

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

A Randomized Controlled Trial

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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.

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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

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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 m²; 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 m², or a sustained decrease in eGFR of $\geq 25\%$ 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 m² from pre-AKI baseline that is ≥ 60 ml/min per 1.73 m²) or progressive CKD ($\geq 25\%$ eGFR decrease from pre-AKI baseline that is < 60 ml/min per 1.73 m²), 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 categorical 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 \pm 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).

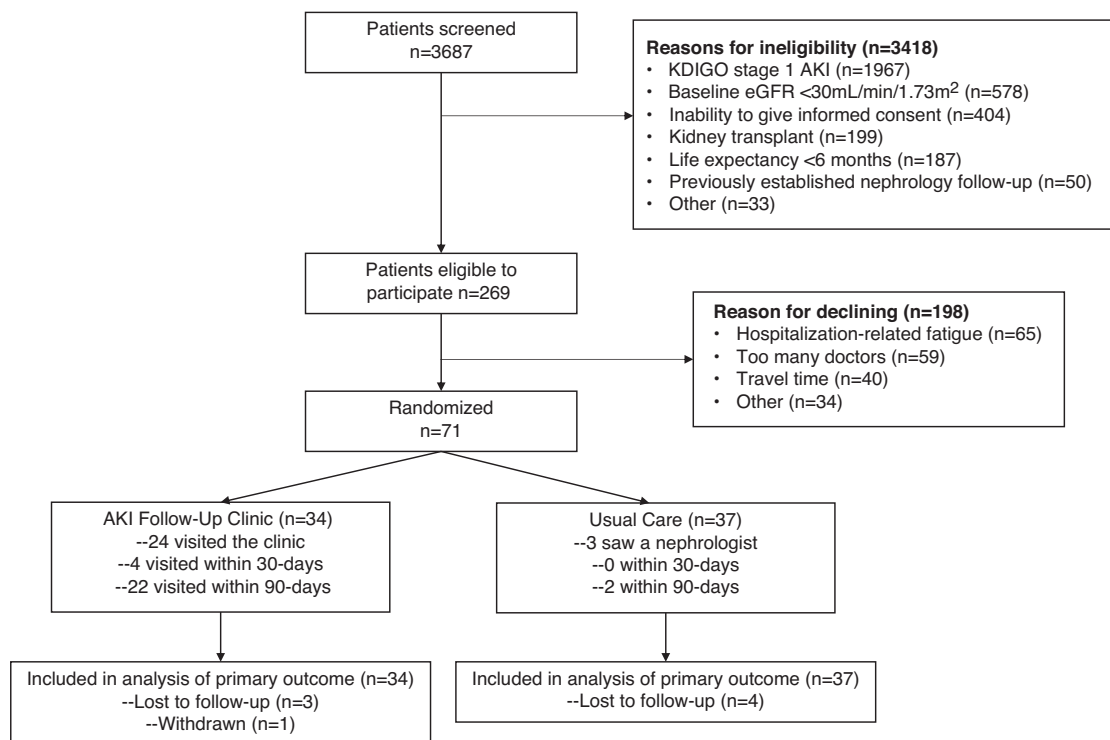


Figure 1. | Patient flow through the trial. KDIGO, Kidney Disease Improving Global Outcomes.

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)

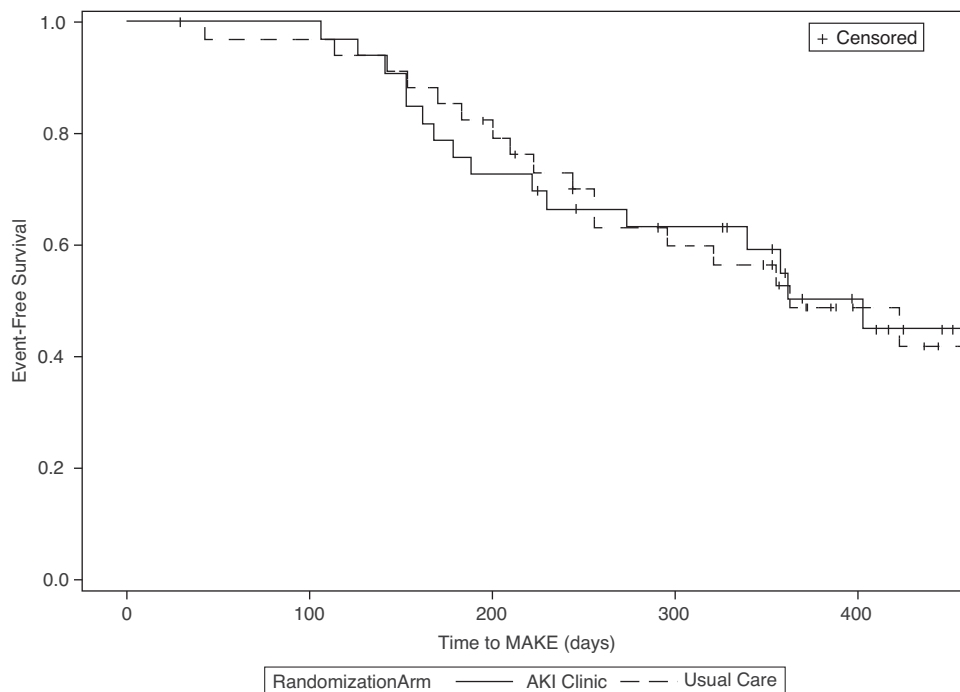


Figure 2. | Time to major adverse kidney event (MAKE), stratified by treatment strategy ($P=0.98$). The median (interquartile range) time to an event was 211 (154–296) days.

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 \pm 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 \pm 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 m² 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 \pm SD loss in eGFR from baseline was 36.3 ± 17.2 ml/min per 1.73 m² and 18.6 ± 5.2 ml/min per 1.73 m² 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

^aWe 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 <i>n</i> (%)	Preadmission		Hospital Discharge			1-Year Postdischarge ^a		
	AKI Follow-Up Clinic (<i>n</i> =34)	Usual Care (<i>n</i> =37)	AKI Follow-Up Clinic (<i>n</i> =34)	Usual Care (<i>n</i> =37)	<i>P</i> Value ^b	AKI Follow-Up Clinic (<i>n</i> =34)	Usual Care (<i>n</i> =37)	<i>P</i> 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
Spirolactone	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.

^aFor patients without 1-year data (died [*n*=7] or missing [*n*=8]), the last prior outpatient record was carried forward.

^bMantel–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>i.e.</i> , 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 More prescriptive direction on when to use ACEi/ARB	For rehospitalization/recurrent AKI, intervention must reach patients early (<i>i.e.</i> , ≤7 days from discharge) Patient-reported outcomes (<i>e.g.</i> , 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 m², 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.

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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.

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