Kidney Medicine

Medication Holds in CKD During Acute Volume-Depleting Illnesses: A Randomized Controlled Trial of a "Sick-Day" Protocol

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Rationale & Objective: Some drugs prescribed for chronic kidney disease (CKD) may become hazardous on sick days with volume depletion by increasing the risk of acute kidney injury (AKI) and kidney function loss; however, the risks and benefits of their use during intercurrent illness is unknown.

Study Design: 6-month pragmatic trial examining a sick-day protocol to determine if withholding prespecified drugs during a volume-depleting illness reduces the incidence AKI or kidney function loss in CKD.

Setting & Participants: 315 veterans with stage 3-5 CKD, treated with a renin-angiotensin-aldosterone inhibitor blocker, diuretic, nonsteroidal anti-inflammatory drug, or metformin were randomized into the study with n = 159 and n = 156 in sick-day protocol and usual care groups, respectively.

Intervention: Sick-day protocol administered via interactive voice response system (IVRS) or usual care with 6-month follow-up.

Outcomes: The outcomes of the study are as follows: (1) Change in kidney function, (2) incidence of AKI based on *International Classification of Diseases, Tenth Revision* codes and ambulatory laboratory testing, (3) urgent service utilizations, and (4) sick days.

Results: The mean age was 70.1 ± 7.4 and 69.2 ± 8.1 years, with a mean baseline glomerular filtration rate (GFR) of 43.1 ± 13.1 and 43.8 ± 13.0 mL/min/1.73 m^2, and 112 (70%) and 100 (64%) of participants with diabetes in the sick-day protocol and usual care groups, respectively. The mean change in GFR in the sick-day protocol and usual care groups from baseline to 6-month follow-up, adjusting for baseline GFR, was −0.71 (95% CI, −2.11 to 0.69) and −0.72 (95% CI, −2.12 to 0.68), respectively, with no significant difference, P = 0.99. Hospitalizations in the sick-day protocol and usual care groups were 11.5/100 and 8.4/100 events per person-months, respectively, with the adjusted rate ratio not significantly increased (prevalence ratio, 1.30; 95% CI, 0.96-1.76). Participants interacted with the IVRS in 81% of expected weeks and 19 had one or more qualifying events. In 33 true sick days, participants correctly followed the protocol in only 14.

Limitations: Low incidence of sick days over the 6-month period of the study.

Conclusions: The sick-day protocol was not associated with a significant reduction in AKI episodes or kidney function loss in a high-risk CKD population. Engagement with the IVRS was high, but successful implementation of the sick-day protocol was not optimal.

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Renin-angiotensin-aldosterone system (RAAS) blockers and diuretics are cornerstone therapies in chronic kidney disease (CKD). The benefits of these drugs may be offset by adverse effects from conditions such as volume depletion where kidney autoregulation is impeded by RAAS blockade.[1] "Sick days" with volume depletion related to nausea, vomiting, or diarrhea are not unusual in CKD and can potentially transform RAAS blockers and diuretics from salutary to harmful exposures and increase susceptibility to hypotension, diminished glomerular filtration rate (GFR), acute kidney injury (AKI), and other adverse events such as hyperkalemia. Other drugs can enhance the risk of AKI,[2-4] especially nonsteroidal anti-inflammatory drugs (NSAIDs). Temporary suspension of RAAS blockers and diuretics might reduce the risks of a decrease in GFR and other adverse events during volume depletion, but there are also other risks of withholding these drugs, for example, fluid retention, hypertension, and worsening of heart failure. Furthermore, patients might suspend these medications too readily and not restart them because they now perceive these agents to be harmful, thus overlooking their prognostic benefits.[5] The risks and benefits of this therapeutic tactic during an illness have not been formally evaluated and represent a situation of equipoise. We evaluated such a sick-day protocol administered with interactive voice response system (IVRS) surveillance to accommodate the population of patients with CKD with variable use of digital tools and determine its safety and efficacy in reducing adverse events and preserving kidney function versus usual care.

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METHODS

This pragmatic trial was conducted under usual clinical conditions at the Baltimore Veterans Affairs (VA) Medical

PLAIN-LANGUAGE SUMMARY

The study assessed a self-managed sick-day protocol with telephone prompts temporarily withholding specific medications during a dehydrating illness to determine if it could improve outcomes in chronic kidney disease such as kidney function loss, incidence of acute kidney injury episodes, and unplanned hospital encounters. The sick-day protocol was not associated with a significant change in kidney function loss or acute kidney injury versus usual care. Engagement with the telephone prompts was high, but successful implementation of the sick-day protocol was not optimal. Design of self-management strategies for patients with chronic kidney disease is a unique challenge, and additional studies are needed to ensure adherence and determine efficacy of such protocols.

Center in the VA Maryland Health Care System (VAMHCS). Eligible veterans were identified from a retrospective data file procured from the VA Informatics and Computing Infrastructure containing laboratory results up to 18 months before recruitment, which commenced on October 1, 2017. The data file was updated on December 1, 2018. The veterans in the file were screened using medical record review to confirm eligibility, and their primary care providers were contacted via electronic medical record for their assent and to determine the patients' suitability for participation. Patients eligible for the study were contacted inperson at a previously scheduled clinic visit or by mail with an institutional review board-approved correspondence announcing the study with an opportunity to opt-out if not interested. Screenees were contacted for confirmation of eligibility including determination of competence to use a telephone, proficiency with English, and willingness to use a sick-day protocol.

The study was waived from the need for written consent, but those patients willing to participate had the consent reviewed with them with a copy provided for their records. The first participant was enrolled on October 6, 2017 and the final on December 16, 2019. The study was approved by the University of Maryland Institutional Review Board (HP-00069775) and the Baltimore VA Medical Center Research & Development Committee and was conducted in adherence to the Declaration of Helsinki (NCT03141905).

Enrollment

The target enrollment was 600 veterans, based on the assumption that 25% of the population of patient with CKD would experience a volume-depleting gastrointestinal illness over the study period with 40% having a rapid decline of kidney function. With this sample size, we estimated the 80% power (1 - β) to detect a 1.8-fold higher risk of rapid decline in the usual care versus the sick-day protocol groups. Veterans with stage 3-5 CKD were enrolled based on an estimated GFR (eGFR) of < 60 mL/min/1.73 m^2 documented as part of their routine visits to the VAMHCS on at least 2 occasions, ≥ 90 days apart and within 18 months before the study entry. Estimates of GFR were made using the prevailing equation used for clinical reporting in electronic medical records at the VAMHCS. Candidates for the study needed an active prescription of a drug from one or more drug classes identified to be associated with AKI, including RAAS blockers, loop or thiazide diuretics, mineralocorticoid receptor antagonists, metformin, or NSAIDs.

Participants were randomized to the intervention or usual care arms in 1 of 2 blocks based on RAAS blocker use versus not. All participants were provided with a script describing a sick-day event (eg, vomiting, diarrhea, fever, and poor fluid intake); signs of volume depletion including thirst, weight loss, fatigue, and lightheadedness; and the significance of such an event persisting for more than a day and its implications to their health. All participants were asked to go to their local VA laboratory for a preordered blood test for a kidney function panel at baseline and 6 months, and during, or soon after, any sick-day event.

The baseline and 6-month final visits were conducted by telephone. Baseline assessment for all participants included medical history, demographics, comorbid conditions, and recent medical events. At the final 6-month visit, medical histories and medication profiles were updated, all hospitalizations and emergency department visits were recorded, and use of medications specified in the sick-day protocol were ascertained. A satisfaction survey was administered to all participants in the sick-day protocol intervention.

Sick-Day Protocol (Intervention)

Participants in the sick-day protocol arm received a fold-over business card (3" × 5"), originally developed by the National Health Service (NHS) Highland in Scotland aiming to prevent AKI and made available through the NHS Scotland and Scottish Patient Safety Programme on "Medicine Sick Day Rules."[6] The card listed drugs deemed hazardous (by the group's consensus) with a sick-day experience, including those impairing kidney autoregulation, effecting unregulated diuresis, or associated with lactic acidosis (metformin). The card directed patients to stop these agents for up to 48 hours while sick, with resumption upon event resolution. The sick-day protocol arm participants were also given a pamphlet describing a sick-day event and instructions for withholding and resuming reference drugs. All participants were also asked to obtain blood tests on a presumed sick day.

Sick-day protocol participants designated a telephone number (wireless or landline) and preferred time for weekly calls from an automated IVRS to survey for sick-day

events (CircleLink Health). This telecommunication platform was chosen over text or a smartphone application to be inclusive of all populations of patients with CKD, including those suspected to be without access to or with limited proficiency using digital platforms. Participants were instructed how to self-initiate calls to the IVRS if a sick day occurred between weekly calls. The IVRS protocol presented a query menu asking if a sick-day event occurred or was ongoing during the last 7 days. In respondents with no sick day, the call ended, and the next call occurred 7 days later at the same time. If a participant registered a sick-day event, a query algorithm solicited actions in response to the sick-day. In sick-day protocol participants with an ongoing sick day, a follow-up call was initiated 3 days later to determine subsequent adherence with the self-management protocol and whether withheld medications were resumed (Table S1).

Usual Care Protocol

Usual care included standard CKD management in the VAMHCS. There was no alteration in the established visit schedule beyond the baseline and final study visit. Usual care participants were given a card identifying the sick-day features without instructions to cease medications that only included recommendations to call their clinical provider in the event of a sick day. They did not use the IVRS and were instructed to obtain preordered laboratory tests at their home clinic during the sick day or as soon as possible after the event (unless they had need for an emergency room visit or admission).

All participants had baseline and end-of-study measurements of kidney function through the VAMHCS laboratory services.

Outcomes

The primary outcome was change in GFR from baseline to 6-month follow-up. Secondary outcomes included incidence of AKI as designated by *International Classification of Diseases, Tenth Revision* code (obtained for all VAMHCS hospital encounters); a 50% decrement in eGFR during the study; or need for hospitalization, emergency department, or urgent care visit based on participant report across all hospitals during the study period. Additional outcomes included frequency of reported sick-day events, and adherence to use of the sick-day protocol among participants assigned to the sick-day protocol arm.

Statistical Methods

We adhered to the principle of intent-to-treat with participants maintained within their group assignment regardless of protocol adherence. We compared continuous variables using mean ± standard error and t test. Dichotomous and categorical variables were compared using n (%) and χ^2 test. We employed analysis of covariance to assess the effect of the intervention on the primary outcome of change in eGFR from baseline to 6 months, adjusting for baseline kidney function. Distributions of the eGFR change in both groups were examined by graphical approach and approximated normal distributions with some outliers, but, because the sample size was large enough, the use of t test and analysis of covariance was justified. For analytic purposes, all estimates of GFR were recalculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[7]

For service utilization, we used repeated-measures Poisson regression containing an indicator variable for group assignment, adjusting for baseline eGFR, age, sex, race, hypertension, cancer, diabetes, smoking, employment, and baseline use of RAAS blockers, diuretics, metformin, and NSAIDs. Because follow-up time varied (if participants were lost to follow-up), we used person-months by converting the number of events for each subject to an event rate and compared event rates between the 2 groups. To examine the impact of potential missing not at random data on the primary outcome, we applied the delta-based multiple imputation technique to conduct a sensitivity analysis, with delta being ±20% or 50% of the mean eGFR change among participants in the sick-day protocol group with eGFR change observed.

RESULTS

In total, 2,720 veterans met study eligibility criteria, and 1,661 with the earliest qualifying laboratory measurements during the 18-month window or presenting to clinic were reviewed during the project for study participation. Of those screened, 477 did not meet study eligibility on chart review, 435 declined to participate, 229 were excluded for other reasons, and 178 did not respond to invitations to participate (Fig S1). Of the 342 participants who consented to study participation, 116 and 226 participants were approached by telephone and inperson visit, respectively. Twenty-seven individuals withdrew before study participation. Five participants died, 10 were lost to follow-up, and 1 additional participant dropped out because of lost interest. Loss to follow-up was not significantly different by study arm, and 299 participants completed all visits, with 280 completing end-of-study laboratory measurements. Four participants (3 randomized to usual care and 1 to the sick-day protocol group) completed the baseline survey and protocol training but did not present to the laboratory. Of these 4 participants, 2 had 6-month follow-up eGFRs and 2 did not complete laboratory examinations.

Table 1 depicts the baseline characteristics by group assignment and reveals the preponderance of RAAS blocker users and the high proportion of participants with diabetes. The intervention and usual care groups were balanced in demographic and case-mix characteristics. Table 2 compares changes in kidney function in sick-day protocol versus usual care group participants. The adjusted mean change in GFR in the sick-day protocol and usual care groups from baseline to 6-month follow-up was −0.71 (95% confidence interval [CI], −2.11 to

Table 1. Baseline Characteristics

Baseline Characteristics	Sick-Day Protocol Group	Usual Care Group
Participants, n (%)	159 (50.5)	156 (49.5)
Follow-up time (mo), median (25th percentile, 75th percentile)[a]	6.0 (5.0, 6.0)	6.0 (5.0,6.0)
Age (y), mean ± SD	70.1 ± 7.4	69.2 ± 8.1
≥65	130 (81.8)	119 (76.3)
<65	29 (18.2)	37 (23.2)
Sex		
Male	152 (95.6)	149 (95.5)
Female	7 (4.4)	7 (4.5)
Black		
Yes	100 (62.9)	99 (63.5)
No	59 (37.1)	57 (36.5)
CKD stage[b]		
eGFR, mean ± SD	43.1 ± 13.1	43.8 ± 13.0
CKD stage 2, 60-89 mL/min/1.73 m^2	12 (7.6)	15 (9.8)
CKD stage 3A, 45-59 mL/min/1.73 m^2	59 (37.3)	54 (35.3)
CKD stage 3B, 30-44 mL/min/1.73 m^2	63 (39.9)	62 (40.5)
CKD stage 4, 15-29 mL/min/1.73 m^2	21(13.3)	20 (13.1)
CKD stage 5, <15 mL/min/1.73 m^2	3 (1.9)	2 (1.3)
Hypertension	155 (97.5)	151 (96.8)
Cancer	45 (28.3)	44 (28.2)
Diabetes	112 (70.4)	100 (64.1)
Smoking ever	122 (76.7)	118 (75.6)
Education		
< High school diploma	16 (10.1)	13 (8.3)
High school graduate/GED/vocational degree	56 (35.2)	52 (33.3)
Some college	65 (40.9)	60 (38.5)
College graduate/graduate degree	22 (13.8)	31 (19.9)
Employment status		
Employed full or part time	34 (21.4)	23 (14.7)
Unemployed/retired/permanently disabled	125 (78.6)	133 (85.3)
Qualifying medications		
RAAS blockers[c] only	31 (19.5)	36 (23.1)
Diuretics[d] only	23 (14.5)	26 (16.7)
Metformin only	5 (3.1)	1 (0.6)
NSAIDs only	0 (0.0)	0 (0.0)
more than one of these	100 (62.9)	93 (59.6)
Internet use ever	118 (74.2)	117 (75.0)

Abbreviations: CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; GED, general educational development; NSAID, nonsteroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation.
[a]Follow-up time calculated only for those who completed the protocol. N = 152 for sick-day protocol group and N = 147 for usual care group.
[b]Missing 4 participants because of lack of baseline creatinine measurements.
[c]254 participants on RAAS blockers were in first randomization block and the 61 participants not on RAAS blockers were in the second randomization block.
[d]Loop and thiazide diuretics and mineralocorticoid receptor antagonists

0.69) and −0.72 (95% CI, −2.12 to 0.68) mL/min/1.73 m^2, respectively, and there was no significant difference when comparing 6-month mean change in eGFR between the sick-day protocol and usual care groups, adjusting for baseline eGFR, $P = 0.99$. The mean differences in eGFR changes between the 2 groups, under the assumption of missing values having a 20% or 50% more or less decline in eGFR in the sick-day protocol group, also showed no significant difference.

Four participants in both the sick-day protocol and usual care groups had AKI episodes defined as 50% decrement in GFR from baseline at any time during the study including final 6-month measurement, with one participant with laboratory criteria for AKI among those with an *International Classification of Diseases, Tenth Revision* code-defined AKI event in the sick-day protocol group. Table 3 shows the rate of hospitalization including emergency department and urgent care visits in the sick-day protocol and usual care groups with 11.5/100 and 8.4/100 events per person-month in the former and latter, respectively. The adjusted prevalence ratio of hospitalizations in the sick-day protocol versus usual care group was not significantly increased (prevalence ratio, 1.30; 95% CI, 0.96-1.76), and there were no significant differences in the frequency of hospitalizations, emergency department, or urgent care visits in the 2 groups when treated distinctly.

Table 2. Change in Kidney Function and AKI Over 6-month Study Period

	Sick-Day Protocol Group	Usual Care Group	Mean Difference
Participants completing final laboratory assessments, n	140	140	
eGFR (mL/min/1.73 m²), mean (95% CI)			
Baseline	43.19 (40.95-45.44)	43.87 (41.63-46.12)	−0.68 (−3.85 to 2.48)
Follow-up	42.54 (40.19-44.89)	43.10 (40.70-45.51)	−0.57 (−3.92 to 2.78)
Change from baseline to follow-up[a]	−0.71 (−2.11 to 0.69)	−0.72 (−2.12 to 0.68)	0.013 (−1.97 to 2.0)
Creatinine (mg/dL), mean (95% CI)			
Baseline	1.90 (1.77, 2.02)	1.85 (1.74, 1.96)	0.048 (−0.12, 0.21)
Follow-up	1.97 (1.81, 2.13)	1.93 (1.79, 2.07)	0.044 (−0.17, −0.25)
Change from baseline to follow-up[b]	0.07 (−0.01, 0.15)	0.08 (0.01, 0.16)	−0.01 (−0.12, 0.10)
AKI by laboratory measurements, n (%)	4 (2.9)	4 (2.9)	–
AKI events by admission N17.9 ICD-10 code, n (%)	1 (0.7)	1 (0.0)	–

Abbreviations: AKI, Acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; ICD-10, *International Classification of Diseases, Tenth Revision*.
[a]Adjusted for baseline eGFR
[b]Adjusted for baseline creatinine

Table 4 shows patients in the sick-day protocol arm maintained high rates of engagement with the IVRS over the duration of participation. With 4,263 expected weeks of participation for the 159 veterans assigned to the sick-day protocol, users engaged the system in 3,483 (81.7%) of those weeks. There was a slight increase in compliance with the IVRS over the study period. During the first 13 weeks of participation, 20.5% of calls were not responded to compared with 16.3% during the subsequent 13 weeks of participation ($P < 0.001$). Of those weeks engaging the IVRS, 3,417 (80.2%) calls reported no events, and 66 (1.6%) calls were during weeks when the users experienced what they considered a sick-day event.

Table 3. Hospital and Urgent Service Utilization[a]

	Sick-Day Protocol Group	Usual Care Group
Hospitalization		
Participants, n (%)	29 (18.2)	23 (14.7)
Events	46	32
Event rate per 100 participant-months	5.04	3.57
Emergency department visits		
Participants, n (%)	35 (22.0)	30 (19.2)
Events	49	38
Event rate per 100 participant-months	5.37	4.24
Urgent care visits		
Participants, n (%)	5 (0.3)	5 (0.3)
Events	10	6
Event rate per 100 participant-months	1.01	0.68
All		
Participants	159	156
Events	105	76
Total participant-months	913	896
Event rate per 100 participant-months	11.5	8.4

[a]Hospital and urgent service utilization events were self-reported by participants at the final study visit.

One hundred twenty-two (76.7%) of the sick-day protocol arm enrollees never reported an event, and 37 (23.3%) dialed in what they believed was a sick-day event. On follow-up, 19 of those believing they had a sick-day event had an experience correctly qualifying as such. Of the 66 distinct events reported, 19 were erroneous data entries, 14 (21.2%) were false alerts (medical events misclassified as sick days), and 33 (50.0%) true sick days. In these 33 instances of true sick-day events, participants correctly followed the sick-day protocol instructions in 14 (49.2%) and violated the sick-day protocol instruction in the remainder by not stopping specified medicines in 12 instances and stopping the wrong medications in 7 events. Of the participants who had true sick-day events, all but 2 reported actively taking the same medications at their 6-month follow-up visit. The 2 participants reporting medication changes confirmed (via IVRS or call from coordinator) that they resumed medications after their sick-day event during study participation.

Sick-day protocol arm participants rated use of the protocol with the IVRS framework favorably on all counts including ease of use, comprehension of instructions, and desire to continue use (Table S2). Figure 1 depicts the 35 participants who made at least 1 error with the sick-day protocol or IVRS distributed by their Likert rating of confidence in the sick-day protocol use and willingness to continue using it. All individuals who made at least 1 error were confident with their use of the protocol, and most agreed with continued use.

DISCUSSION

In this trial examining the effectiveness of an IVRS-enhanced self-management sick-day protocol, we showed no difference in short-term kidney outcomes between patients with CKD assigned to the intervention

Table 4. Engagement with IVRS and Adherence to Sick-Day Protocol Instructions

Participant-weeks[a], N = 4,263	n (%)
Total weeks with no response	780 (18.3)
Total weeks with events reported	66 (1.6)
Total weeks with no events reported	3417 (80.2)
Participants, N = 159	
Participants never reported an event	122 (76.7)
Participants ever reported any event	37 (23.3)
True sick-day events	19 (51.4)
Events, N = 66	
Data entry error	19 (28.8)
False alert[b]	14 (21.2)
True sick-day events	33 (50.0)
Followed sick-day protocol instructions	14 (42.4)
Did not stop medicines	12 (36.4)
Stopped other medicines in addition to sick-day protocol-qualifying medicines	7 (21.2)

Abbreviation: IVRS, Interactive voice response system.
[a]Weeks of study participation ranged from 12-32 for each study participant.
[b]Assessed by staff as nonqualifying illness

versus usual care. Although the frequency of AKI was low, the change in kidney function between the 2 groups over 6 months was comparable, with no difference in hospitalization rates. When examining IVRS participation and success of implementation of the self-management sick-day protocol, we observed high rates of engagement but a notable frequency of errors in IVRS use, identification of qualifying sick days, and proper protocol execution. Common missteps included erroneous reporting of sick days, failure to withhold prespecified medications, or stopping the incorrect medicines during qualifying sick days. Despite these errors, all participants still rated the system and sick-day protocol highly with potentially misguided confidence about its use.

The reported frequency of AKI has increased over the last several years.[8] Although there are reports examining the epidemiology of hospitalized-acquired AKI,[4,9] determining the incidence of AKI among community dwellers has been challenging and ranges from 100-500 cases of nondialysis-requiring AKI per million community dwellers, with dialysis-requiring AKI about 10-fold less common.[8,10] Drugs are implicated in ≥20% incidents of AKI, especially among the elderly, with NSAIDs and RAAS blockers the most prominent potential causative agents.[2-4] Hypotension with RAAS blockers is more common than expected among elderly individuals submitting to 24-hour blood pressure monitoring,[11] and AKI is not infrequent among nursing home patients treated with RAAS blockers.[2] Patients with congestive heart failure on angiotensin-converting enzyme inhibitors have a higher incidence of AKI, with intensified diuretic regimens compared with their counterparts on lower doses or no diuretics.[12] The addition of an NSAID to an RAAS blocker and diuretic amplifies the risk of AKI because of what has been described as a "triple whammy."[13] However, the benefits of avoiding these risks need to be weighed against the potential hazards of discontinuing therapy and concern for worsened long-term outcomes, including cardiovascular events and mortality.[14]

Kidney providers recognize medications, along with other interventions administered without special considerations, for CKD have the potential to cause adverse events such as AKI, and guidelines have recommended temporary cessation of medicines, including RAAS blockers during intercurrent illnesses because of potential risks to patients with CKD.[15-18] However, a recent systematic review highlighted a disparity between the volume of educational resources promoting sick-day guidance and the low number of primary research studies evaluating their usability and effectiveness. To date, there remains "very little empirical evidence for the effectiveness of current approaches in implementing sick-day medication guidance into practice."[19]

Navigating the evidence gap is reflected in the different approaches taken across the United Kingdom. In Scotland,

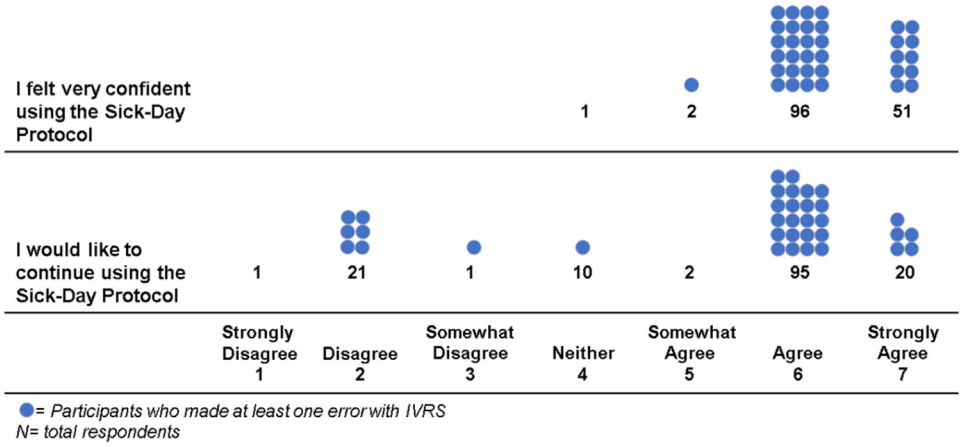

Figure 1. Distribution of all satisfaction survey respondents and those with at least one error based on Likert score for confidence and desire for continued use of Sick-Day Protocol. IVRS, Interactive voice response system.

the Scottish Patient Safety Programme in Primary Care implemented a sick-day protocol campaign across the Highland region starting in July 2013 with the initiative directed at pharmacists and other providers as an effort to prevent AKI. Patients receiving RAAS blockers, diuretics, NSAIDS, or metformin were given a business card describing a qualifying volume-depleting illness, recommendations to withhold these medications, and directions to resume them after 24-48 hours of normalized eating and drinking. The sick-day protocol was well received by the pharmacists and clinicians in the region, with 71% of personnel distributing the cards after they were introduced.[20] However, the NHS England Think Kidneys Programme took a more cautious approach, with a position statement recommending that "investment in a systematic approach to increase uptake of sick-day rules guidance by patients should only be undertaken in the context of a formal evaluation."[21]

In preparation for this trial, we conducted usability testing of the sick-day protocol card as designed by the Scottish Patient Safety Programme and reported a range of failures in understanding and errors with its simulated use.[22] We made modifications to the sick-day protocol and associated card and distributed it for use in conjunction with an IVRS platform for reminders of protocol engagement among sick-day protocol participants. The discrepancy between participant enthusiasm to use the sick-day protocol, evidenced by high rates of IVRS interaction, and the ability to successfully identify sick days and implement sick-day protocol instructions illustrates the challenges common with patient education materials. The instructions ask users to self-identify and act on vague symptoms and to manage starting and stopping pills, which may be overwhelming because of polypharmacy, common among patients with CKD. Patients on the margins of adequate health literacy may be challenged with the multistep executive functioning required to self-identify symptoms, seek sick-day protocol guidance, and ultimately manage medication changes. This may be an indication that, despite prior testing supporting sick-day protocol usability in smaller patient subsets, wider implementation may fail with diverse patient health literacy levels.

The findings from this study should be interpreted with inherent limitations in mind. The incidence of sick days as well AKI events were low and may have obscured any detectable effect associated with the sick-day protocol that might be detected with a larger sample size recruited beyond a single health care system. Moreover, subclinical AKI may have been overlooked because there were no scheduled blood tests over the 6-month period of the study, and participants may have underreported clinical events. We also did not evaluate other pertinent outcomes including hypotension or other electrolyte abnormalities (eg, hyperkalemia). The study did not track whether primary care providers might have intervened in sick-day events as intercurrent ambulatory visits for nonurgent or ambulatory events were not tracked. Similarly, we were unable to determine clinical events potentially related to the sick-day events (eg, hyperglycemia and volume overload) during active study participation. Importantly, the modest but suboptimal frequency of errors in use of the sick-day protocol may have mitigated any benefit that otherwise would be associated with flawless use of the intervention and calls for refinement in self-care protocols patients were asked to adopt.

Nevertheless, to our knowledge, this is one of a limited number of studies to assess a population of patients with CKD and the adoption of a self-management protocol in clinical practice. Prior studies have not shown self-care protocols to improve kidney outcomes, including the incidence of kidney failure or death.[23] Such disappointing findings puts into question the value of health guidance as currently designed to prevent adverse outcomes such as community-acquired AKI. The study shows strategies to foster patient engagement in self-management, even those with reminder prompts like an IVRS, warrant reassessment and redesign with attention to the target population. We recognize that design of self-management strategies for patients with CKD is a unique challenge given the abstract nature of the illness, with vague symptomatology and reliance on medications with complex mechanisms of action (eg, RAAS blockers). Nevertheless, studies such as this direct us to improve self-management strategies usable to the diverse population of patients with CKD, with the intent of improving health outcomes.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: CONSORT Flow Diagram.

Table S1: Sick-Day Protocol Interactive Voice Response System (IVRS) Survey Script.

Table S2: Satisfaction Survey Results

ARTICLE INFORMATION

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