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, 3,306 (40.2%) individuals did not have pre-prescription labs done within 2 weeks, and 5,957 (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 1,547 (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%. Diuretics also represent a critical component of antihypertensive therapy, particularly in combination with other agents, and prescribed to patients with similar comorbidities. 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. RAASi and diuretics were selected given their prevalent use in CKD care practices with 1,718 prescribers as previously described.

De-identified laboratory values for creatinine and potassium were extracted from the Electronic Health Record (EHR) as previously described Pre-existing CKD stage was abstracted directly from the estimated glomerular filtration rate (eGFR) automatically calculated by the Modification of Diet in Renal Disease (MDRD) Study 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 m2, 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 m2). 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 (ACEIs), 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.

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 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 χ2 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. χ2 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 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. 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%
were newly prescribed a diuretic (Table 1, Supplemental Table 1, http://links.lww.com/CKD). Among the
8,217 individuals, 91.3% were stage 3 CKD (Fig. 1). There were 54 individuals excluded because of end
stage renal disease (eGFR < 10 ml/min/1.73 m² 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).

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).

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

Table 1

| Baseline Characteristics of the Study. | n = 8,217 |
|----------------------------------------|-----------|
| **Demographics, n (%)**                |           |
| Age (years), mean ± SD                 | 72 ± 13.4 |
| Age ≥ 65 years                         | 5970 (72.7) |
| Sex, M                                 | 3602 (43.0) |
| 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 (23.9) |
| Hypertension                           | 4832 (60.0) |
| Cardiovascular disease                 | 1792 (21.7) |
| Hyperlipidemia                         | 1964 (33.6) |
| Medications, n (%)                     |           |
| Renin angiotensin aldosterone system inhibitor | 4217 (50.2) |
| Angiotensin converting enzyme inhibitor | 3007 (37.0) |
| Angiotensin receptor blocker           | 1049 (25.4) |
| Aldosterone antagonists                | 116 (2.8)  |
| Diuretics                              | 3762 (45.0) |
| Loops                                  | 2237 (59.4) |
| Thiiazides                             | 1525 (40.5) |
| RAAS/diuretic combination              | 328 (4.0) |
| NSAIDs                                 | 1519 (18.5) |
| Labs, mean ± SD                        |           |
| Creatinine mg/dL                       | 1.41 ± 0.7 |
| eGFR m/l/min/1.73 m²                   | 45.9 ± 0.5 |
| 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, RAAS = renin angiotensin aldosterone system inhibitors.
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 initiation.[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

|                     | 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 |               |                              |                          |                           |         |
| ≤2 weeks, n (%)       | 41.3 ± 79.3    | 42.6 ± 80.8                  | 26.2 ± 55.6              | 32.9 ± 72.0               | <.001   |
|                      | 4911 (59.8)    | 3064 (40.8)                 | 386 (66.1)              | 87 (66.4)                 | .001    |
| **Post-prescription lab monitoring** |               |                              |                          |                           |         |
| Number of days, mean ± SD |               |                              |                          |                           |         |
| ≤2 weeks, n (%)       | 78.0 ± 97.6    | 79.5 ± 98.5                  | 61.3 ± 86.2              | 65.3 ± 91.7               | <.001   |
|                      | 2256 (27.5)    | 2002 (26.7)                 | 207 (35.5)              | 47 (35.9)                 | <.001   |
| 2–4 weeks, n (%)      | 1077 (13.1)    | 962 (11.8)                  | 95 (16.3)               | 20 (15.3)                 |         |
| ≥4–6 weeks, n (%)     | 662 (8.3)      | 641 (8.5)                  | 35 (6.0)               | 6 (4.6)                   |         |
| ≥6 weeks, n (%)       | 3678 (44.8)    | 3406 (45.4)                | 224 (38.3)            | 46 (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

| 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) | <.001               | 1.0 (ref) | <.001 |
| 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) | <.001               | 1.0 (ref) | <.001 |
| 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            | 657/3,180 (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 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, RAASIs 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 RAASIs 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 RAASIs and diuretics, there are no guidelines on the optimal monitoring strategy during their initiation. Resolution of this important
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 incurred 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.[12,23] 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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