combination RAASi/ diuretics were excluded from comparisons between classes but were included in the overall analyses. Baseline pre-prescription lab monitoring was defined as lab testing occurring up to 2 days after to the prescription date. This two-day window allowed the opportunity for the medication to be filled and taken by the patient while clinicians waited for results of "baseline labs". The follow-up post-prescription period began >2 days from prescription date.

Demographics and comorbidities were extracted from the clinical problem list in the EHR. Cardiovascular disease included heart failure, reduced ejection fraction, coronary artery disease, and valvular heart disease. The Partners Institutional Review Board approved the study with a waiver of informed consent.[6,9,10]

2.2. Exposures and outcomes

Since there are no well recognized standard of care guidelines, we defined close pre-prescription lab monitoring occurring ≤2 weeks prior to the prescription through 2 days after the prescription and post-prescription lab monitoring occurring within 3-days to ≤2 weeks after the prescription date. Pre and post prescription lab monitoring and were assessed individually and as a combined outcome termed "close monitoring". We proposed two weeks as the reference because pooled evidence from RCTs suggest creatinine levels peak near this time point[11] and this is a common follow up period in clinical practice. Hyperkalemia was defined as >5.0 mmol/L and hypokalemia ≤3.5 mmol/L.

The primary endpoint was acute care utilization, which was extracted from the EHR using administrative codes for first hospitalization and ED visits from the prescription date. We looked at endpoints occurring within one year given that event occurring beyond that time frame are unlikely to be impacted by initial lab monitoring.

2.3. Statistical analysis

The t tests for normally distributed continuous variables and Pearson $\chi 2$ tests for categorical variables were used to compare baseline demographics, comorbidities, and lab values between groups. Trend tests were used for race, insurance, and CKD stage. The frequency and time intervals of pre- and post-prescription lab monitoring were described as continuous variables with the proportion occurring within 2 weeks of the prescription date also reported. χ^2 tests were used to compare proportions in CKD stage 3 compared with and stages 4/5. Logistic regression was used to determine predictors of close lab monitoring using univariate models and a multivariate model adjusting for demographics, CKD stage, comorbidities, baseline hyperkalemia, baseline hypokalemia, and medication type in the model.

ED visit or hospitalization within 365 days of incident prescription were compared using logistic regression with lab monitoring, CKD stage, baseline potassium, and medication type as predictors. A competing risk model with the Fine and Gray method[12] including death as a competing risk was used to test associations of close monitoring with time to ED visit or

hospitalization. This analysis accounts for a diminishing risk set from censoring due to mortality and is utilized in CKD cohort studies where mortality rates are often high.[13,14] Subgroup analyses were conducted by CKD stage 3–5. All analyses were run in STATA 14.2 using a two-sided P value of <.05 for significance.

3. Results

3.1. Study population

Among 8,217 individuals with stage 3–5 CKD non-dialysis (mean age 72 ± 13.4 years, 43.9% male, 86.4% white, 91.3% CKD stage 3) 52.3% were newly prescribed a RAASi and 47.7% a diuretic (Table 1, Supplemental Table 1, http://links.lww.com/MD/D409). There were 54 individuals excluded because of end stage renal disease (eGFR$\leq$ 10 ml/min/1.73 m^2 or baseline serum creatinine >6 mg/dL) (Fig. 1). Data were complete for all baseline variables except race and potassium (2.2% and 1.0% missing respectively).

Table 1
Baseline Characteristics of the Study.

Population Characteristic	n=8,217
Demographics, n (%)	
Age (years), mean ±SD	72±13.4
Age ≥65 years	5970 (72.7)
Sex, M	3602 (43.9)
Race	
White	6926 (86.4)
Black	514 (6.4)
Hispanic	250 (3.1)
Asian	133 (1.7)
Other	25 (0.3)
Insurance	
Medicare/Medicaid/Mass Health	4683 (57.0)
Private	3396 (41.3)
Self-Pay	138 (1.7)
Comorbidities, n (%)	
Chronic kidney disease	
Stage 3	7502 (91.3)
Stage 4	584 (7.1)
Stage 5	131 (1.6)
Diabetes mellitus	1926 (32.9)
Hypertension	4832 (82.6)
Cardiovascular disease	1792 (30.7)
Hyperlipidemia	1964 (33.6)
Medications, n (%)	
Renin angiotensin aldosterone system inhibitor	4127 (50.2)
Angiotensin converting enzyme inhibitor	3007 (72.9)
Angiotensin receptor blocker	1049 (25.4)
Aldosterone antagonists	116 (2.8)
Diuretics	3762 (45.8)
Loops	2237 (59.4)
Thiazides	1525 (40.5)
RAASi/diuretic combination*	328 (4.0)
NSAIDs	1519 (18.5)
Labs, mean ±SD	
Creatinine mg/dL	1.41±0.7
eGFR ml/min/1.732 m^2	45.9±10.5
Potassium mmol/dL	4.3±0.5

* Combination diuretic/RAASi medications and mineralocorticoid receptor antagonists were excluded (n=328 (4.0%)) from comparisons. Cardiovascular disease includes preserved and reduced ejection fraction heart failure, coronary artery disease, and valvular disease. NSAID=non-steroidal anti-inflammatory drugs, RAASi=Renin angiotensin aldosterone system inhibitors.

3.2. Pre- and post-prescription lab monitoring

Pre-prescription lab monitoring was not done within 2 weeks in 3,306 (40.2%) while post-prescription monitoring was not done within 2 weeks in 5957 (72.5%) which includes 524 (6.4%) individuals without post-prescription within 1 year. Close lab monitoring with pre- and post-prescription lab monitoring within 2 weeks was present in only 1547 (20.1%). There was a trend towards closer monitoring with more severe CKD (Table 2). The proportion of post prescription lab monitoring done ≥6 weeks after a prescription was 44.8% in the total population and declined with more advanced CKD (P<.001). Close lab monitoring was more frequent in individuals prescribed diuretics 827 (22.0%) compared to RAASi 684 (16.6%) (P<.001) (Supplemental Table 2, http://links.lww.com/MD/D410).

3.3. Associations with baseline characteristics and close lab monitoring

Following adjustment for baseline demographics (age, sex, race, insurance), comorbidities (hypertension, diabetes mellitus), and baseline presence of hyperkalemia or hypokalemia), CKD stage 4/5 and cardiovascular disease were associated with increased likelihood of close lab monitoring (CKD stage 4/5 vs stage 3 adjusted OR 1.47; 95%CI 1.16–1.86 and CVD vs no CVD adjusted OR 1.42; 95%CI 1.21–1.66). New RAASi users were less likely to receive close monitoring (diuretics vs RAASi adjusted OR 1.39; 95%CI 1.20–1.62) (Table 3). Associations of baseline hypokalemia with close lab monitoring were significant in the total cohort but did not achieve significance in sensitivity analyses individually examining the RAASi and diuretics subgroups. Otherwise, associations were qualitatively similar in sensitivity analyses by medication type (Supplemental Table 3, http://links.lww.com/MD/D411).

3.4. Associations of close lab monitoring with acute care utilization

Close lab monitoring was not associated with the likelihood of an emergency department visit or hospitalization in models adjusted for baseline demographics, comorbidities, potassium, eGFR, and medication type (Table 4). Results were consistent in sensitivity analyses examining outcomes separately by CKD stage, however the sample size was limited (n=584 in stage 4 and n=131 in stage 5). (Supplemental Table 4, http://links.lww.com/MD/D412).

In competing risk-analyses with death as a competing event, the cumulative incidence of an ED visit or hospitalization within 1 year of the incident prescription date did not differ in those with vs without close lab monitoring (subdistribution hazard ratio (SHR) 1.06; 95%CI 0.83–1.37). Likewise, when examined individually, neither the presence of pre-prescription labs or post prescription labs within 14 days were associated with ED visits or hospitalization (SHR 1.04; 95%CI 0.87- 1.25 and SHR 1.06; 95%CI 0.85–1.30 respectively). These associations were also evaluated at 7 weeks from the incident prescription date and the results were qualitatively similar (data not shown).

4. Discussion

We evaluated individuals with CKD starting on RAASi or diuretics and found that nearly 80% did not receive close lab monitoring before or after drug initiation. Similarly, nearly half did not undergo post-prescription lab monitoring within 6 weeks
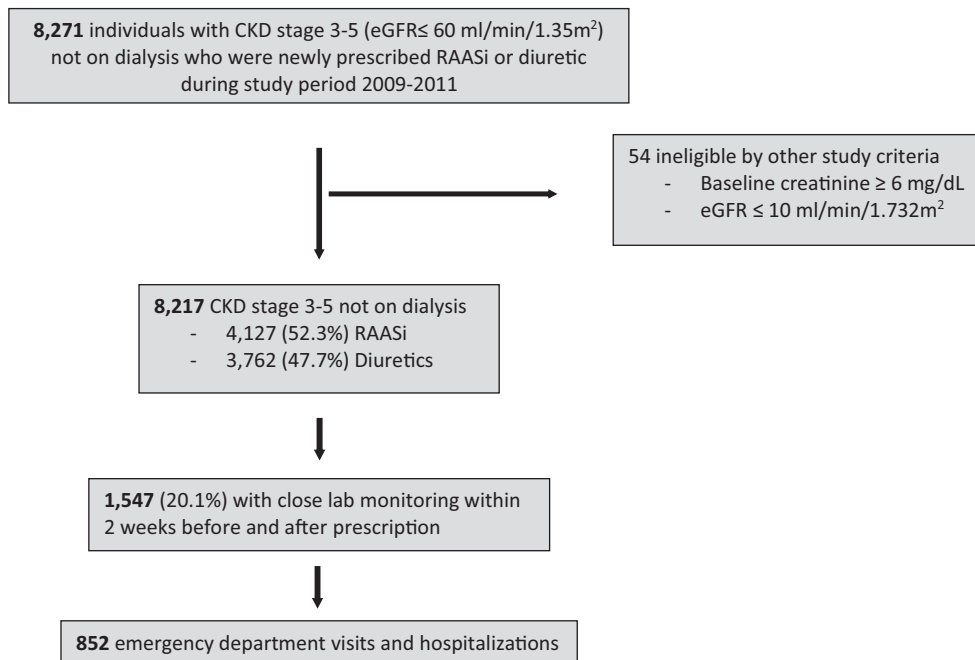
Figure 1. Study flow diagram. eGFR = estimated glomerular filtration rate, RAASi = Renin angiotensin aldosterone system inhibitors. All follow up labs were within 365 days of the prescription date. Combination RAASi and diuretic n = 328 (4.0%).

of drug initiation. Close lab monitoring was more frequent in patients with cardiovascular disease, advanced CKD stage 4/5, hypokalemia, and diuretic initiation. Contrary to our hypothesis, close lab monitoring was not associated with reduced risk of acute care utilization from ED visits or hospitalizations.

Although we found a low rate of lab monitoring, it is clearly essential for identifying and diagnosing hyperkalemia, which if unrecognized, may potentially lead to fatal arrhythmia. RCTs have highlighted the increased incidence of hyperkalemia following RAASi initiation in patients with CKD compared to the general population and suggest the highest risk occurs within the first few weeks of therapy.[11,15] In individuals with CKD stage 3b, hyperkalemia occurred in 38% to 41% of patients

following new prescription of ACEi or ARB and 86% of these cases occurred within the first 4 weeks after drug intiation.[16] Furthermore, the severity of CKD represents an established risk factor for hyperkalemia; estimated GFR <30 mL/min was associated with a 3-fold higher risk compared to eGFR >50 mL/min.[17] In the general population the risk appears much lower; incidence of hyperkalemia with ACEi ranges from 0.20% to 0.80% in a pooled cohort of RCTs and meta-analysis respectively.[18,15] In addition, CKD patients are at increased risk of azotemia following RAASi initiation compared with the general public.[7,16,17] In the general population, meta-analyses report the incidences of increased serum creatinine ≥0.5 mg/dL is about 1.5% at 2 weeks.[15,18] Whereas in individuals with CKD,

Table 2

Outpatient lab monitoring before and after initiation of renin angiotensin aldosterone inhibitor or diuretic therapy categorized by chronic kidney disease stage.

	Total n = 8,217	CKD stage 3 n = 7,502 (91.3%)	CKD stage 4 n = 584 (7.1%)	CKD stage 5 n = 131 (1.6%)	P Value*
Pre-prescription lab monitoring					
Number of days, mean ±SD	41.3±79.3	42.6±80.8	26.2±55.6	32.9±72.0	<.001
≤2 weeks, n (%)	4911 (59.8)	3064 (40.8)	386 (66.1)	87 (66.4)	.001
Post-prescription lab monitoring					
Number of days, mean ±SD	78.0±97.6	79.5±98.5	61.3±86.2	65.3±91.7	<.001
Intervals					<.001
≤2 weeks, n (%)	2256 (27.5)	2002 (26.7)	207 (35.5)	47 (35.9)	
2–4 weeks, n (%)	1077 (13.1)	962 (11.8)	95 (16.3)	20 (15.3)	
≥4–6 weeks, n (%)	682 (8.3)	641 (8.5)	35 (6.0)	6 (4.6)	
≥6 weeks, n (%)	3678 (44.8)	3406 (45.4)	224 (38.3)	48 (36.6)	
Not done, n (%)	524 (6.4)	491 (6.5)	23 (3.9)	10 (7.6)	.04
Close lab monitoring					
n (%)	1547 (20.1)	1361 (19.4)	146 (26.0)	40 (33.1)	<.001

Pre-prescription number of days refers to the time from lab monitoring to prescription. Post-prescription number of days refers to the time from prescription to lab monitoring.
* Students independent t-test was used to compare numerical values between CKD stage 3 and stages 4/5. Pearson χ² test was used to compare proportions between CKD stage 3 and stages 4/5. RAASi = renin angiotensin aldosterone system inhibitor, CKD = chronic kidney disease.

Table 3

Associations of baseline characteristics with close lab monitoring before and after initiation of renin angiotensin aldosterone inhibitor or diuretic therapy.

	Event Rate n/N (%)	Univariate OR (95%CI)	*P* Value	Adjusted OR (95%CI)	*P* Value
Incident medication					
RAASi	689/3,639 (18.9)	1.0 (ref)		1.0 (ref)	
Diuretics	858/4,054 (21.2)	1.44 (1.29–1.61)	<.001	1.39 (1.20–1.62)	<.001
Baseline potassium, mmol/L					
Normal, 3.4–5.0	1,423/7,121 (20.0)	1.0 (ref)		1.0 (ref)	
Hyperkalemia, >5.0	124/572 (21.7)	1.11 (0.90–1.36)	.331	1.18 (0.91–1.53)	.22
Hypokalemia, ≤3.5	84/296 (28.4)	1.61 (1.24–2.08)	<.001	1.50 (1.04–2.14)	.03
Co-morbidities, n (%)					
Chronic Kidney Disease					
Stage 3	1,361/7,011 (19.4)	1.0 (ref)		1.0 (ref)	
Stage 4	146/561 (26.0)	1.46 (1.19–1.78)	<.001	1.47 (1.16–1.86)	.001
Stage 5	40/121 (33.1)	2.05 (1.40–3.01)	<.001		
Hypertension					
No	185/949 (19.5)	1.0 (ref)		1.0 (ref)	
Yes	765/4,545 (16.8)	0.83 (0.70–1.0)	.049	0.90 (0.74–1.08)	.26
Cardiovascular Disease					
No	589/3,797 (15.5)	1.0 (ref)		1.0 (ref)	
Yes	361/1,697 (21.3)	1.47 (1.27–1.70)	<.001	1.42 (1.21–1.66)	<.001
Diabetes mellitus					
No	619/3,691 (16.8)	1.0 (ref)		1.0 (ref)	
Yes	331/1,803 (18.4)	1.12 (0.96–1.29)	.144	0.98 (0.84–1.15)	.84
Demographics, n (%)					
Age					
<65 yr	552/2,139 (25.8)	1.0 (ref)		1.0 (ref)	
≥65 yr	995/5,554 (17.9)	0.63 (0.56–0.71)	<.001	0.71 (0.60–0.85)	<.001
Sex					
F	786/4,292 (18.3)	1.0 (ref)		1.0 (ref)	
M	761/2,640 (22.4)	1.29 (1.15–1.44)	<.001	1.28 (1.10- 1.48)	.001
Race					
White	1,369/6,866 (19.9)	1.0 (ref)		1.0 (ref)	
Non white	110/488 (22.5)	0.86 (0.69–1.07)	.166	0.87 (0.65–1.15)	.32
Insurance					
Public[†]	852/4,380 (19.5)	1.0 (ref)		1.0 (ref)	
Private	657/3,181 (20.7)	1.08 (0.96–1.21)	.197	0.97[*] (0.84–1.13)	.71
Self-Pay	38/132 (28.8)	1.67 (1.14–2.46)	.009		

Models are adjusted for baseline demographics (age, sex, race, insurance), comorbidities (chronic kidney disease stage, hypertension, cardiovascular disease, diabetes mellitus), baseline potassium values (hyperkalemia >5.0 mmol/L, hypokalemia <3.5 mmol/L) and incident medication (diuretic, RAASi). Diuretics includes both loop and thiazide diuretics. Combination diuretic/RAASi medications and mineralocorticoid receptor antagonists were excluded (n=328). Patients missing baseline potassium were also excluded (n=196).
[*]Chronic kidney disease stage 4 and 5 were combined due to small sample size. [†]Public insurance includes Medicare/Medicaid/Mass Health. Private and self-pay insurance were collapsed into one variable due to small sample size. RAASi=renin angiotensin aldosterone inhibitor.

16% developed a fall in eGFR of ≥15% at 2 weeks. However, this only persisted at 8 weeks in 7%, and most patients regardless of initial change in kidney function benefited from long term CV and renal protection.[19]

Recent studies also raise concern for patient harm and increased healthcare expenditure associated with metabolic disturbances that can readily be identified by lab monitoring. A United Kingdom nation-wide cohort study reported that incremental rises in serum creatinine following RAASi initiation were associated with mortality, cardiovascular events, and end stage renal disease.[20] Among cardiovascular agents in the United States, RAASi were the most frequently associated with emergency department (ED) use due to adverse drug events, leading to inpatient hospitalization in up to 25% of cases.[21]

Despite these risks of acute metabolic disturbances in patients with CKD following RAASi initiation, few studies have examined lab monitoring within the first few weeks of therapy. There is little data on -if close monitoring improves patient outcomes. Our study confirmed the high incidence of acute care utilization in patients with CKD (over 10%) with the majority due to hospitalization (65%). We hypothesized that close lab monitoring would facilitate early recognition of metabolic abnormalities thereby reducing acute care utilization. However, no such association was detected even after subgroup analyses for CKD stage and medication class. Our data suggest that despite the potential benefit, patients with CKD do not frequently receive lab monitoring during RAASi or diuretic initiation which may reflect the clinician's decision to save costs or reduce patient burden. However, we also found that CVD and advanced CKD were associated with close lab monitoring suggesting that physicians may select high risk patients to receive increased monitoring. Given the ability to identify asymptomatic and potentially important laboratory disturbances, our data support the need for future studies designed to determine the optimal timing and frequency for lab monitoring based on patient risk categories. Though there are strong guidelines on indications for RAASi and diuretics, there are no guidelines on the optimal monitoring strategy during their initiation. Resolution of this important

Table 4

Associations of lab monitoring with emergency department visits or hospitalization within 365 days of new initiation of renin angiotensin aldosterone inhibitor or diuretic therapy.

	n/N (%)	Crude SHR (95% CI)	P Value	Adjusted SHR (95% CI)	P Value
Emergency department visit or hospitalization					
Overall cohort					
	852/8217 (10.4)				
Close lab monitoring					
Yes	147/1547 (9.5)	1.0 (ref)		1.0 (ref)	
No	705/6670 (10.6)	1.12 (0.93–1.36)	.22	1.06 (0.83–1.37)	.63
Pre-prescription lab monitoring within 2 weeks					
Yes	509/4911 (10.4)	1.0 (ref)		1.0 (ref)	
No	434/3306 (10.4)	1.00 (0.87–1.16)	.99	1.04 (0.87–1.25)	.68
Post prescription lab monitoring within 2 weeks					
Yes	221/2256 (9.8)	1.0 (ref)		1.0 (ref)	
No	575/5437 (10.6)	1.09 (0.92–1.28)	.31	1.06 (0.85–1.30)	.62
Post prescription lab monitoring					
Done	796/7693 (10.4)	1.0 (ref)		1.0 (ref)	
Not done or missing	56/524 (10.7)	1.04 (0.72–1.28)	.81	0.89 (0.62–1.28)	.51

Missing or not done post prescription lab monitoring is included in "no". Models are adjusted for baseline demographics (age, sex, race, insurance), comorbidities (chronic kidney disease stage, hypertension, cardiovascular disease, diabetes mellitus), baseline potassium, baseline estimated glomerular filtration rate, and incident medication (diuretic, RAASi). RAASi = renin angiotensin aldosterone system inhibitor. Diuretics includes thiazides and loops.

question would be helpful for these widely used anti-hypertensives.

The strengths of the study are that we evaluated a large group of patients with CKD and hypertension in routine care settings, and addressed questions pertinent to a wide physician audience. The inclusion criteria were restricted to patients with three baseline measures of eGFR within one year of the prescription date. As opposed to a single eGFR value, this criterion improves confidence in the diagnosis and stage of CKD and increases the likelihood that eGFR calculations reflect steady state. The two-week interval was selected as pooled evidence from RCTs suggest creatinine and potassium levels peak near this time after starting RAASi.[10,15] Although standard of care guidelines are lacking, this is also a generally acceptable follow up time in clinical practice for patients with CKD. Finally, the primary outcome of acute care utilization, measured by ED visits and hospitalizations, has important implications for patient safety and healthcare costs.

Bias of indication is a limitation of the study design. Lab monitoring may be influenced by the severity of illness, concomitant medications, drug-drug interactions, a history of electrolyte lab disturbances, patient compliance, or healthcare access. Largely related to the retrospective study design we were not able to adjust for these factors. The study design also did not allow for adjustment of practice variability or physician preferences that may influence lab monitoring and we cannot rule out the potential for site effects. Labs in this database were captured from both the primary care and specialty practices within the Partners network. Thus, we believe it is unlikely that many patients received routine monitoring outside of the system. Nevertheless, labs done outside the network are indistinguishable from labs that not checked at all. Similarly, ED visits and hospitalizations that occurred outside the EHR would not have been captured. Missed events for these reasons could have influenced the absence of detectable associations between lab monitoring and acute care utilization. We also were unable to reliably assess the admission diagnoses which limit our interpretation of electrolyte and kidney function in association with ED visits and hospitalizations during initiation of RAASi and diuretics. Additionally, the academic and metropolitan

nature of this cohort that is maintained in a PCP network under a unified EHR is likely to limit its generalizability as there may be differences in practice patterns and patient characteristics compared to other settings.

Practice networks with low monitoring rates may benefit from physician support tools to improve quality of care. In hospitalized patients, automated decision aids have been shown to improve patient care, optimize prescribing behavior, and reduce medical error.[22,23] Similar electronic decision aids have reduced the risk of drug-drug interactions and improved appropriate prescriptions resulting in shorter hospitalizations.[24] The utility of such automated tools in outpatient primary care management is less well-described. However, electronic physician support systems designed to improve implementation of CKD guidelines at the point of care were shown to improve physician workflow in large primary care networks.[25] Similarly, a pharmacist intervention has been shown to reduce cardiovascular disease risk,[26] and online resources have facilitated uptake of guidelines and nephrology referral for CKD patients in primary care settings.[27] These data suggest the potential for automated tools to increase lab monitoring in patients with CKD during initiation of RAASi or diuretic therapy.

This study provides new insights on laboratory monitoring in high risk patients and its effectiveness on acute care utilization. Results show that nearly 45% of individuals did not receive lab monitoring until over 6 weeks after RAASi or diuretic initiation. Though there was no association with ED visits or hospitalizations, this may not represent optimal care. Our results highlight the low utilization of lab monitoring during initiation of RAASi and diuretics in high risk patients as an area for potential quality improvement through development of clinical guidelines and electronic physician aid tools.

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References

[1] Gu Q, Burt VL, Dillon CF, et al. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health and Nutrition Examination Survey, 2001 to 2010. Circulation 2012;126:2105.

[2] Healthy People 2020. U. S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion (2016). https://www.healthypeople.gov/2020/topics-objectives/topic/chronic-kidney-disease/objectives. (access date August 30, 2018)

[3] Heerspink HJ, Ninomiya T, Persson F, et al. Is a reduction in albuminuria associated with renal and cardiovascular protection? A post hoc analysis of the ALTITUDE trial. Diabetes Obes Metab 2016;18:169–77.

[4] Hunt SA, Abraham WT, et al. Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the american college of cardiology Foundation/American heart association task force on practice guidelines: developed in collaboration with the international society for heart and lung transplantation. Circulation 2009;119:e479.

[5] Weber M, Schiffrin E, White W, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the american society of hypertension and the international society of hypertension. J Hypertens 2014;32:3–15.

[6] Insook Cho, Sarah P, Slight , et al. Understanding physicians' behavior toward alerts about nephrotoxic medications in outpatients: a cross-sectional analysis. BMC Nephrol 2014;15:200.

[7] Beddhu S, Greene T, Boucher R, et al. Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. Lancet Diabetes Endocrinol 2018;6:555–63.

[8] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

[9] Nanji KC, Slight SP, Seger DL, et al. Overrides of medication-related clinical decision support alerts in outpatients. J Am Med Inform Assoc 2014;21:487–91.

[10] Garlo KG, Bates DW, Seger DL, et al. Association of changes in creatinine and potassium levels after initiation of renin angiotensin aldosterone system inhibitors with emergency department visits, hospitalizations, and mortality in individuals with chronic kidney disease. JAMA Netw Open 2018;1(7.):

[11] Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor–associated elevations in serum creatinine. Arch Intern Med 2000;160:

[12] Fine JPGR. A proportional hazards model for the subdistribution of competing risks in survival analysis. J Am Stat Assoc 1999;94:496–509.

[13] Lim HJ, Zhang X, Dyck R, et al. Methods of competing risks analysis of end-stage renal disease and mortality among people with diabetes. BMC Med Res Methodol 2010;10:97.

[14] Noordzij M, Leffondré K, Van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant 2013;28:2670–7.

[15] Lakhdar R, Al-Mallah MH, Lanfear DE. Safety and tolerability of angiotensin-converting enzyme inhibitor versus the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker in patients with left ventricular dysfunction: a systematic review and meta-analysis of randomized controlled trials. J Card Fail 2008;14:181–8.

[16] Espinel E, Joven J, Gil I, et al. Risk of hyperkalemia in patients with moderate chronic kidney disease initiating angiotensin converting enzyme inhibitors or angiotensin receptor blockers: a randomized study. BMC Res Notes 2013;6:1–9.

[17] Weinberg JM, Appel LJ, Bakris G, et al. Risk of hyperkalemia in nondiabetic patients with chronic kidney disease receiving antihypertensive therapy. Arch Intern Med 2009;169:1587–94.

[18] Phillips CO, Kashani A, Ko DK, et al. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials. Arch Intern Med 2007;167:1930–6.

[19] Clase CM, Barzilay J, Gao P, et al. Acute change in glomerular filtration rate with inhibition of the renin-angiotensin system does not predict subsequent renal and cardiovascular outcomes. Kidney Int 2017;91:683–90.

[20] Schmidt M, Mansfield KE, Bhaskaran K, et al. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: Cohort study. BMJ 2017;356:j791.

[21] Shehab N, Lovegrove MC, Geller AI, et al. US emergency department visits for outpatient adverse drug Events, 2013–2014. JAMA 2016;316:2115–25.

[22] Tawadrous Davy, Salimah Z. Shariff, R. Brian Haynes, et al. Use of clinical decision support systems for kidney-related drug prescribing: a systematic review. Am J Kidney Dis 2011;58:903–14. 6.

[23] Park S, Baek SH, Ahn S, et al. Impact of electronic acute kidney injury (AKI) alerts with automated nephrologist consultation on detection and severity of AKI: a quality improvement study. Am J Kidney Dis 2018;71:9–19.

[24] Chertow GM, Lee J, Kuperman GJ, et al. Guided medication dosing for inpatients with renal insufficiency. JAMA 2001;286:2839–44.

[25] Gulla J, Neri PM, Bates DW, et al. User requirements for a chronic kidney disease clinical decision support tool to promote timely referral. Int J Med Inform 2017;101:50–7.

[26] Al Hamarneh YN, Hemmelgarn BR, Hassan I, et al. The effectiveness of pharmacist interventions on cardiovascular risk in adult patients with type 2 diabetes: the multicentre randomized controlled RxEACH trial. Can J Diabetes 2017;41:580–6.

[27] Donald M, McBrien K, Jackson W, et al. Development and implementation of an online clinical pathway for adult chronic kidney disease in primary care: A mixed methods study. BMC Med Inform Decis Mak 2016;16:1–1.