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Medication use, renin–angiotensin system inhibitors, and acute care utilization after hospitalization in patients with chronic kidney disease

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Abstract

Objectives: The aims of this secondary analysis were to: (a) characterize medication use following hospital discharge for patients with chronic kidney disease (CKD), and (b) investigate relationships of medication use with the primary composite outcome of acute care utilization 90 days after hospitalization.

Methods: The CKD-Medication Intervention Trial (CKD-MIT) enrolled acutely ill hospitalized patients with CKD stages 3–5 not dialyzed (CKD 3–5 ND). In this post hoc analysis, data for medication use were characterized, and the relationship of medication use with the primary outcome was evaluated using Cox proportional hazards models.

Results: Participants were taking a mean of 12.6 (standard deviation=5.1) medications, including medications from a wide variety of medication classes. Nearly half of study participants were taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB). ACE inhibitor/ARB use was associated with decreased risk of the primary outcome (hazard ratio=0.51; 95% confidence interval 0.28–0.95; p=0.03) after adjustment for baseline estimated glomerular filtration rate, age, sex, race, blood pressure, albuminuria, and potential nephrotoxin use.

Conclusions: A large number, variety, and complexity of medications were used by hospitalized patients with CKD 3–5 ND. ACE inhibitor or ARB use at hospital discharge was associated with a decreased risk of 90-day acute care utilization.

Keywords

Acute illness, hospitalization, medication regimen complexity index, pharmacotherapy, renin–angiotensin system inhibitors

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Introduction

Chronic kidney disease (CKD) is a serious chronic condition associated with high rates of morbidity, use of complex medication regimens, and poor overall survival, all of which contribute to high costs of care.[1–3] In 2014, expenditures exceeded $50 billion for Medicare beneficiaries with CKD—representing 20% of all Medicare spending in beneficiaries >65 years of age.[4] Other chronic conditions such as hypertension, dyslipidemia, diabetes mellitus, and mood disorders are often inadequately managed in this high-risk population.[5,6] Reflecting a high comorbidity burden, patients with CKD use more medications than patients without CKD and frequently have complex medication regimens.[7] Previous studies have reported that the number of medications taken by patients

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with CKD ranges widely from 1 to 38 medications.[7–9] Two recent reports of medication utilization in patients with CKD reported a mean of eight medications taken per participant. As expected, with increased regimen complexity, the potential for medication-related adverse events and adherence difficulties increases.[10,11]

Hospitalization is a common occurrence in CKD. Compared to Medicare beneficiaries without CKD, those with CKD stages 3–5 not dialyzed (CKD 3-5 ND) have three- to fivefold higher rates of hospitalization (200 vs. 600–1000 admissions per 1000 patient years, respectively).[4] They are also more likely to be re-hospitalized when compared to patients without CKD. Overall readmissions and readmissions resulting in death increase in a stepwise fashion with increased CKD severity.[12] Risks of medication-related adverse events are heightened during acute illness and hospital admission, and medication changes made during the hospital stay may increase the risk of adverse events.[13,14] Therefore, more complete characterization of medication use in hospitalized patients with CKD is needed to understand usage patterns better and to identify opportunities to improve care following acute illness.

The study aim was to determine relationships between medication use (number of medications taken, medication classes used, and medication regimen complexity) and risk of hospital readmissions and emergency department and urgent care visits for 90 days after hospitalization in patients with CKD 3–5 ND.

Methods

Study design

For patients with CKD 3–5 ND, post hoc analyses were conducted with data on medication use at the hospital-to-home transition from the CKD-Medication Intervention Trial (CKD-MIT; www.clinicaltrials.gov; NCT01459770).[15,16] The CKD-MIT was conducted at Providence Sacred Heart Medical Center and Providence Holy Family Hospital in Spokane, Washington, between February 2012 and May 2015. The Providence Institutional Review Board approved the CKD-MIT trial. Conduct of the trial adhered to the principles set forth by the Declaration of Helsinki. All participants provided written informed consent prior to study participation.

The study design and main results of the trial have been reported previously.[15,16] Briefly, the CKD-MIT was designed to test the impact of a pharmacist-led, in-home medication management intervention compared to usual care on a primary composite outcome of acute care utilization (hospital readmissions and visits to emergency departments or urgent care centers) for 90 days following hospital discharge in adult participants with CKD 3–5 ND. The intervention involved assessment and resolution of medication discrepancies and medication errors during transition from hospital to home. Pharmacists additionally assessed suitability of medication use based on consideration of participants' kidney function and other comorbidities, with the pharmacists recommending medication changes when appropriate. Participants enrolled in the CKD-MIT were adults (≥21 years of age) with CKD 3–5 ND identified by at least two measures of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 for more than 3 months during the year prior to the index hospital admission for acute illness. For study eligibility, eGFR was calculated based on local laboratory reports of creatinine values. A detailed review of prescription and non-prescription medication use was conducted at the baseline assessment within 7 days of hospital discharge.

Study definitions

Medication data were systematically categorized by a pharmacist investigator according to a pre-specified classification system developed for the CKD-MIT by two members of the study team.[15,16] For non-prescription medications, over-the-counter (OTC)/herbal medications were operationally defined as any medications that could be obtained without a prescription regardless of whether the participant was instructed to take the product by a healthcare provider. Frequently occurring OTC products (e.g., aspirin, vitamin D) were reported individually. OTC/herbal medications encountered less frequently (e.g., cinnamon, vitamin C) were placed into a single "other OTC/herbal" category. While select insulin products can be purchased without a prescription (e.g., regular and isophane (NPH) insulins), all insulin products were classified as "antihyperglycemic agents." Medication use was analyzed and reported by CKD stage. A single drug category of "ACE inhibitor/ARB" was created for renin–angiotensin system (RAS) inhibitors. All medication classifications were verified by a second pharmacist investigator. Any discordance in classification was discussed among a larger group of study investigators, inclusive of pharmacists and physicians, to reach a consensus. Medication complexity scores were calculated by a study pharmacist and validated by a second study pharmacist using the Medication Regimen Complexity Index (MRCI).[10,17–19]

Statistical analyses

Descriptive statistics for key demographic variables, number of medications taken, medication class use by CKD 3–5 ND stage, and MRCI scores were calculated (mean±standard deviation (*SD*) or *n*/*N* and %). Associations of the medication use with the primary outcome of 90-day acute care utilization were evaluated using Cox proportional hazards models. The models applied predictors (total number of medications taken, medication classes taken, and MRCI scores) and were adjusted for pre-specified covariates within each model (baseline eGFR, age, sex, race, blood pressure, albuminuria, and

Table 1. Demographic and clinical characteristics of participants in the CKD-MIT by CKD stage.

	CKD stage 3A (eGFR 45–59 mL/min/1.73 m^2), *n*/*N*=49/141		CKD Stage 3B (eGFR 30–44 mL/min/1.73 m^2), *n*/*N*=52/141		CKD stage 4/5 (eGFR 15–29 mL/min/1.73 m^2), *n*/*N*=40/141		Total combined in CKD-MIT (eGFR 15–59 mL/min/1.73 m^2), *N*=141	
Age (*M*±*SD*)	68±11		72±9		67±13		69±11	
	n	%	*N*	%	*n*	%	*n*	%
Sex								
Male	28	57	23	44	23	56	74	52
Female	21	43	29	56	17	43	67	48
Race								
White	46	94	43	83	30	75	119	84
Non-white	3	6	9	17	10	25	22	16
Ethnicity								
Hispanic	0	0	3	6	0	0	3	2
Non-Hispanic	49	100	49	94	40	100	138	98
Diabetes	22	45	31	60	26	65	79	56
Hypertension	43	88	43	83	31	78	117	83
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Prescription medications	8.2	3.8	8.8	3.4	8.9	2.8	8.6	3.4
OTC/herbal medications	3.8	3.6	4.1	3.2	4.0	4.1	4.0	3.6
Total medications	12.0	5.5	12.9	4.5	12.9	5.2	12.6	5.1
Total MRCI score	22.8	12.6	23.9	9.8	25.1	9.5	23.9	10.7

CKD: chronic kidney disease; CKD-MIT: CKD-Medication Intervention Trial; eGFR: estimated glomerular filtration rate; *M*: mean; MRCI: medication regimen complexity index; OTC: over-the-counter; *SD*: standard deviation.

potential nephrotoxin use (nonsteroidal anti-inflammatory drugs and/or proton pump inhibitors (PPI)). As some participants experienced more than one event during the study follow-up period, all Cox proportional hazard models represent time to first event. All medication classes outlined were tested for relationships with the primary outcome (Table 2). *p*-Values <0.05 were considered statistically significant. Data analyses and computations were conducted using IBM SPSS Statistics for Windows v25.0 (IBM Corp., Armonk, NY).

Results

Of 141 participants enrolled in the CKD-MIT, 35% (49/141) had CKD stage 3A, 37% (52/141) had CKD stage 3B, and 28% (40/141) had CKD stage 4/5 ND (Table 1). For all CKD stages, the mean age of participants was ⩾67 years. Most participants were white, although the CKD stage 4/5 ND group was composed of a relatively higher proportion of non-white participants compared to the CKD stage 3A and 3B groups. The majority of participants had diabetes and/or hypertension.

Participants in the CKD-MIT were taking a mean of 8.6 (*n*=141, *SD*=3.4) prescription medications when assessed in the home within 7 days after hospital discharge. They were also taking a mean of 4.0 (*SD*=3.6) OTC/herbal medications, giving a mean of 12.6 (*SD*=5.1) total medications (Table 2). The mean number of prescription, OTC/herbal, and total medications utilized by patients with CKD-ND stage 3A, stage 3B, and stage 4/5 was found to be similar. When exploring the complexity of medication regimens, mean MRCI scores were similar among groups when examined by CKD stage (means of 23–25).

The most common medication class utilized in the combined cohort was antihypertensive agents (92% of participants; 130/141). Nearly half (46%; 65/141) of all participants received angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB), with the highest use in earlier CKD stages (59%; 29/141). No participants were receiving both an ACE inhibitor and an ARB in combination. Other commonly used classes were OTC/herbal medications (74% of participants; 105/141), platelet inhibitors (63% of participants; 89/141), statins (61% of participants, 86/141), gastrointestinal agents (55% of participants; 77/141), and antihyperglycemic agents (51% of participants; 72/141). PPIs were taken by 38% of participants (53/141) in the combined CKD-MIT, and 33% of participants (46/141) were receiving opioid agonists.

The primary outcome (acute care use within 90 days of hospital discharge) occurred in 43% (60/141) of

Table 2. Medication use by class in the CKD-MIT by CKD stage.

Medication class	CKD stage 3A (eGFR 45–59 mL/min/1.73 m^2), *n*/*N*=49/141		CKD stage 3B (eGFR 30–44 mL/min/1.73 m^2), *n*/*N*=52/141		CKD stage 4/5 (eGFR 15–29 mL/min/1.73 m^2), *n*/N=40/141		Total combined medication use in CKD-MIT, *N*=141	
	n	%	*n*	%	*n*	%	*n*	%
Antihypertensive agent	**45**	**92**	**46**	**89**	**39**	**98**	**130**	**92**
ACE inhibitor/ARB	29	59	19	37	17	43	65	46
Diuretic	21	43	31	60	31	78	83	59
Loop	19	39	24	46	28	70	71	50
Thiazide	4	8	6	12	6	15	16	11
Potassium sparing	5	10	7	14	2	5	14	10
Beta blocker	21	43	28	54	20	50	69	49
Calcium channel blocker	13	27	13	25	18	45	44	31
Dihydropyridine	7	14	9	17	16	40	32	23
Non-dihydropyridine	6	12	5	10	3	8	14	10
Other antihypertensive	0	0	7	14	6	15	13	9
Other OTC/herbal	**32**	**65**	**41**	**79**	**32**	**80**	**105**	**74**
Platelet inhibitor	**35**	**71**	**31**	**60**	**23**	**58**	**89**	**63**
Aspirin	33	67	26	50	21	53	80	57
Other platelet inhibitor	6	12	17	33	6	15	29	21
Statin	**29**	**59**	**35**	**67**	**22**	**55**	**86**	**61**
Gastrointestinal agent	**27**	**55**	**29**	**56**	**21**	**53**	**77**	**55**
Proton pump inhibitor (PPI)	17	35	22	42	14	35	53	38
Other gastrointestinal agent	17	35	15	29	10	25	42	30
Antihyperglycemic agent	**18**	**37**	**29**	**56**	**25**	**63**	**72**	**51**
Insulin	13	27	19	37	21	53	53	38
Oral antihyperglycemic agent	10	20	16	31	6	15	32	23
Sulfonylurea	4	8	7	14	5	13	16	11
Metformin	7	14	6	12	1	3	14	10
DPP-4 Inhibitor	2	4	2	4	0	0	4	3
Thiazolidinedione	0	0	2	4	0	0	2	1
GLP-1 receptor agonist	1	2	1	2	0	0	2	1
Vitamin D	**20**	**41**	**28**	**54**	**24**	**60**	**72**	**51**
Psychoactive agents	**24**	**49**	**28**	**54**	**17**	**43**	**69**	**49**
Antidepressant	18	37	20	39	10	25	48	34
Anticonvulsant	8	16	9	17	5	13	22	16
Anxiolytic	8	16	4	8	5	13	17	12
Insomnia medication	3	6	4	8	0	0	7	5
Other psychoactive agent	1	2	0	0	0	0	1	<1
Opioid agonist	**16**	**33**	**19**	**37**	**11**	**28**	**46**	**33**
Acetaminophen	**13**	**27**	**21**	**40**	**10**	**25**	**44**	**31**
Thyroid supplement	**13**	**27**	**13**	**25**	**11**	**28**	**37**	**26**
Antibiotic agent	**15**	**31**	**10**	**19**	**11**	**28**	**36**	**26**
Anticoagulant	**11**	**22**	**14**	**27**	**11**	**28**	**36**	**26**
Warfarin	9	18	11	21	10	25	30	21
Direct oral anticoagulant	2	4	3	6	0	0	5	4
Heparin	0	0	0	0	1	3	1	<1
Low molecular weight heparin	0	0	0	0	1	3	1	<1
Uric acid lowering agent	**13**	**27**	**9**	**17**	**13**	**33**	**35**	**25**
Iron supplements	**10**	**20**	**13**	**25**	**11**	**28**	**34**	**24**
Nitrate	**10**	**20**	**13**	**25**	**7**	**18**	**30**	**21**
Prescription phosphate binder	**0**	**0**	**2**	**4**	**3**	**8**	**12**	**9**
Parkinson's disease medication	**3**	**6**	**2**	**4**	**1**	**3**	**6**	**4**

(Continued)

Table 2. (Continued)

Medication class	CKD stage 3A (eGFR 45–59 mL/min/1.73 m^2), *n*/*N*=49/141		CKD stage 3B (eGFR 30–44 mL/min/1.73 m^2), *n*/*N*=52/141		CKD stage 4/5 (eGFR 15–29 mL/min/1.73 m^2), *n*/N=40/141		Total combined medication use in CKD-MIT, *N*=141	
	n	%	*n*	%	*n*	%	*n*	%
NSAID	**2**	**4**	**3**	**6**	**0**	**0**	**5**	**4**
Erythropoietin stimulating agent	**0**	**0**	**1**	**2**	**1**	**3**	**2**	**1**
Potassium binder	**0**	**0**	**1**	**2**	**0**	**0**	**1**	**<1**
Dementia medication	**0**	**0**	**1**	**2**	**0**	**0**	**1**	**<1**
Anti-neoplastic	**0**	**0**	**1**	**2**	**0**	**0**	**1**	**<1**

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; NSAID: nonsteroidal anti-inflammatory drug.

participants in the CKD-MIT. In total, 37 hospitalizations and 30 visits to the emergency department or urgent care occurred in the 90-day CKD-MIT follow-up period. The three most common diagnoses for hospital readmission were: cardiovascular events (30%; 11/37 re-hospitalizations); gastrointestinal diseases (30%; 11/37), and infections (27%; 8/37). The most frequent diagnostic categories for emergency department urgent care visits were: infections (27%; 8/30 visits), gastrointestinal diseases (17%; 5/30 visits), and cardiovascular events (17%; 5/30 visits).[16] Neither MRCI scores nor total number of medications taken were related to the primary outcome. Of all medication classes, ACE inhibitor or ARB use was associated with a decreased risk of experiencing the primary outcome (hazard ratio=0.51; 95% confidence interval 0.28–0.95; p=0.03) in the fully adjusted model (Table 3 and Figure 1). ACE inhibitor or ARB dose did not influence the fully adjusted model.

Table 3. Cox proportional hazards analyses for ACE inhibitor/ARB use with model covariate adjustments for the primary outcome (acute care utilization: hospital readmissions and emergency department and urgent care visits within 90 days after hospitalization).

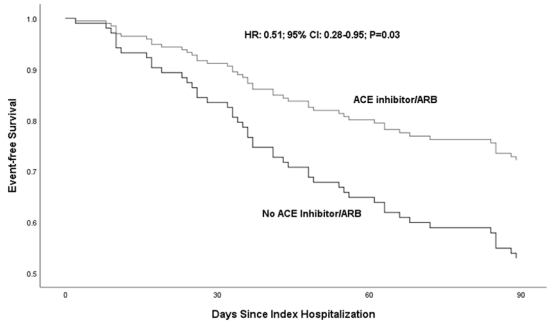
	HR (95% CI)
Model 1	
ACE inhibitor/ARB use	0.52 (0.29–0.94)
Model 2	
ACE inhibitor/ARB use	0.53 (0.29–095)
Baseline eGFR	0.99 (0.97–1.01)
Model 3	
ACE inhibitor/ARB use	0.47 (0.25–0.86)
Baseline eGFR	0.99 (0.97–1.02)
Age	0.98 (0.97–1.01)
Sex	0.96 (0.54–1.70)
Race	0.94 (0.41–2.13)
*Model 4**	
ACE inhibitor/ARB use	0.51 (0.28–0.95)
Baseline eGFR	1.00 (0.97–1.02)
Age	0.98 (0.96–1.01)
Sex	1.02 (0.57–1.82)
Race	1.03 (0.44–2.40)
Mean SBP	1.01 (0.99–1.02)
Use of potential nephrotoxic agent†	0.76 (0.42–1.40)
Albuminuria (urine albumin–creatine ratio)	
30–300 mg/g	0.67 (0.28–1.61)
>300 mg/g	1.31 (0.58–2.97)

*Fully adjusted model.
†Use of NSAID and/or PPI.
CI: confidence interval; HR: hazard ratio; SBP: systolic blood pressure.

Discussion

This analysis of CKD-MIT data provides a comprehensive account of medication use during the hospital-to-home transition in people with CKD 3–5 ND, a population at high risk for adverse drug events and hospital readmissions.[12] Information about medication use was obtained from study participants, their family members, and/or caregivers and categorized by a CKD-MIT classification algorithm to provide an accurate account of medications taken. Following discharge, participants took more than a dozen medications on average, with the most frequently used classes being antihypertensive agents, followed by OTC/herbal medications, antiplatelet agents, and statins. ACE inhibitor or ARB use following discharge from hospital was associated with a decreased risk of experiencing the primary outcome of acute care utilization within 90 days following hospitalization. However, the total number of medications and MRCI scores did not predict the primary outcome.

Acute care utilization in the first 90 days after hospitalization occurred in 43% (60/141) of participants enrolled in the CKD-MIT.[16] ACE inhibitors or ARBs were prescribed to 46% (65/141) of study participants at hospital discharge. This relatively low rate of ACE inhibitor or ARB use could be accounted for, at least in part, by the common clinical practice of discontinuing RAS inhibitors during acute illness ("sick days") because of concerns of acute kidney



Number at Risk

ACE Inhibitor/ARB	65	58	52	44
No ACE Inhibitor/ARB	76	59	45	37

Figure 1. Kaplan–Meier event-free survival for the primary outcome (acute care utilization: hospital readmissions and emergency department and urgent care visits within 90 days after hospitalization) by ACE inhibitor/ARB use in the fully adjusted Cox proportional hazards model (*N*=141). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker.

injury (AKI), hyperkalemia, or hypotension.[20] Conversely, it is possible that bias by indication for ACE inhibitor or ARB use may contribute to the observed favorable effects, which should be evaluated in future studies. Nevertheless, the risk of 90-day acute care utilization was reduced by nearly half in ACE inhibitor or ARB users. A recent study reported that medication appropriateness and regimen complexity were not associated with 30- or 90-day hospital readmissions, but use of RAS inhibitors was associated with reduced occurrence of 30- or 90-day readmissions by about half.[21] Another study reported that ACE inhibitor or ARB use within 6 months following hospital discharge for AKI was associated with lower mortality after 2 years.[22]

Patients re-hospitalized for an adverse drug event were reported to take more medications after hospitalization compared to those who were not readmitted (11.2 vs. 7.8 medications, respectively).[10] We found that patients with CKD were taking more than a dozen medications on average following hospitalization. However, a relationship between the number of medications and risk of acute care visits following hospitalization was not detected. A systematic review reported that outcomes such as hospital readmission and medication adherence were significantly impacted by higher MRCI scores.[23] Patients who were readmitted had a mean MRCI of 30 at the index hospitalization discharge compared to an MRCI of 20 for those who were not readmitted. Mean calculated MRCI scores in this analysis of the CKD-MIT were similar to scores seen in those studies. However, one study demonstrated that mean MRCI scores for adults with multiple chronic conditions that were calculated based on the hospital discharge list were significantly higher than mean MRCI scores that were calculated based on participant-reported home medication use.[11] In that study, MRCI scores calculated using the hospital discharge list were predictive of hospital readmission within 30 days of discharge, whereas MRCI scores calculated based on participant-reported medication use were not predictive of hospital readmission.[11] Similarly, in the current analysis, MRCI scores calculated in participants with CKD based on participant-reported medication use did not relate to post-hospitalization use of acute care. It is possible the high severity of illness in CKD may have subsumed most of the risk.

Another area of heightened interest is the treatment of pain and use of psychotropic agents in the CKD population. The high rates of opioid (~30% across all groups) and psychotropic medication (~50% across all groups) use was notable in the CKD-MIT. Pain is a common symptom in patients with CKD. Yet, use of pain medication in this population has risks.[24–26] Previous reports have suggested psychotropic medication use and co-occurring serious mental illness as a potential mediator of increased re-hospitalization risk in patients with CKD.[27]

The findings of this study should be considered within its limitations. First, medication use was recorded by interviewing patients and caregivers during a home visit or during a visit to the research center within 7 days following hospital discharge. Thus, medication use reported in the present analysis included short-term medication use after hospitalization and did not account for medications under temporary discontinuation. Second, interest in study participation was likely greater in CKD-aware patients, which may introduce selection bias for adherence and other health-related behaviors. Third, the main diagnoses for which medications were being utilized were not always known, and therefore could not be consistently used to determine medication indication. For example, if a medication such as duloxetine was part of a patient's regimen, it may not be apparent whether it was being used to treat depression or neuropathy. To avoid inaccurate assumptions concerning indications, medications were categorized generally by class. Due to the limited sample size, there was insufficient power to determine associations of ACE inhibitors or ARBs separately. Fourth, confounding variables such as changes in laboratory values, types of care (e.g., specialists, in-home caregivers), socioeconomic status, and health literacy were not available. Overall, these limitations speak to the difficulties of assessing and managing medications in this complex, severely ill population. Yet, despite its limitations, the present study provides valuable new knowledge about overall medication use, as well as observations about possible benefits of RAS inhibitor use in the early post-discharge period for hospitalized patients with CKD.

Conclusions

In conclusion, this post hoc analysis of the CKD-MIT highlights the large number and variety of medication classes

utilized and the complexity of regimens consumed by patients in the CKD 3–5 ND population. Notably, ACE inhibitor or ARB use at hospital discharge in patients with CKD 3–5 ND was associated with a decreased risk of the primary outcome of 90-day acute care utilization. This finding warrants further investigation to evaluate for improved clinical outcomes by early reinstitution of ACE inhibitor or ARB therapy following hospitalization for acute illness.

Declaration of conflicting interests

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