Nephrologist Follow-Up versus Usual Care after an Acute Kidney Injury Hospitalization (FUSION)
A Randomized Controlled Trial

Samuel A. Silver,[1] *Neill K. Adhikari*,[2,3] *Chaim M. Bell*,[3,4] *Christopher T. Chan*,[5] *Ziv Harel*,[6] *Abhijat Kitchlu*,[5] *Alejandro Meraz-Muñoz*,[6] *Patrick A. Norman*,[7,8] *Adic Perez*,[2] *Alireza Zahirieh*,[9] and *Ron Wald*[6]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence: Dr. Samuel A. Silver, Division of Nephrology, Queen's University, 76 Stuart Street, 3-Burr 21-3-039, Kingston, ON K7L 2V7, Canada. Email: samuel.silver@queensu.ca

Abstract

Background and objectives Survivors of AKI are at higher risk of CKD and death, but few patients see a nephrologist after hospital discharge. Our objectives during this 2-year vanguard phase trial were to determine the feasibility of randomizing survivors of AKI to early follow-up with a nephrologist or usual care, and to collect data on care processes and outcomes.

Design, setting, participants, & measurements We performed a randomized controlled trial in patients hospitalized with Kidney Disease Improving Global Outcomes (KDIGO) stage 2–3 AKI at four hospitals in Toronto, Canada. We randomized patients to early nephrologist follow-up (standardized basket of care that emphasized BP control, cardiovascular risk reduction, and medication safety) or usual care from July 2015 to June 2017. Feasibility outcomes included the proportion of eligible patients enrolled, seen by a nephrologist, and followed to 1 year. The primary clinical outcome was a major adverse kidney event at 1 year, defined as death, maintenance dialysis, or incident/progressive CKD.

Results We screened 3687 participants from July 2015 to June 2017, of whom 269 were eligible. We randomized 71 (26%) patients (34 to nephrology follow-up and 37 to usual care). The primary reason stated for declining enrollment included hospitalization-related fatigue ($n=65$), reluctance to add more doctors to the health care team ($n=59$), and long travel times ($n=40$). Nephrologist visits occurred in 24 of 34 (71%) intervention participants, compared with three of 37 (8%) participants randomized to usual care. The primary clinical outcome occurred in 15 of 34 (44%) patients in the nephrologist follow-up arm, and 16 of 37 (43%) patients in the usual care arm (relative risk, 1.02; 95% confidence interval, 0.60 to 1.73).

Conclusions Major adverse kidney events are common in AKI survivors, but we found the in-person model of follow-up posed a variety of barriers that was not acceptable to many patients.

Clinical Trial registry name and registration number: Nephrologist Follow-up versus Usual Care after an Acute Kidney Injury Hospitalization (FUSION), NCT02483039

CJASN 16: 1005–1014, 2021. doi: https://doi.org/10.2215/CJN.17331120

Introduction

AKI is a common complication of severe illness that affects up to 20% of patients who are hospitalized (1–3). As outcomes of AKI-associated hospitalizations improve, 75%–80% of patients are surviving to hospital discharge (4), which has been accompanied by a heightened appreciation that survivors of AKI remain at risk of adverse outcomes. These complications include CKD and kidney failure (5), and cardiovascular events such as new-onset hypertension (6), cerebrovascular disease (7), and myocardial infarction (8).

Over 80% of hospitalized patients are unaware they experienced AKI, including some patients who received dialysis (9). Similarly, post-AKI care is not a traditional component of many nephrologists' outpatient practice (10,11). Even among patients with dialysis-requiring AKI who recover sufficient kidney function to no longer require dialysis, only 40% see a nephrologist within 90 days of hospital discharge (12). The potential benefits of early nephrologist follow-up were highlighted in an observational study that demonstrated a 24% relative reduction in mortality among survivors of dialysis-receiving AKI (12).

Although AKI is associated with adverse postdischarge outcomes, it is unclear if routine ambulatory follow-up of AKI survivors is feasible or improves outcomes. Therefore, we initiated a multicenter, randomized controlled trial to determine whether early follow-up with a nephrologist after Kidney Disease Improving Global Outcomes (KDIGO) stage 2–3 AKI conferred a lower risk of major adverse kidney events, as compared with usual care. Herein, we report the

feasibility of conducting this trial after completion of a planned 2-year vanguard phase trial.

Materials and Methods

Study Design

We conducted an open-label, parallel-arm, randomized controlled trial at four academic hospitals in Toronto, Canada, between July 2015 and June 2017. The trial was registered on June 26, 2015, and we made no changes to the protocol after trial commencement. The research ethics boards at participating sites approved the trial, which adhered to the Declaration of Helsinki, and each participant provided written informed consent.

Patient Recruitment

Trained coordinators manually screened adult (≥18 years of age) nephrology, critical care, cardiology, general medicine/surgery, and cardiovascular surgery inpatient rosters, daily on weekdays, to identify patients who met the eligibility criteria. Because electronic serum creatinine alerts were not available at participating sites, we first identified patients with any potential kidney dysfunction on the basis of the case description listed on the inpatient roster. We then assessed additional inclusion criteria (all of which needed to be fulfilled and could be met at any time during the hospitalization) as follows: (*1*) a two-fold increase in serum creatinine from baseline known or presumed to have occurred within the prior 7 days (*i.e.*, KDIGO stage 2 AKI and above by serum creatinine criteria); and (*2*) ability to provide informed consent (13). We excluded patients who required follow-up care with a nephrologist as part of standard practice, including those with a baseline eGFR of <30 ml/min per 1.73 m^2; persistent requirement for KRT at hospital discharge; patients with a functioning kidney transplant; previously established and ongoing nephrology follow-up; and a clinical suspicion of GN, polycystic kidney disease, myeloma cast nephropathy, or thrombotic microangiopathy. We also excluded patients who were pregnant, resided in a nursing home, or had an estimated life expectancy of ≤6 months.

We defined baseline creatinine as the most recent outpatient serum creatinine between 7 and 365 days before hospital admission, or, if not available, as the post-AKI nadir (14,15). We approached all eligible patients for informed consent only if they were in a noncritical care unit. This recruitment strategy targeted patients approaching hospital discharge so as to avoid randomization of patients with unexpected deterioration/death.

Randomization and Interventions

We randomized patients 1:1 to early nephrologist follow-up at each hospital's AKI follow-up clinic or usual care using randomly permuted blocks of size four and six, stratified by center. An independent statistician generated sequential, opaque, sealed envelopes that were unsealed after enrollment and indicated treatment allocation. The AKI follow-up clinic standardized assessment forms included management advice, using prevailing evidence for management of CKD (16), hypertension (17), hyperlipidemia (18), and diabetic kidney disease (19), but nephrologists were free to tailor treatment to the individual patient's needs (Supplemental Figure 1). All patients received a sick-day medication list (Supplemental Figure 2) and were asked to complete blood work at 3-month intervals through 1 year. We targeted the initial appointment within 30 days of discharge to ensure all patients could be assessed by 90 days, as recommended by KDIGO guidelines (13); we permitted later appointments beyond 90 days and did not consider these to be protocol violations. The treating nephrologist decided on the frequency of any subsequent appointments.

For participants randomized to usual care, we alerted patients and primary care providers of their AKI diagnosis with a letter (as required by the research ethics boards; Supplemental Figure 3). Health care providers could still refer patients to a nephrologist, but not the AKI follow-up clinic, at their discretion.

Data Collection

We collected the following baseline demographic data: age, sex, race, comorbidities, details of the index hospitalization, episode of AKI (*i.e.*, maximum KDIGO AKI stage), and medication use. We contacted all patients quarterly to ascertain medications, emergency department visits, hospitalizations, and vital status. All patients completed laboratory investigations at 1 year.

Outcomes

As part of the 2-year planned vanguard phase trial, feasibility outcomes included the proportion of eligible patients enrolled, the proportion of randomized patients seen by a nephrologist, and the proportion of patients followed to 1 year. The primary clinical outcome was a major adverse kidney event at 1 year postrandomization, defined as a composite of death, maintenance dialysis, or incident/progressive CKD (defined as a newly sustained eGFR of <60 ml/min per 1.73 m^2, or a sustained decrease in eGFR of ≥25% from the pre-AKI baseline). The CKD component of the end point was met when the decline in eGFR was first satisfied, as long as it was sustained for at least 3 more months and the second value occurred within 15 months of randomization. This composite end point has been endorsed by the National Institute of Diabetes and Digestive and Kidney Diseases Clinical Trials Workgroup (20).

Prespecified secondary outcomes included the individual components of major adverse kidney events at 1 year; time to a major adverse kidney event; proportion with a major adverse cardiac event, and the individual components of the adverse event (hospitalization/emergency department visit for stroke, heart failure, myocardial infarction, or cardiac revascularization procedure) at 1 year; time to a major adverse cardiac event; time to first rehospitalization/emergency department visit; time to first rehospitalization with AKI (biochemical evidence of AKI of any KDIGO stage) (21); the number of rehospitalizations with AKI; and change in health-related quality of life, using the European Quality of Life Five Dimensions Five Level (EQ-5D-5L) questionnaire (22). Other exploratory outcomes included differences in processes of care (*e.g.*, nephrologist visits, medication changes, laboratory tests), the CKD outcome categorized as incident CKD (eGFR of <60 ml/min per

1.73 m^2 from pre-AKI baseline that is ≥60 ml/min per 1.73 m^2) or progressive CKD (≥25% eGFR decrease from pre-AKI baseline that is <60 ml/min per 1.73 m^2), albuminuria, and serum creatinine/eGFR over 1 year.

Sample Size

The vanguard phase of this trial had adequate institutional support to enroll patients for a total of 2 years. On the basis of our previous experience (23), we anticipated that approximately 400 patients would meet eligibility criteria across the four sites. Therefore, we specified that enrollment of 200 patients (50% of those eligible; 95% confidence interval [95% CI]), 45%–55%) would provide a reasonable demonstration of feasibility. If successful, we planned to enroll these patients into a larger trial powered for a major adverse kidney event at 1 year.

Statistical Analyses

All analyses adhered to an intention-to-treat principle. Patients who were lost to follow-up could contribute events (*e.g.*, CKD) until the last follow-up date, and were assumed to be alive at 1 year. We expressed continuous variables as means (SD) or medians (interquartile range [IQR]), and categoric variables as numbers (percentage). We compared continuous outcomes with the Wilcoxon rank-sum test, and binary outcomes using the Fisher exact test. We reported major adverse kidney events and their components at 1 year as relative risks (RR) with 95% CIs, and as a Kaplan–Meier time-to-event analysis comparing arms with a log-rank test. We compared the total number of AKI rehospitalizations with a Poisson regression model to obtain the RR and 95% CI. We assessed differences in medication use between arms with a Mantel–Haenszel test stratified by preadmission medication use. For other time-to-event outcomes, we used Cox regression to calculate hazard ratios (HRs) and their associated 95% CIs, and accounted for the competing risk of death (where appropriate) using the method described by Fine and Gray. We considered a two-sided $P<0.05$ as statistically significant. We performed all analyses using SAS version 9.4 (SAS Institute, Cary, NC).

Results

We identified 3687 participants who met preliminary screening criteria, of whom 269 were fully eligible and 71 (26% of those eligible) were randomized (Figure 1). The primary reason provided (one permitted for each patient) for declining participation included hospitalization-related fatigue ($n=65$), reluctance to add more doctors to the health care team ($n=59$), and long travel times to the hospital for scheduled clinic visits ($n=40$). The trial was stopped due to slow recruitment and insufficient funding for further enrollment, which ceased in June 2017, with last event follow-up in June 2018.

Patient Characteristics

Patient characteristics by treatment group were similar, except those in the early nephrologist arm were slightly younger (mean±SD, 64±10 versus 67±12 years), were less likely to have preexisting heart failure (18% versus 30%) and hypertension (56% versus 78%), and had a shorter length of hospital stay (median [IQR], 11 [7–19] versus 16 [10–22] days). They were also more likely to have experienced KDIGO stage 3 AKI (68% versus 54%; Table 1).

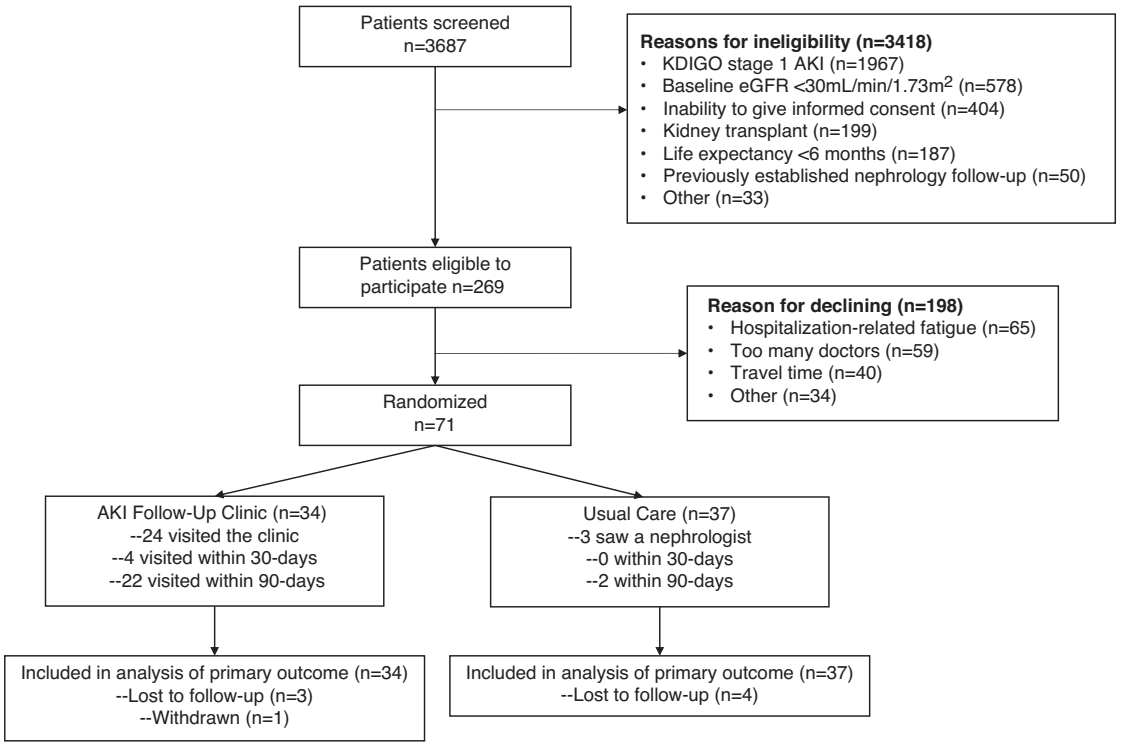

Figure 1. | **Patient flow through the trial.** KDIGO, Kidney Disease Improving Global Outcomes.

Table 1. Baseline characteristics of participants enrolled in the vanguard phase of a clinical trial evaluating nephrologist follow-up versus usual care after a hospitalization with AKI

Characteristics	AKI Follow-Up Clinic (n=34)	Usual Care (n=37)
Demographics		
Age (years), mean (SD)	64 (10)	67 (12)
Female, *n* (%)	10 (29)	12 (32)
Baseline serum creatinine (mg/dl), mean (SD)	0.98 (0.35)	1.01 (0.32)
Baseline eGFR (ml/min per 1.73 m^2), mean (SD)	79 (23)	73 (22)
Comorbidities, *n* (%)		
Diabetes	14 (41)	17 (46)
Heart failure	6 (18)	11 (30)
Coronary artery disease	11 (32)	9 (24)
Hypertension	19 (56)	29 (78)
Cancer	9 (26)	12 (32)
Preadmission medications, *n* (%)		
ACEi or ARB	20 (59)	23 (62)
Statin	20 (59)	21 (57)
β-Blocker	12 (35)	15 (40)
Calcium channel blocker	5 (15)	12 (32)
Loop diuretic	4 (12)	10 (27)
Thiazide diuretic	8 (24)	5 (14)
Metformin	12 (35)	11 (30)
NSAIDs	5 (15)	4 (11)
Total no. of medications, mean (SD)	5.7 (3.4)	6.4 (3.8)
Details of hospitalization		
Intensive care unit, *n* (%)	15 (44)	18 (49)
Mechanical ventilation, *n* (%)	10 (29)	13 (32)
Admitted to surgical service, *n* (%)	8 (24)	11 (30)
Length of stay (days), median (IQR)	11 (7–19)	16 (10–22)
KDIGO AKI stage 2, *n* (%)	11 (32)	17 (46)
KDIGO AKI stage 3, *n* (%)	23 (68)	20 (54)
Dialysis, *n* (%)	2 (6)	3 (8)
Discharge serum creatinine (mg/dl), mean (SD)	1.48 (0.75)	1.40 (0.71)
Discharge eGFR (ml/min per 1.73 m^2), mean (SD)	55 (23)	59 (27)
Discharge serum creatinine >50% of pre-AKI baseline, *n* (%)	17 (50)	13 (35)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Outcomes.

Nephrologist Visits and Patient Follow-Up to 1 Year

Among the 34 participants randomized to early nephrology follow-up, four (12%) visited the AKI follow-up clinic within 30 days of hospital discharge, and 22 (65%) visited within 90 days. Two more patients visited the AKI follow-up clinic later than 90 days, and one patient saw an outside nephrologist. The median (IQR) time from hospital discharge to any nephrology follow-up was 48 (34–74) days. Of the nine participants who did not see a nephrologist, two died before the appointment, one could not be contacted, and six declined in-person visits (five of whom agreed to telephone follow-up and blood work for event ascertainment).

Among the 37 participants randomized to usual care, no patients visited a nephrologist within 30 days of hospital discharge, and two (5%) visited a nephrologist within 90 days. An additional patient also saw a nephrologist after 90 days, such that three of 37 (8%) participants received some form of nephrology follow-up in the year after hospital discharge.

Primary Outcome

The primary outcome of a major adverse kidney event at 1 year occurred in 15 of 34 (44%) patients in the early nephrology group and 16 of 37 (43%) patients in the usual care group (RR, 1.02; 95% CI, 0.60 to 1.73; Table 2).

Secondary Outcomes

No patients in either group commenced maintenance dialysis, and four (12%) patients died in the AKI follow-up clinic group and three (8%) patients died in the usual care group (RR, 1.45; 95% CI, 0.35 to 6.02). There were no differences in time to a major adverse kidney event (Figure 2). There were

Table 2. Primary outcome and its components at 1-year postrandomization

Outcome	AKI Follow-Up Clinic (n=34)	Usual Care (n=37)	Relative Risk (95% Confidence Interval)
Primary outcome			
Major adverse kidney event	15 (44)	16 (43)	1.02 (0.60 to 1.73)
Secondary outcomes			
Death before CKD	3 (9)	1 (3)	3.26 (0.36 to 29.9)
Maintenance dialysis	0 (0)	0 (0)	—
CKD	12 (35)	15 (41)	0.87 (0.48 to 1.59)

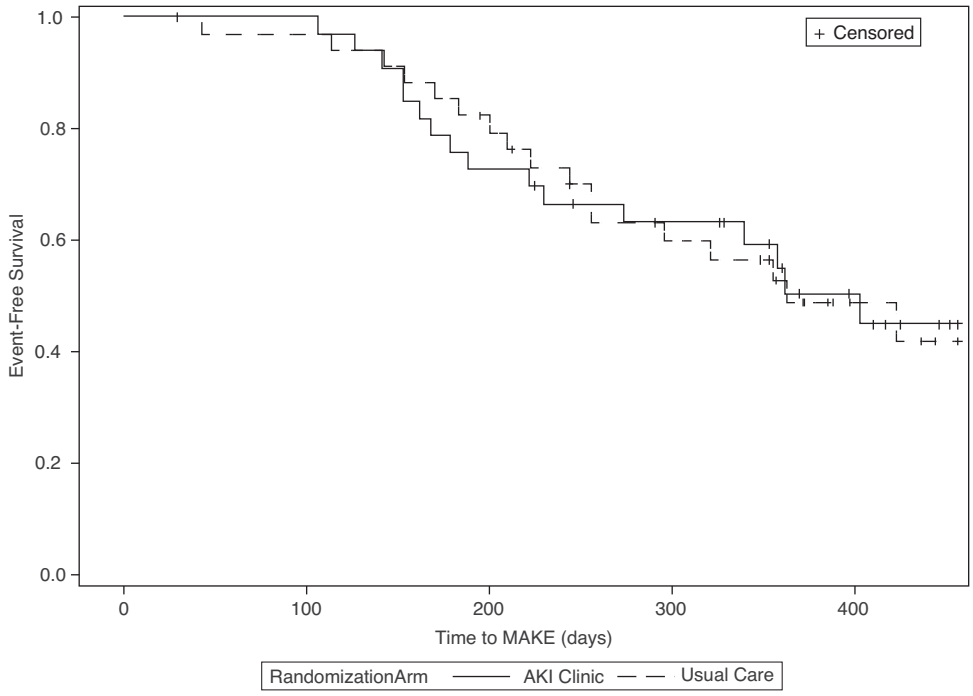

Figure 2. | **Time to major adverse kidney event (MAKE), stratified by treatment strategy (P=0.98).** The median (interquartile range) time to an event was 211 (154–296) days.

also no differences in major adverse cardiac events at 1 year, or time to a major adverse cardiac event (Supplemental Figure 4, Supplemental Table 1). The time to first hospitalization/emergency department visit did not differ between groups (subdistribution HR, 0.85; 95% CI, 0.48 to 1.52), and there were 86 total hospitalizations/emergency department visits for any cause, experienced by 44 of 71 (62%) participants. The time to first rehospitalization with AKI did not differ between groups (subdistribution HR, 1.09; 95% CI, 0.39 to 3.05); these episodes occurred a median (IQR) of 100 (9–241) days after randomization in the AKI follow-up clinic group (with three occurring before the first clinic visit) and 141 (6–181) days after randomization in the usual care group. There were ten rehospitalizations with AKI in each arm of the trial (RR, 1.09; 95% CI, 0.45–2.61), experienced by 17 of 71 (24%) participants; 50% of the episodes were KDIGO stage 1, 25% stage 2, and 25% were stage 3. EQ-5D-5L questionnaires at 1 year were missing in 17 patients in the AKI follow-up clinic group and 21 patients in the usual care group; therefore, we did not analyze these data further.

Exploratory Outcomes

Processes of Care. Patients in the early nephrologist arm received a mean±SD of 1.9±1.4 in-person nephrology visits per patient (versus 0.4 ±1.0 visits per patient in the usual care group; P<0.001). Among patients still alive at 90 days, a greater proportion in the AKI follow-up clinic group received both serum creatinine and urine albumin-creatinine ratio tests within 90 days of hospital discharge, as recommended by KDIGO guidelines (52% versus 17%; RR, 3.01; 95% CI, 1.35 to 6.69); this finding was driven by differences in urine albumin-creatinine ratio tests (52% versus 17%) rather than serum creatinine tests (85% versus 89%). Imaging tests and referrals to other disciplines were similar between groups (Table 3).

Patients in the early nephrology and usual care groups received a mean±SD of 0.9±1.6 and 0.6±1.1 medication changes per person after hospital discharge (P=0.47). The groups were similar at 1 year postdischarge, except that fewer patients in the AKI follow-up clinic arm received angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs; 35% versus 49% in the usual care arm), loop diuretics (24% versus 43% in the usual care arm), and nonsteroidal anti-inflammatory drugs (3% versus 8% in the usual care arm); however, none of these differences reached statistical significance (Table 4).

At the last follow-up in the AKI follow-up clinic group, 22 of 24 (92%) patients who attended the clinic reached their BP target (Supplemental Figure 1). In all intervention group participants, 16 of 20 participants with an eGFR of <60 ml/min per 1.73 m^2 were on a statin, and 12 of 27 (44%) with established cardiovascular disease, diabetes, and/or albuminuria (≥600 mg/g) were on an ACEi/ARB. In the 15 patients not prescribed an ACEi/ARB, 12 (80%) had a systolic BP <90 mm Hg.

Kidney Function. Overall, kidney function decline accounted for most events in the composite outcome, which were primarily incident CKD (n=20 events) rather than progressive CKD (n=7 events). The mean±SD loss in eGFR from baseline was 36.3±17.2 ml/min per 1.73 m^2 and 18.6±5.2 ml/min per 1.73 m^2 for patients with incident and progressive CKD, respectively. Further details on changes in serum creatinine and albuminuria over time are depicted in Supplemental Tables 2 and 3.

Table 3. Processes of care after hospital discharge

Process of Care	AKI Follow-Up Clinic	Usual Care	*P* Value[a]
Nephrology visits, mean (SD) per patient	1.9 (1.4)	0.4 (1.0)	<0.001
Medication changes, mean (SD) per patient	0.9 (1.6)	0.6 (1.1)	0.47
Imaging tests, mean (SD) per patient	0.2 (0.7)	0.1 (0.4)	0.82
Referrals to other health care providers, mean (SD) per patient	0.3 (0.6)	0.2 (0.5)	0.61
Serum creatinine test within 90 days of discharge (among survivors to 90 days), *n* (%)	28 (85)	31 (89)	0.65
Urine albumin-creatinine ratio within 90 days of discharge (among survivors to 90 days), *n* (%)	17 (52)	6 (17)	0.007

[a]We compared continuous outcomes with the Wilcoxon rank-sum test, and binary outcomes with the Fisher exact test.

Discussion

In the vanguard phase of this randomized controlled trial, we compared structured nephrologist follow-up versus usual care in survivors of AKI and showed that enrollment of fully eligible patients was a barrier, primarily due to the requirement for postdischarge, in-person visits. Among enrolled patients, there was good fidelity to the allocated treatment arm with few crossovers, and 1 year follow-up was achieved for the majority of participants. We did not identify any difference in major adverse kidney events at 1 year, but the high frequency of events highlights the vulnerability of this population and the urgent need for feasible and effective interventions for survivors of AKI.

Eligible patients who declined participation cited long hospital travel times/hospital-related fatigue and concerns about having multiple specialists already being involved in their postdischarge care. Concerns about travel times may be related to the fact that all participating sites were tertiary/quaternary care hospitals that serve as provincial referral centers, so some patients lived as far as 100 miles from the hospital. Wariness of further hospital visits may have been secondary to the posthospitalization syndrome (24), noting that almost half of the patients spent part of their index hospital stay in the intensive care unit, with hospital stays of approximately 2 weeks in duration. It is also possible that many patients viewed other health problems to be a higher priority than AKI (25). Even in patients randomized to the AKI follow-up clinic, few attended clinic within the 30-day target, despite frequent reminders from the study team. Our experience underscores the complexity of integrating post-AKI care in the context of a clinical trial in a manner that respects both patient multimorbidity and different preferences for care intensity after discharge.

Although underpowered for clinical outcomes, this randomized controlled trial provides some valuable insights into the clinical course of AKI survivors. The main effects of the AKI follow-up clinic were more in-person nephrology visits and more consistent and timely testing for proteinuria. Although a higher urine albumin-creatinine ratio is associated with higher risk of kidney disease progression after AKI (26,27), this better recognition of AKI and follow-up of kidney function did not seem to affect medication use, major adverse kidney events, or rehospitalizations. In addition to being underpowered, there are several reasons for these findings. First, it is possible the recommended basket of care was not prescriptive enough and failed to influence treatment beyond routine care. Patients in the early nephrology arm did achieve excellent BP control, high statin use, and low nonsteroidal anti-inflammatory drug use; but they also received less ACEi/ARB medications than the usual care group. Most patients not on ACEi/ARB in the intervention arm lacked evidence-based indications (*i.e.*, cardiovascular disease, diabetes, or albuminuria) or exhibited hypotension; however, recent observational studies suggest the use of ACEi/ARB after AKI is associated with lower mortality, so perhaps being more prescriptive on ACEi/ARB use should be considered in future post-AKI bundles (28,29). It is also possible that our basket emphasizing timely CKD recognition, cardiovascular risk reduction, and medication safety could not be expected to decrease major adverse kidney events after only 1 year. Most death and incident/progressive CKD does occur within the first year (30,31), so it seems reasonable that intensive management of diuretics, ACEi/ARB, and nephrotoxins could have an immediate effect on kidney perfusion, but we acknowledge that following patients over a longer time period is warranted. Last, although very common, rehospitalizations may not have been lower in the AKI follow-up clinic group because, despite targeting post-AKI visits <30 days when many events occur (32), our median (IQR) appointment time was only 48 (34–74) days. This unintended delay may have limited our ability to detect common adverse drug effects after AKI (*e.g.*, bleeding and hypoglycemia), although these were not formally adjudicated (33,34). Episodes of recurrent AKI may also not have been reduced due to lack of evidence on how to properly administer education and sick-day medication interventions, which is an ongoing area of active research (35).

Table 4. Patterns of medication use

Medication *n* (%)	Preadmission		Hospital Discharge			1-Year Postdischarge[a]		
	AKI Follow-Up Clinic (*n*=34)	Usual Care (*n*=37)	AKI Follow-Up Clinic (*n*=34)	Usual Care (*n*=37)	*P* Value[b]	AKI Follow-Up Clinic (*n*=34)	Usual Care (*n*=37)	*P* Value[b]
ACEi or ARB	20 (59)	23 (62)	9 (27)	15 (41)	0.22	12 (35)	18 (49)	0.27
Statin	20 (59)	21 (57)	23 (68)	24 (65)	0.94	19 (56)	23 (62)	0.34
β-Blocker	12 (35)	15 (40)	17 (50)	18 (49)	0.66	17 (50)	18 (49)	0.73
Calcium channel blocker	5 (15)	12 (32)	7 (21)	14 (38)	0.54	7 (21)	10 (27)	0.57
Loop diuretic	4 (12)	10 (27)	9 (27)	17 (46)	0.30	8 (24)	16 (43)	0.38
Thiazide	8 (24)	5 (14)	2 (6)	2 (5)	0.75	4 (12)	5 (14)	0.40
Spironolactone	3 (9)	2 (5)	4 (12)	5 (14)	0.53	3 (9)	5 (14)	0.42
Metformin	12 (35)	11 (30)	11 (32)	7 (19)	0.16	11 (32)	6 (16)	0.10
Oral hypoglycemic agent	6 (18)	6 (16)	7 (21)	4 (11)	0.14	9 (27)	7 (19)	0.34
NSAIDs	5 (15)	4 (11)	0 (0)	1 (3)	0.36	1 (3)	3 (8)	0.34

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]For patients without 1-year data (died [*n*=7] or missing [*n*=8]), the last prior outpatient record was carried forward.
[b]Mantel–Haenszel test stratified by preadmission medication status.

Our experience provides important lessons for future trials that will study post-AKI interventions. We decided to exclude patients with preexisting nephrology follow-up to target the highest risk patients, because observational data suggest patients who have never seen a nephrologist benefit most from such a visit (12). In addition to considering inclusion of these patients and those with severe CKD, newly developed risk scores should also be used to increase the eligibility pool, including the selection of high-risk patients with stage 1 AKI and/or incomplete recovery of kidney function at discharge (26). Next, any post-AKI intervention should involve flexible follow-up pathways that do not rely solely on in-person clinic visits, with a level of intensity that is tailored to the individual patient's needs. These themes were prominently expressed by patients at a recent National Institutes of Health symposium on post-AKI care and trial design (36), where it was emphasized that a "one-size-fits-all" approach is unlikely to engage patients with different post-AKI needs (*e.g.*, kidney health, cardiac morbidity, psychologic burden). Instead, suggested options for care delivery included phone calls and/or telehealth visits, administered by nurses or discharge planners, with early risk stratification (*e.g.*, within 7 days of hospital discharge) (37). Our initial experience with post-AKI follow-up during the coronavirus disease 2019 pandemic suggests patient preference for phone visits over in-person visits, and enhancing follow-up care for the frail elderly and patients living remotely. Lastly, although close to 50% of participants experienced a major adverse kidney event at 1 year, this was driven mainly by incident CKD. A decrease in eGFR is important (38,39), but stage 3–4 CKD is often asymptomatic. Therefore, we suggest subsequent post-AKI interventions also explicitly target preventable rehospitalizations and patient-reported outcomes (*e.g.*, symptom burden, frailty, quality of life), which may require providing education on AKI and medication safety to patients before discharge.

Strengths of this trial include its multicenter design; use of an outcome (*i.e.*, major adverse kidney events) endorsed by the National Institute of Diabetes and Digestive and Kidney Diseases Clinical Trials Workgroup (20); little crossover in the usual care group; and near complete ascertainment of the primary outcome, even for patients who received usual care or did not attend the AKI follow-up clinic (aided by the quarterly telephone calls to both groups). It is also the first trial to test any intervention in survivors of AKI.

Table 5. Considerations for future trials in survivors of AKI

Population	Intervention	Outcomes
Target the highest risk patients (*i.e.*, severe AKI, preexisting CKD, nonrecovery at discharge)	Flexible follow-up pathways that do not rely solely on in-person clinic visits with a level of intensity tailored to the patient's needs	Longer follow-up period for major adverse kidney events
Randomize patients as close to discharge as possible to ensure engagement	Early remote risk stratification by nurse/discharge planners to reach patients as soon as possible after discharge	For rehospitalization/recurrent AKI, intervention must reach patients early (*i.e.*, ≤7 days from discharge)
	More prescriptive direction on when to use ACEi/ARB	Patient-reported outcomes (*e.g.*, symptom burden, frailty, anxiety)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Our trial also has limitations. Despite being a multicenter study, it took place in one city, with all hospitals affiliated with a single university; therefore, generalizability of the logistic issues (*i.e.*, travel time) to other settings is not guaranteed. In addition, the nonblinded intervention means that cointerventions could have attenuated differences between groups. Notably, serum creatinine completion within 90 days of discharge was 89% in the usual care group compared with 70%–75% on the basis of United States Renal Data System data (40). Last, we excluded patients with a baseline eGFR of <30 ml/min per 1.73 m^2, prior nephrology follow-up, and persistent requirement for RRT at hospital discharge; these results should not be used to defer follow-up in these groups.

The vanguard phase of this randomized controlled trial identified feasibility barriers to the conduct of a definitive trial comparing in-person nephrology follow-up versus usual care in survivors of AKI. The rates of death, deterioration of kidney function, and rehospitalization were high, which highlights the vulnerability of this population and the urgent need to generate evidence that improves outcomes. Lessons learned from this trial, summarized in Table 5, will inform the design of a more flexible and pragmatic interventional trial that will better address the needs of AKI survivors.

Disclosures

N.K. Adhikari reports receiving research funding from Baxter Healthcare Corporation and support from Baxter Canada, outside the submitted work. C.M. Bell reports being employed by Sinai Health System, University of Toronto. C.T. Chan reports serving as an Associate Editor of *CJASN*; having consultancy agreements with DaVita, Medtronic, and Quanta; serving as a scientific advisor for, or member of, DaVita, Medtronic, and Quanta; receiving research funding from Medtronic, through their external grant program; and being employed by Toronto General Hospital, University Health Network. A. Kitchlu reports being employed by University of Toronto. A. Meraz-Muñoz reports being employed by Unity Health Network. P.A. Norman reports being employed by Kingston General Health Research Institute. A. Perez Sanchez reports being employed by St. Michael's Hospital. S.A. Silver reports receiving support from Baxter Canada, outside the submitted work; receiving honoraria from Baxter and Sanofi; serving on the editorial board of *Canadian Journal of Kidney Health and Disease*; and being employed by Queen's University. R. Wald reports receiving research funding from Baxter; serving on the editorial board of *CJASN*, *Kidney360*, and *Kidney Medicine*; being employed by the Division of Nephrology, St. Michael's Hospital; and serving as a contributor of UpToDate. A. Zahirieh reports being employed by Sunnybrook Health Sciences Centre. Z. Harel is employed by the Division of Nephrology, St. Michael's Hospital.

Funding

S.A. Silver was supported by a Kidney Research Scientist Core Education and National Training (KRESCENT) Program New Investigator Award (co-funded by the Kidney Foundation of Canada, Canadian Society of Nephrology, and Canadian Institutes of Health Research). This work was supported by the Innovation Fund of the Alternative Funding Plan for the Academic Health Sciences Centres of Ontario (St. Michael's Hospital and Sunnybrook Health Sciences Centre). It was also conducted with the support of the Ontario Renal Network through funding provided by the Government of Ontario.

Acknowledgments

The authors wish to thank all of the research staff at each of the centers and the patients for their participation in this trial.

Because Dr. Christopher T. Chan is an Associate Editor of *CJASN*, he was not involved in the peer-review process for this manuscript. Another editor oversaw the peer-review and decision-making process for this manuscript.

S.A. Silver and R. Wald were responsible for study concept and design; S.A. Silver drafted the manuscript; S.A. Silver, P.A. Norman, and R. Wald were responsible for statistical analysis; C.M. Bell and R. Wald provided supervision; and all authors were responsible for acquisition, analysis, or interpretation of data; critically revised the manuscript for important intellectual content; and approved the final version of the submitted manuscript.

The authors certify that this manuscript, nor one with substantially similar content, has been published or is being considered for publication elsewhere, except in abstract form.

The opinions, results, views, and conclusions reported in this publication are those of the authors and do not necessarily reflect those of Ontario Renal Network. No endorsement by the Ontario Renal Network is intended or should be inferred.

Data Sharing Statement

The study protocol, manual of operations, and consent form are available by contacting the corresponding author. Deidentified patient data will be available up to 3 years after manuscript publication to researchers with methodologically sound proposals approved by the principal investigator.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.17331120/-/DCSupplemental.

Supplemental Figure 1. Acute kidney injury follow-up clinic template.

Supplemental Figure 2. Sick day medication advice.

Supplemental Figure 3. Acute kidney injury information letter.

Supplemental Figure 4. Time to major adverse cardiac event stratified by treatment strategy.

Supplemental Table 1. Major adverse cardiac events and its components at 1-year postrandomization.

Supplemental Table 2. Serum creatinine and eGFR at baseline and follow-up.

Supplemental Table 3. Albuminuria at baseline and follow-up.

References

1. Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS: Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. *Clin J Am Soc Nephrol* 9: 12–20, 2014
2. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, Jaber BL; Acute Kidney Injury Advisory Group of the American Society of Nephrology: World incidence of AKI: A meta-analysis. *Clin J Am Soc Nephrol* 8: 1482–1493, 2013
3. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA: Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med* 41: 1411–1423, 2015

4. Waikar SS, Curhan GC, Wald R, McCarthy EP, Chertow GM: Declining mortality in patients with acute renal failure, 1988 to 2002. *J Am Soc Nephrol* 17: 1143–1150, 2006
5. Coca SG, Singanamala S, Parikh CR: Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. *Kidney Int* 81: 442–448, 2012
6. Hsu CY, Hsu RK, Yang J, Ordonez JD, Zheng S, Go AS: Elevated BP after AKI. *J Am Soc Nephrol* 27: 914–923, 2016
7. Wu VC, Wu PC, Wu CH, Huang TM, Chang CH, Tsai PR, Ko WJ, Chen L, Wang CY, Chu TS, Wu KD; National Taiwan University Study Group on Acute Renal Failure (NSARF) Group: The impact of acute kidney injury on the long-term risk of stroke. *J Am Heart Assoc* 3: e000933, 2014
8. Odutayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, Hunn BH: AKI and long-term risk for cardiovascular events and mortality. *J Am Soc Nephrol* 28: 377–387, 2017
9. Siew ED, Parr SK, Wild MG, Levea SL, Mehta KG, Umeukeje EM, Silver SA, Ikizler TA, Cavanaugh KL: Kidney disease awareness and knowledge among survivors of acute kidney injury. *Am J Nephrol* 49: 449–459, 2019
10. Siew ED, Peterson JF, Eden SK, Hung AM, Speroff T, Ikizler TA, Matheny ME: Outpatient nephrology referral rates after acute kidney injury. *J Am Soc Nephrol* 23: 305–312, 2012
11. Karsanji DJ, Pannu N, Manns BJ, Hemmelgarn BR, Tan Z, Jindal K, Scott-Douglas N, James MT: Disparity between nephrologists' opinions and contemporary practices for community follow-up after AKI hospitalization. *Clin J Am Soc Nephrol* 12: 1753–1761, 2017
12. Harel Z, Wald R, Bargman JM, Mamdani M, Etchells E, Garg AX, Ray JG, Luo J, Li P, Quinn RR, Forster A, Perl J, Bell CM: Nephrologist follow-up improves all-cause mortality of severe acute kidney injury survivors. *Kidney Int* 83: 901–908, 2013
13. Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. Available at: https://kdigo.org/guidelines/acute-kidney-injury/. Accessed May 27, 2021
14. Siew ED, Ikizler TA, Matheny ME, Shi Y, Schildcrout JS, Danciu I, Dwyer JP, Srichai M, Hung AM, Smith JP, Peterson JF: Estimating baseline kidney function in hospitalized patients with impaired kidney function. *Clin J Am Soc Nephrol* 7: 712–719, 2012
15. Siew ED, Matheny ME, Ikizler TA, Lewis JB, Miller RA, Waitman LR, Go AS, Parikh CR, Peterson JF: Commonly used surrogates for baseline renal function affect the classification and prognosis of acute kidney injury. *Kidney Int* 77: 536–542, 2010
16. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Available at: https://kdigo.org/guidelines/ckd-evaluation-and-management/. Accessed: May 27, 2021
17. Dasgupta K, Quinn RR, Zarnke KB, Rabi DM, Ravani P, Daskalopoulou SS, Rabkin SW, Trudeau L, Feldman RD, Cloutier L, Prebtani A, Herman RJ, Bacon SL, Gilbert RE, Ruzicka M, McKay DW, Campbell TS, Grover S, Honos G, Schiffrin EL, Bolli P, Wilson TW, Lindsay P, Hill MD, Coutts SB, Gubitz G, Gelfer M, Vallée M, Prasad GVR, Lebel M, McLean D, Arnold JMO, Moe GW, Howlett JG, Boulanger J-M, Larochelle P, Leiter LA, Jones C, Ogilvie RI, Woo V, Kaczorowski J, Burns KD, Petrella RJ, Hiremath S, Milot A, Stone JA, Drouin D, Lavoie KL, Lamarre-Cliche M, Tremblay G, Hamet P, Fodor G, Carruthers SG, Pylypchuk GB, Burgess E, Lewanczuk R, Dresser GK, Penner SB, Hegele RA, McFarlane PA, Khara M, Pipe A, Oh P, Selby P, Sharma M, Reid DJ, Tobe SW, Padwal RS, Poirier L; Canadian Hypertension Education Program: The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 30: 485–501, 2014
18. Kidney Disease Improving Global Outcomes (KDIGO) Lipid Work Group: KDIGO clinical practice guideline for lipid management in chronic kidney disease. Available at: https://kdigo.org/guidelines/ckd-evaluation-and-management/. Accessed: May 27, 2021
19. Cheng AY; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee: Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. *Can J Diabetes* 37[Suppl 1]: S1–S3, 2013
20. Palevsky PM, Molitoris BA, Okusa MD, Levin A, Waikar SS, Wald R, Chertow GM, Murray PT, Parikh CR, Shaw AD, Go AS, Faubel SG, Kellum JA, Chinchilli VM, Liu KD, Cheung AK, Weisbord SD, Chawla LS, Kaufman JS, Devarajan P, Toto RM, Hsu CY, Greene T, Mehta RL, Stokes JB, Thompson AM, Thompson BT, Westenfelder CS, Tumlin JA, Warnock DG, Shah SV, Xie Y, Duggan EG, Kimmel PL, Star RA: Design of clinical trials in acute kidney injury: Report from an NIDDK workshop on trial methodology. *Clin J Am Soc Nephrol* 7: 844–850, 2012
21. Siew ED, Parr SK, Abdel-Kader K, Eden SK, Peterson JF, Bansal N, Hung AM, Fly J, Speroff T, Ikizler TA, Matheny ME: Predictors of recurrent AKI. *J Am Soc Nephrol* 27: 1190–1200, 2016
22. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X: Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 20: 1727–1736, 2011
23. Silver SA, Harel Z, Harvey A, Adhikari NK, Slack A, Acedillo R, Jain AK, Richardson RM, Chan CT, Chertow GM, Bell CM, Wald R: Improving care after acute kidney injury: A prospective time series study. *Nephron* 131: 43–50, 2015
24. Krumholz HM: Post-hospital syndrome–An acquired, transient condition of generalized risk. *N Engl J Med* 368: 100–102, 2013
25. Silver SA, Saragosa M, Adhikari NK, Bell CM, Harel Z, Harvey A, Kitchlu A, Neyra JA, Wald R, Jeffs L: What insights do patients and caregivers have on acute kidney injury and posthospitalisation care? A single-centre qualitative study from Toronto, Canada. *BMJ Open* 8: e021418, 2018
26. James MT, Pannu N, Hemmelgarn BR, Austin PC, Tan Z, McArthur E, Manns BJ, Tonelli M, Wald R, Quinn RR, Ravani P, Garg AX: Derivation and external validation of prediction models for advanced chronic kidney disease following acute kidney injury. *JAMA* 318: 1787–1797, 2017
27. Hsu CY, Chinchilli VM, Coca S, Devarajan P, Ghahramani N, Go AS, Hsu RK, Ikizler TA, Kaufman J, Liu KD, Parikh CR, Reeves WB, Wurfel M, Zappitelli M, Kimmel PL, Siew ED; ASSESS-AKI Investigators: Post–acute kidney injury proteinuria and subsequent kidney disease progression: The assessment, serial evaluation, and subsequent sequelae in acute kidney injury (ASSESS-AKI) study. *JAMA Intern Med* 180: 402–410, 2020
28. Brar S, Ye F, James MT, Hemmelgarn B, Klarenbach S, Pannu N; Interdisciplinary Chronic Disease Collaboration: Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with outcomes after acute kidney injury. *JAMA Intern Med* 178: 1681–1690, 2018
29. Gayat E, Hollinger A, Cariou A, Deye N, Vieillard-Baron A, Jaber S, Chousterman BG, Lu Q, Laterre PF, Monnet X, Darmon M, Leone M, Guidet B, Sonneville R, Lefrant JY, Fournier MC, Resche-Rigon M, Mebazaa A, Legrand M; FROG-ICU investigators: Impact of angiotensin-converting enzyme inhibitors or receptor blockers on post-ICU discharge outcome in patients with acute kidney injury. *Intensive Care Med* 44: 598–605, 2018
30. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM: Increased risk of death and *de novo* chronic kidney disease following reversible acute kidney injury. *Kidney Int* 81: 477–485, 2012
31. Silver SA, Harel Z, McArthur E, Nash DM, Acedillo R, Kitchlu A, Garg AX, Chertow GM, Bell CM, Wald R: Causes of death after a hospitalization with AKI. *J Am Soc Nephrol* 29: 1001–1010, 2018
32. Silver SA, Harel Z, McArthur E, Nash DM, Acedillo R, Kitchlu A, Garg AX, Chertow GM, Bell CM, Wald R: 30-Day readmissions after an acute kidney injury hospitalization. *Am J Med* 130: 163–172.e4, 2017
33. Cox ZL, McCoy AB, Matheny ME, Bhave G, Peterson NB, Siew ED, Lewis J, Danciu I, Bian A, Shintani A, Ikizler TA, Neal EB, Peterson JF: Adverse drug events during AKI and its recovery. *Clin J Am Soc Nephrol* 8: 1070–1078, 2013

34. Hung AM, Siew ED, Wilson OD, Perkins AM, Greevy RA Jr, Horner J, Abdel-Kader K, Parr SK, Roumie CL, Griffin MR, Ikizler TA, Speroff T, Matheny ME: Risk of hypoglycemia following hospital discharge in patients with diabetes and acute kidney injury. *Diabetes Care* 41: 503–512, 2018
35. Doerfler RM, Diamantidis CJ, Wagner LA, Scism BM, Vaughn-Cooke M, Fink WJ, Blakeman T, Fink JC: Usability testing of a sick-day protocol in CKD. *Clin J Am Soc Nephrol* 14: 583–585, 2019
36. Siew ED, Liu KD, Bonn J, Chinchilli V, Dember LM, Girard TD, Greene T, Hernandez AF, Ikizler TA, James MT, Kampschroer K, Kopp JB, Levy M, Palevsky PM, Pannu N, Parikh CR, Rocco MV, Silver SA, Thiessen-Philbrook H, Wald R, Xie Y, Kimmel PL, Star RA: Improving care for patients after hospitalization with AKI. *J Am Soc Nephrol* 31: 2237–2241, 2020
37. Kashani K, Rosner MH, Haase M, Lewington AJP, O'Donoghue DJ, Wilson FP, Nadim MK, Silver SA, Zarbock A, Ostermann M, Mehta RL, Kane-Gill SL, Ding X, Pickkers P, Bihorac A, Siew ED, Barreto EF, Macedo E, Kellum JA, Palevsky PM, Tolwani AJ, Ronco C, Juncos LA, Rewa OG, Bagshaw SM, Mottes TA, Koyner JL, Liu KD, Forni LG, Heung M, Wu VC: Quality improvement goals for acute kidney injury. *Clin J Am Soc Nephrol* 14: 941–953, 2019
38. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, Arima H, Chadban SJ, Cirillo M, Djurdjev O, Green JA, Heine GH, Inker LA, Irie F, Ishani A, Ix JH, Kovesdy CP, Marks A, Ohkubo T, Shalev V, Shankar A, Wen CP, de Jong PE, Iseki K, Stengel B, Gansevoort RT, Levey AS: Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 311: 2518–2531, 2014
39. Turin TC, James MT, Jun M, Tonelli M, Coresh J, Manns BJ, Hemmelgarn BR: Short-term change in eGFR and risk of cardiovascular events. *J Am Heart Assoc* 3: e000997, 2014
40. United States Renal Data System: 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2020. Available at: https://adr.usrds.org/2020/chronic-kidney-disease/5-acute-kidney-injury. Accessed May 27, 2021

Received: November 5, 2020 **Accepted:** April 16, 2021

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "Planning Patient Care after Acute Kidney Injury: Not as Easy as It May Seem," on pages 999–1001.

AFFILIATIONS

[1]Division of Nephrology, Kingston Health Sciences Centre, Queen's University, Kingston, Ontario, Canada
[2]Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
[3]Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada
[4]Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
[5]Division of Nephrology, University Health Network–Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada
[6]Division of Nephrology and Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
[7]Kingston General Health Research Institute, Kingston, Ontario, Canada
[8]Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada
[9]Division of Nephrology, Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada