

Trimethoprim-Sulfamethoxazole–Induced Hyperkalemia in Patients Receiving Inhibitors of the Renin-Angiotensin System

A Population-Based Study

Tony Antoniou, BScPharm, PharmD; Tara Gomes, MHSc; David N. Juurlink, MD, PhD; Mona R. Loutfy, MD, MPH; Richard H. Glazier, MD, MPH; Muhammad M. Mamdani, PharmD, MPH

Background: Trimethoprim therapy can cause hyperkalemia and is often coprescribed with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). The objective of this study was to characterize the risk of hyperkalemia-associated hospitalization in elderly patients who were being treated with trimethoprim-sulfamethoxazole along with either an ACEI or an ARB.

Methods: We conducted a population-based, nested case-control study of a cohort of elderly patients 66 years or older who were residents of Ontario, Canada, and who were receiving continuous therapy with either an ACEI or an ARB. Case patients were those with a hyperkalemia-associated hospitalization within 14 days of receiving a prescription for trimethoprim-sulfamethoxazole, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin. For each case, we identified up to 4 control patients from the same cohort matched for age, sex, and presence or absence of chronic renal disease and diabetes. Odds ratios were de-

termined for the association between hyperkalemia-associated hospitalization and previous antibiotic use.

Results: During the 14-year study period, we identified 4148 admissions involving hyperkalemia, 371 of which occurred within 14 days of antibiotic exposure. Compared with amoxicillin, the use of trimethoprim-sulfamethoxazole was associated with a nearly 7-fold increased risk of hyperkalemia-associated hospitalization (adjusted odds ratio, 6.7; 95% confidence interval, 4.5-10.0). No such risk was found with the use of comparator antibiotics.

Conclusions: Among older patients treated with ACEIs or ARBs, the use of trimethoprim-sulfamethoxazole is associated with a major increase in the risk of hyperkalemia-associated hospitalization relative to other antibiotics. Alternate antibiotic therapy should be considered in these patients when clinically appropriate.

Arch Intern Med. 2010;170(12):1045-1049

ANGIOTENSIN-CONVERTING enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are cornerstones of therapy for patients with congestive heart failure, chronic renal disease, and hypertension.¹⁻⁴ Although ACEIs and ARBs are generally well tolerated, the potential for serious hyperkalemia is an important consideration in patients who are receiving these drugs, particularly when other risk factors for hyperkalemia are present.^{5,6} In clinical practice, hyperkalemia develops in approximately 10% of outpatients within 1 year of the initiation of ACEI therapy.⁵ Risk factors for ACEI- or ARB-induced hyperkalemia are well described and include renal insufficiency, diabetes mellitus, reduced left ventricular function, and advanced age.^{6,7}

Coadministration of drugs that impair potassium excretion is another important and potentially avoidable risk factor for hy-

perkalemia in patients who are receiving ACEIs or ARBs.⁶⁻¹⁰ It is well established that the concomitant use of potassium-sparing diuretics with ACEIs or ARBs increases the risk of hyperkalemia, which can sometimes be life-threatening.^{8,9} Trimethoprim exhibits structural and pharmacologic similarities to the potassium-sparing diuretic amiloride and reduces urinary potassium excretion by approximately 40%.^{11,12} In combination with sulfamethoxazole, the drug is commonly used for the treatment of urinary tract infection.

Because trimethoprim-sulfamethoxazole, ACEIs, and ARBs are widely used medications, the likelihood of coprescription of these drugs is high. However, to our knowledge, the risk of hyperkalemia with the use of these drug combinations has not been studied. We sought to characterize the clinical significance of this drug interaction by determining the risk of hyperkalemia after the prescription of tri-

Author Affiliations are listed at the end of this article.

methoprim-sulfamethoxazole to older patients who are being treated with either an ACEI or an ARB.

METHODS

We conducted a population-based, nested case-control study of a cohort of elderly patients 66 years or older who were residents of Ontario, Canada, between April 1, 1994, and March 31, 2008, and who were receiving continuous therapy with either an ACEI or an ARB. Patients who were receiving combination ACEI-ARB therapy were excluded. Data regarding prescription drug use were obtained from the records of the Ontario Drug Benefit Program, which captures prescriptions dispensed to all Ontario residents 65 years or older. Hospitalization data and demographic information were obtained from the Canadian Institute for Health Information Discharge Database and the Registered Persons Database, respectively. The Canadian Institute for Health Information Discharge Database contains demographic and clinical information regarding all hospital admissions, discharges, and same-day surgical procedures from participating hospitals in Canada. Abstraction of patient charts is undertaken by trained health information professionals using standard diagnosis and procedure codes. The Ontario Health Insurance Plan database provided information regarding claims for all physician services, and the Ontario Diabetes Database was examined for information regarding diabetes diagnoses. These databases were linked in an anonymous fashion using encrypted health card numbers and have previously been used to study population-based health outcomes.^{8,9,13,14}

The period of continuous use for each patient began with the first prescription for either an ACEI or an ARB after the patient's 66th birthday. The observation period ended with the first occurrence of hyperkalemia-related hospitalization, death, or discontinuation of treatment with an ACEI or an ARB, whichever occurred first. Patients were considered to have discontinued treatment if more than 100 days lapsed between prescriptions.

Within the cohort of continuous users of ACEIs or ARBs, we identified all hospitalizations involving a diagnosis of hyperkalemia at the time of admission (*International Classification of Diseases, 9th and 10th Revisions*, codes 276.7 and E87.5, respectively). We included only patients who had hyperkalemia coded as an admission diagnosis, as opposed to individuals in whom this problem emerged during the course of hospitalization. For the primary analysis, cases were defined as patients with a hyperkalemia-associated hospitalization within 14 days of receiving a prescription for trimethoprim-sulfamethoxazole, ciprofloxacin, norfloxacin, nitrofurantoin, or amoxicillin. We restricted our analyses to antibiotics that are primarily used to treat urinary tract infections to avoid the potential confounding effects of other systemic infections. The date of hospitalization served as the index date for all analyses, and only the first instance of hospitalization with hyperkalemia was considered for patients with more than 1 such admission during the study period. Patients were excluded if they received prescriptions for any other antibiotic in the 30 days preceding the index date.

From within the cohort of patients receiving an ACEI or an ARB, we selected up to 4 controls for each case using incidence density sampling.¹⁵ Control patients were required to not have been hospitalized for hyperkalemia before the index date and also to have received 1 of the study antibiotics within 14 days preceding the index date. Consequently, all cases and controls were elderly patients who were receiving long-term therapy with either an ARB or an ACEI and who had received treatment with 1 of the study antibiotics. Controls and cases were matched for age at the index date, sex, and presence or absence of renal disease (based on review of physician claims, hospitalization records,

and receipt of inpatient or outpatient dialysis in the preceding year) and diabetes based on a review of the Ontario Diabetes Database.¹⁶ When the number of available controls who could be matched to patients was fewer than 4, we analyzed only those controls and maintained the matching process.

We compared the baseline demographic and clinical characteristics between cases and controls by using conditional logistic regression models. We also computed the standardized difference between the 2 groups for each variable, with differences of less than 0.1 taken to indicate good balance between the cases and controls for a given covariate.¹⁷ The primary analysis examined the association between hyperkalemia-related hospitalization and receipt of a prescription for trimethoprim-sulfamethoxazole in the preceding 14 days using amoxicillin-treated patients as the reference group. With rare exception, the use of amoxicillin should not cause hyperkalemia.¹⁸ To contextualize our findings, we conducted similar analyses for norfloxacin, ciprofloxacin, and nitrofurantoin because these antibiotics have similar indications as trimethoprim-sulfamethoxazole but are not major risk factors for hyperkalemia. We conducted secondary analysis using prescription exposure windows of 7 and 21 days preceding the index admission for hyperkalemia.

For each analysis, conditional logistic regression was used to estimate the odds ratio and the 95% confidence interval for the association between hyperkalemia-related hospitalization and recent antibiotic use. Multivariable conditional logistic regression analysis was performed to adjust for concomitant medical conditions and classes of prescription drugs that could potentially be associated with an increased risk of ACEI- or ARB-associated hyperkalemia (eAppendix; <http://www.archinternmed.com>).¹⁹ Individuals with missing data or a Charlson Comorbidity Index designation of *no hospitalization* were given a separate classification variable for inclusion in the adjusted models. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Among 439 677 patients in the cohort, we identified 4148 admissions involving hyperkalemia over the 14-year study period. Of these, 371 occurred within 14 days of the patient receiving an antibiotic of interest. Virtually all cases ($n=367$; 98.9%) were matched to at least 1 control. Cases and controls were well matched with respect to age, sex, and history of renal disease and diabetes (**Table 1**). As expected, the use of medications associated with an increased risk of hyperkalemia was more prevalent among cases than among controls.

More than half of all patients who were hospitalized for hyperkalemia within 14 days of receiving a urinary tract antibiotic had received trimethoprim-sulfamethoxazole. The median (interquartile range) length of hospitalization was 6 (3-13) days. In the primary analysis, cases were almost 7 times more likely than controls to have received a prescription for trimethoprim-sulfamethoxazole than for amoxicillin in the 14 days preceding admission (adjusted odds ratio, 6.7; 95% confidence interval, 4.5-10.0). No association was found between hyperkalemia-related hospitalization and the use of any other study antibiotic (**Table 2**). Similar results were obtained when the index hospitalization occurred within 7 and 21 days of the patient receiving a prescription for trimethoprim-sulfamethoxazole (Table 2). Again, no increased risk was seen with the use of any of the comparator antibiotics.

Table 1. Characteristics of Cases and Controls^a

Variable	Cases (n=367)	Controls (n=1417)	P Value ^b	Standardized Difference ^c
Age at index date, median (interquartile range), y	82 (75-87)	81 (75-87)	.07	0.022
Male	145 (39.5)	551 (38.9)	Matched	0.013
Charlson Comorbidity Index			.002	
No hospitalization	86 (23.4)	388 (27.4)		0.089
0	65 (17.7)	339 (23.9)		0.149
1	69 (18.8)	260 (18.3)		0.012
≥2	147 (40.1)	430 (30.3)		0.208
History of congestive heart failure, 3 y	78 (21.3)	203 (14.3)	.001	0.191
History of hyperkalemia, 3 y	≤5 (1.1)	8 (0.6)	.49	0.064
History of renal disease, 3 y	53 (14.4)	166 (11.7)	Matched	0.083
Diabetes	188 (51.2)	733 (51.7)	Matched	0.010
Residence in a long-term care facility	54 (14.7)	231 (16.3)	.44	0.043
No. of prescription drugs in previous year, median (interquartile range)	11 (7-16)	9 (6-14)	<.001	0.268
Drug therapy				
Nonsteroidal anti-inflammatory drugs	138 (37.6)	461 (32.5)	.05	0.107
β-Adrenergic receptor antagonists	123 (33.5)	345 (24.3)	<.001	0.209
Potassium-sparing diuretics	86 (24.3)	97 (6.8)		0.560
Nonpotassium-sparing diuretics	256 (69.8)	745 (52.6)	<.001	0.348
Potassium supplements	14 (3.8)	23 (1.6)	.02	0.154
Income quintile			.26	
1 (lowest)	100 (27.2)	338 (23.9)		0.079
2	86 (23.4)	327 (23.1)		0.008
3	72 (19.6)	296 (20.9)		0.031
4	60 (16.3)	216 (15.2)		0.031
5	46 (12.5)	236 (16.7)		0.113
Missing	≤5 (0.8)	≤5 (0.3)		0.086

^aValues are expressed as number (percentage) unless otherwise indicated.

^bBased on global Wald statistic for test of association between variable and case-control status using conditional logistic regression.

^cDifference between cases and controls divided by standard deviation.

Table 2. Association Between Hospital Admission Involving Hyperkalemia and Recent Antibiotic Use

Antibiotic	No. (%)		Crude OR (95% CI)	Adjusted OR (95% CI) ^b
	Cases	Controls		
Primary analysis				
14-Day exposure window				
Total	367	1417		
Trimethoprim-sulfamethoxazole	204 (55.6)	323 (22.8)	6.2 (4.3-9.1)	6.7 (4.5-10.0)
Norfloxacin	20 (5.4)	163 (11.5)	0.8 (0.5-1.5)	0.8 (0.4-1.5)
Ciprofloxacin	76 (20.7)	413 (29.1)	1.5 (1.0-2.3)	1.4 (0.9-2.2)
Nitrofurantoin	18 (4.9)	129 (9.1)	1.2 (0.6-2.1)	1.1 (0.6-2.0)
Amoxicillin ^a	49 (13.4)	389 (27.5)	1 [Reference]	1 [Reference]
Secondary analysis				
7-Day exposure window				
Total	213	809		
Trimethoprim-sulfamethoxazole	112 (52.6)	143 (17.7)	6.2 (3.9-9.9)	6.8 (4.1-11.3)
Norfloxacin	8 (3.8)	96 (11.9)	0.7 (0.3-1.7)	0.7 (0.3-1.8)
Ciprofloxacin	52 (24.4)	222 (27.4)	1.9 (1.1-3.1)	1.5 (0.9-2.6)
Nitrofurantoin	10 (4.7)	90 (11.1)	1.0 (0.5-2.1)	0.9 (0.4-2.1)
Amoxicillin ^a	31 (14.6)	258 (31.9)	1 [Reference]	1 [Reference]
21-Day exposure window				
Total	368	1193		
Trimethoprim-sulfamethoxazole	204 (55.4)	236 (19.8)	6.1 (4.2-8.9)	6.5 (4.3-9.9)
Norfloxacin	21 (5.7)	154 (12.9)	0.8 (0.5-1.5)	0.8 (0.4-1.5)
Ciprofloxacin	76 (20.6)	346 (29.0)	1.5 (1.0-2.3)	1.5 (1.0-2.4)
Nitrofurantoin	18 (4.9)	110 (9.2)	1.2 (0.6-2.2)	1.2 (0.6-2.2)
Amoxicillin ^a	49 (13.3)	347 (29.1)	1 [Reference]	1 [Reference]

Abbreviations: CI, confidence interval; OR, odds ratio.

^aReference group.

^bAdjusted for congestive heart failure, hospitalization for hyperkalemia in previous 3 years, Charlson Comorbidity Index, income quintile, living in long-term care facility, number of prescription drugs in previous year, and medications (β-adrenergic receptor blockers, potassium-sparing diuretics, nonpotassium-sparing diuretics, nonsteroidal anti-inflammatory drugs, and potassium supplements).

In this population-based study spanning 14 years, we found that the use of trimethoprim-sulfamethoxazole was strongly associated with hyperkalemia-related hospitalization among elderly patients who were treated with either an ACEI or an ARB. The similarity between the adjusted and crude odds ratios suggests that there was very little confounding of the observed association between trimethoprim-sulfamethoxazole exposure and hospitalization for hyperkalemia. In contrast, no such risk was seen for commonly used antibiotics with similar indications. These findings support the notion of a potentially life-threatening drug interaction between trimethoprim and inhibitors of the renin-angiotensin aldosterone system.²⁰⁻²³

Although the use of trimethoprim-sulfamethoxazole has decreased over time in Ontario, the drug remains commonly used, with more than 107 000 prescriptions dispensed to individuals older than 65 years in 2007. Among our cohort of patients, exposure to trimethoprim-sulfamethoxazole was appreciable, with 11.6% of continuous ACEI or ARB users receiving at least 1 prescription for the drug during the study period. Given the widespread use of trimethoprim-sulfamethoxazole, ACEIs, and ARBs in the general population, and more specifically among elderly patients with multiple risk factors for hyperkalemia, the clinical implications of our findings are considerable. Serious hyperkalemia can cause sudden death and is one of the most dangerous complications of therapy with ACEIs or ARBs. Consequently, strategies aimed at minimizing the risk of hyperkalemia are necessary corequisites of treatment. When possible, minimizing the use of drugs that further impair potassium excretion is essential. Our findings suggest that for patients receiving an ACEI or an ARB and for whom therapy with antibiotics is required, avoidance of trimethoprim-sulfamethoxazole therapy may be prudent when other options exist. The mechanism by which the use of trimethoprim can precipitate hyperkalemia in users of ACEIs or ARBs is related to an amiloridelike inhibition of sodium channels in the luminal membrane of the distal tube.^{11,12} Consequently, sodium reabsorption and potassium secretion are impaired, resulting in an antikaliuretic effect that may predispose susceptible individuals to clinically important hyperkalemia.

Some limitations of our work merit emphasis. We used administrative data and had no access to serum potassium levels or indices of renal function or medication adherence and no record of nonprescription medications that may have influenced the risk of hyperkalemia. However, these limitations apply equally to all antibiotics. We cannot identify outpatient hyperkalemia and hyperkalemia-related mortality in the prehospital setting, and our study therefore underestimates the clinical consequences of this drug interaction. Some clinicians may be aware of the potential risk of hyperkalemia with the use of trimethoprim-sulfamethoxazole, but differential outcome ascertainment among patients treated with trimethoprim-sulfamethoxazole is unlikely to affect our findings because electrolyte levels are routinely measured in older patients who present to the hospital. Also, our find-

ings may not apply to younger patients with fewer risk factors for hyperkalemia. Finally, the accuracy of hospital discharge coding for hyperkalemia has not been validated, although the same limitation applies to previous research on the clinical consequences of drug interactions leading to hyperkalemia.^{8,9}

In conclusion, we found that prescription of trimethoprim-sulfamethoxazole to elderly patients receiving therapy with either an ACEI or an ARB was associated with a major increase in the risk of hyperkalemia. Other antibiotics commonly used for treating urinary tract infection impart no such risk. Increased awareness of this drug interaction among pharmacists and physicians is necessary to ensure that the potential for life-threatening hyperkalemia with the use of this drug combination is minimized either by selection of alternative antibiotics when appropriate or by close monitoring of patients who are being treated with these medications.

Accepted for Publication: December 10, 2009.

Author Affiliations: Leslie Dan Faculty of Pharmacy (Drs Antoniou and Mamdani and Ms Gomes), Departments of Medicine (Drs Juurlink and Loutfy), Pediatrics (Dr Juurlink), Health Policy, Management, and Evaluation (Drs Juurlink, Loutfy, Glazier, and Mamdani), and Family and Community Medicine (Dr Glazier), and Dalla Lana School of Public Health (Dr Glazier), University of Toronto, Toronto, Ontario, Canada; Department of Family and Community Medicine (Drs Antoniou and Glazier), Centre for Research on Inner City Health (Dr Glazier), and Li Ka Shing Knowledge Institute (Dr Mamdani), St Michael's Hospital, Toronto; Institute for Clinical Evaluative Sciences, Toronto (Ms Gomes and Drs Juurlink, Glazier, and Mamdani); Departments of Medicine, Sunnybrook Health Sciences Centre (Dr Juurlink) and Women's College Hospital (Dr Loutfy), Toronto; and Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia (Dr Mamdani).

Correspondence: Tony Antoniou, BScPharm, PharmD, Department of Family and Community Medicine, St Michael's Hospital, 410 Sherbourne St, Fourth Floor, Toronto, ON M4X 1K2, Canada (tantoniou@smh.toronto.on.ca).

Author Contributions: *Study concept and design:* Antoniou, Gomes, Juurlink, and Mamdani. *Acquisition of data:* Gomes. *Analysis and interpretation of data:* Antoniou, Gomes, Juurlink, Loutfy, Glazier, and Mamdani. *Drafting of the manuscript:* Antoniou. *Critical revision of the manuscript for important intellectual content:* Antoniou, Gomes, Juurlink, Loutfy, Glazier, and Mamdani. *Statistical analysis:* Antoniou, Gomes, and Mamdani. *Obtained funding:* Juurlink. *Administrative, technical, and material support:* Antoniou and Mamdani. *Study supervision:* Juurlink, Loutfy, Glazier, and Mamdani.

Financial Disclosure: Dr Antoniou has received unrestricted research grants from Glaxo-Smith-Kline Inc, Pfizer, and Merck Frosst for different studies. Dr Loutfy has received unrestricted research grants for other projects from, and has acted as a speaker and advisor for, Abbott Canada, Merck Frosst, Pfizer, Bristol-Myers Squibb, Tibotec, Boehringer Ingelheim, and Glaxo-Smith-Kline Inc.

Funding/Support: Dr Antoniou is supported by a scholarship from the Ontario HIV Treatment Network and Ca-

nadian Observational Cohort (CANOC) Collaboration. Dr Loutfy is supported by a New Investigator Award from the Canadian Institutes of Health Research. This project was supported by research funds from the Ontario Drug Policy Research Network, the Canadian Institutes of Health Research, and by the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care.

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Disclaimer: The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by the Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred.

Online-Only Material: An eAppendix is available at <http://www.archinternmed.com>.

REFERENCES

1. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G; The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342(3):145-153.
2. Yusuf S, Teo KK, Pogue J, et al; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559.
3. Agodoa LY, Appel L, Bakris GL, et al; African American Study of Kidney Disease and Hypertension (AASK) Study Group. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA*. 2001;285(21):2719-2728.
4. Thomas GN, Tomlinson B. Prevention of macrovascular disease in type 2 diabetic patients: blockade of the renin-angiotensin-aldosterone system. *Curr Diabetes Rev*. 2008;4(1):63-78.
5. Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors: how much should we worry? *Arch Intern Med*. 1998;158(1):26-32.
6. Ahuja TS, Freeman D Jr, Mahnken JD, Agraharkar M, Siddiqui M, Memon A. Predictors of the development of hyperkalemia in patients using angiotensin-converting enzyme inhibitors. *Am J Nephrol*. 2000;20(4):268-272.
7. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med*. 2004;351(6):585-592.
8. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA*. 2003;289(13):1652-1658.
9. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351(6):543-551.
10. Ponce SP, Jennings AE, Madias NE, Harrington JT. Drug-induced hyperkalemia. *Medicine (Baltimore)*. 1985;64(6):357-370.
11. Eiam-Ong S, Kurtzman NA, Sabatini S. Studies on the mechanism of trimethoprim-induced hyperkalemia. *Kidney Int*. 1996;49(5):1372-1378.
12. Velázquez H, Perazella MA, Wright FS, Ellison DH. Renal mechanism of trimethoprim-induced hyperkalemia. *Ann Intern Med*. 1993;119(4):296-301.
13. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med*. 2006;354(13):1352-1361.
14. Lipscombe LL, Gomes T, Lévesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA*. 2007;298(22):2634-2643.
15. Lubin JH, Gail MH. Biased selection of controls for case-control analyses of cohort studies. *Biometrics*. 1984;40(1):63-75.
16. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25(3):512-516.
17. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med*. 2007;26(4):734-753.
18. Appel GB, Garvey G, Silva F, Francke E, Neu HC, Weissman J. Acute interstitial nephritis due to amoxicillin therapy. *Nephron*. 1981;27(6):313-315.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
20. Bugge JF. Severe hyperkalemia induced by trimethoprim in combination with an angiotensin-converting enzyme inhibitor in a patient with transplanted lungs. *J Intern Med*. 1996;240(4):249-251.
21. Alappan R, Buller GK, Perazella MA. Trimethoprim-sulfamethoxazole therapy in outpatients: is hyperkalemia a significant problem? *Am J Nephrol*. 1999;19(3):389-394.
22. Marinella MA. Trimethoprim-induced hyperkalemia: an analysis of reported cases. *Gerontology*. 1999;45(4):209-212.
23. Canaday DH, Johnson JR. Hyperkalemia in elderly patients receiving standard doses of trimethoprim-sulfamethoxazole. *Ann Intern Med*. 1994;120(5):437-438.