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Clinical Research

No Increase in Adverse Events During Aliskiren Use Among Ontario Patients Receiving Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers

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See editorial by Touyz, pages 521-523 of this issue.

ABSTRACT

Background: Some evidence suggests that the direct renin inhibitor aliskiren may increase the risk of severe hyperkalemia, stroke, or acute kidney injury (AKI) when prescribed with angiotensin-converting enzyme inhibitors (ACEi's) or angiotensin-receptor blockers (ARBs). The extent to which concomitant treatment increases the risk of these outcomes in routine clinical practice is unknown. We addressed this issue with the use of administrative databases.

Methods: We established a cohort of Ontarians treated with an ACEi or an ARB. Within this cohort, we conducted 3 case-control studies. Cases were patients hospitalized with 1 of 3 outcomes (hyperkalemia, AKI, or stroke). In each analysis, we identified up to 5 matched control subjects for each case. Conditional logistic regression was used to examine the association between hospitalization for each outcome and the use of aliskiren in the preceding 60 days.

RÉSUMÉ

Introduction : Certaines données scientifiques suggèrent que l'inhibiteur direct de la rénine, l'aliskirène, peut augmenter le risque d'hyperkaliémie grave, d'accident vasculaire cérébral (AVC) ou d'insuffisance rénale aiguë (IRA) lorsqu'il est prescrit en association avec les inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) ou les antagonistes des récepteurs de l'angiotensine (ARA). La mesure dans laquelle ces traitements concomitants augmentent le risque de ces résultats dans la pratique clinique courante demeure inconnue. Nous abordons ce problème par l'utilisation de bases de données administratives.

Méthodes : Nous avons établi une cohorte d'Ontariens traités par un IECA ou un ARA. À partir de cette cohorte, nous avons mené 3 études cas-témoins. Les cas étaient de patients hospitalisés ayant 1 des 3 résultats cliniques (hyperkaliémie, IRA ou AVC). Dans chacune des

Drugs that modulate the renin-angiotensin-aldosterone system (RAAS) are increasingly important in the care of patients with cardiovascular disease, particularly those with hypertension and heart failure. The most commonly used RAAS inhibitors are angiotensin-converting enzyme inhibitors (ACEi's), angiotensin-receptor blockers (ARBs), and spironolactone, all of which have established mortality benefits in appropriately selected patients.[1-4]

Approved by the US Food and Drug Administration in 2007, aliskiren is the first commercially available direct renin inhibitor. Aliskiren binds to the $S3^{bp}$ binding pocket of renin, preventing the conversion of angiotensinogen to angiotensin I, the rate-limiting step in the RAAS cascade.[5] Because renin inhibitors do not influence kinin metabolism, they are thought to confer fewer adverse effects than ACEi's do. Clinical trials

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Results: Among 903,346 patients aged 66 years and older treated with an ACEi or ARB during the 28-month study period, we identified 4235 hospitalized with hyperkalemia, 18,231 hospitalized with AKI, and 8283 hospitalized with stroke. After extensive multivariable adjustment, aliskiren therapy was not associated with a significant increase in the risk of hospitalization for hyperkalemia, AKI, or stroke. We found similar results in stratified analyses of patients with and without a history of chronic kidney disease, diabetes, or heart failure.
Conclusions: Among community-dwelling patients aged 66 years and older receiving therapy with an ACEi or an ARB, aliskiren use was not associated with hospitalization for hyperkalemia, AKI, or stroke.

Résultats : Parmi les 903 346 patients âgés de 66 ans et plus qui ont été traités par un IECA ou un ARA durant la période d'étude de 28 mois, nous avons identifié 4235 patients hospitalisés ayant eu une hyperkaliémie, 18 231 patients hospitalisés ayant eu une IRA et 8283 patients hospitalisés ayant eu un AVC. Après l'ajustement multivarié complet, le traitement à l'aliskirène n'a pas été associé à une augmentation significative du risque d'hospitalisation pour une hyperkaliémie, une IRA ou un AVC. Nous avons observé des résultats similaires dans les analyses stratifiées de patients ayant des antécédents ou n'ayant pas d'antécédents de maladie rénale chronique, de diabète ou d'insuffisance cardiaque.
Conclusions : Parmi les patients vivant dans la communauté qui étaient âgés de 66 ans et plus et qui recevaient un traitement par un IECA ou un ARA, l'utilisation de l'aliskirène n'a pas été associée à l'hospitalisation pour une hyperkaliémie, une IRA ou un AVC.

have shown that aliskiren lowers blood pressure in combination with an ACEi or an ARB,[6-8] but its place in therapy is still unclear.[9] It is presently approved in Canada and the United States as a third-line agent in resistant hypertension, and in Europe as monotherapy or as part of combination therapy.

Hyperkalemia is a well-recognized and potentially life-threatening adverse effect of drugs that interfere with the RAAS, particularly when they are used in combination.[10] It remains unclear whether aliskiren is associated with a clinically important increase in the risk of hyperkalemia in this setting. One case report describes hyperkalemia in association with aliskiren and coexisting acute kidney injury (AKI).[11] Small randomized trials have yielded inconsistent findings regarding the risk of hyperkalemia during aliskiren therapy, but a meta-analysis by Harel et al. found a significantly increased risk of moderate but not severe hyperkalemia.[12] Recently, a large multicentre randomized trial (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints [ALTITUDE]) was halted on the basis of futility and safety after an interim analysis determined that patients receiving aliskiren together with an ACEi or ARB were at increased risk of hyperkalemia, AKI, and stroke.[13] Consequently, several class action lawsuits have been initiated regarding the drug's safety.[14]

Because clinical trials have yielded conflicting information about adverse events regarding the use of aliskiren in combination with other blockers of the RAAS, and because patients in clinical practice generally differ from those in clinical trials, we sought to characterize the risk of hospitalization for severe hyperkalemia, AKI, and stroke during aliskiren therapy in a cohort of patients aged 66 years and older receiving an ACEi or an ARB.

Methods

Data sources

We conducted 3 population-based, nested case-control studies involving Ontarians aged 66 years or older treated with either an ACEi or an ARB between December 1, 2008, and March 31, 2011. We used the Ontario Public Drug Program database to identify dispensed prescription medications. This database has an overall error rate of less than 1%.[15] Hospitalization data and demographic information were obtained from the Canadian Institute for Health Information Discharge Abstract Database and the Registered Persons Database, respectively. The Discharge Abstract Database contains diagnosis codes regarding all hospital admissions, discharges, and same-day surgical procedures. The Ontario Health Insurance Plan database provided information regarding claims for all physician services, and the presence of diabetes was established using the Ontario Diabetes Database.[16] The data were held securely in a linked, deidentified form and analyzed at the Institute for Clinical Evaluative Sciences. This is regularly done to study postmarket drug safety, including risk factors for hyperkalemia, AKI, and stroke.[10,17-20]

Identification of study subjects

For each patient treated with an ACEi or an ARB, we identified a period of continuous therapy beginning with the first such prescription following the patient's 66th birthday. The observation period within each case-control study ended with the first occurrence of hospitalization with the primary end-point, death, or discontinuation of treatment with an ACEi or an ARB, whichever occurred first. Continuous use of ACEi's and ARBs was defined as the receipt of a refill for the drug within 1.5 times the number of days covered by the previous prescription.[21] Patients who discontinued treatment were followed throughout the duration of their last prescription to identify any events that might have precipitated cessation of therapy. It should be noted that although drugs were identified, doses were not.

Within this cohort we identified cases as those patients hospitalized with a diagnosis of hyperkalemia (*International Classification of Diseases, Tenth Revision* [*ICD-10*] code E87.5), AKI (*ICD-10* codes N17 and R34), and stroke (*ICD-10* codes I63 and I64). We included only patients who had these outcomes on hospital admission, and excluded those in

Table 1. Baseline characteristics for cases and matched controls

Variable	Hyperkalemia		Acute kidney injury		Stroke	
	Control (N = 21,106)	Case (N = 4235)	Control (N = 77,916)	Case (N = 18,231)	Control (N = 41,407)	Case (N = 8283)
Median age (years)	80	81	81	81	81	81
Age categories, n (%)						
66-75 years	6313 (29.9)	1261 (29.8)	22,833 (29.3)	5152 (28.3)	11,752 (28.4)	2350 (28.4)
76-85 years	9511 (45.1)	1862 (44.0)	34,942 (44.9)	8237 (45.2)	18,715 (45.2)	3743 (45.2)
86+ years	5282 (25.0)	1112 (26.3)	20,141 (25.9)	4842 (26.6)	10,940 (26.4)	2190 (26.4)
Male, n (%)	10,274 (48.7)	2062 (48.7)	38,607 (49.6)	9063 (49.7)	18,848 (45.5)	3770 (45.5)
Income quintile, n (%)						
Missing	77 (0.4)	17 (0.4)	260 (0.3)	86 (0.5)	175 (0.4)	43 (0.5)
1	4482 (21.2)	970 (22.9)	16,329 (21.0)	4292 (23.5)	8477 (20.5)	1779 (21.5)
2	4656 (22.1)	927 (21.9)	16,832 (21.6)	4084 (22.4)	8602 (20.8)	1822 (22.0)
3	4059 (19.2)	875 (20.7)	15,191 (19.5)	3543 (19.4)	8095 (19.6)	1657 (20.0)
4	4077 (19.3)	744 (17.6)	14,924 (19.2)	3192 (17.5)	8087 (19.5)	1502 (18.1)
5	3755 (17.8)	702 (16.6)	14,380 (18.5)	3034 (16.6)	7971 (19.3)	1480 (17.9)
Years using ACEi or ARB, median (IQR)	2.17 (1.9-2.3)	1.48 (0.8-2.1)*	2.17 (1.9-2.3)	1.49 (0.7-2.1)*	2.17 (1.9-2.3)	1.72 (0.82-2.2)*
Residence in LTC, n (%)	1618 (7.7)	549 (13.0)*	5701 (7.3)	2232 (12.2)*	2977 (7.2)	579 (7.0)
Number of distinct drugs used in previous year	12 (9-17)	15 (11-20)*	11 (8-16)	14 (10-19)*	10 (7-14)	11 (7-15)*
Previous hospitalization for respective outcome,† n (%)	342 (1.6)	208 (4.9)*	9 (0.0)	1576 (8.6)*	710 (1.7)	520 (6.3)*
Chronic kidney disease,† n (%)	12,772 (60.5)	2568 (60.6)	41,316 (53.0)	10,560 (57.9)*	10,057 (24.3)	2012 (24.3)
Diabetes diagnosis, n (%)	13,300 (63.0)	2672 (63.1)	41,932 (53.8)	10,195 (55.9)	19,203 (46.4)	3842 (46.4)
Congestive heart failure,† n (%)	8250 (39.1)	1663 (39.3)	19,050 (24.5)	6437 (35.3)*	6008 (14.5)	1203 (14.5)
Other medication use in preceding 60 days, n (%):						
β-Adrenergic blocking agent,‡ n (%)	8041 (38.1)	1848 (43.6)*	26,852 (34.5)	7403 (40.6)*	12,792 (30.9)	3180 (38.4)*
Potassium supplements, n (%)	279 (1.3)	117 (2.8)*	860 (1.1)	360 (2.0)	387 (0.9)	87 (1.1)
Potassium-sparing diuretics, n (%)	1458 (6.9)	900 (21.2)*	4240 (5.4)	1952 (10.7)*	1866 (4.5)	348 (4.2)
Other diuretics, n (%)	10,450 (49.5)	2353 (55.6)*	34,772 (44.6)	10,682 (58.6)*	16,958 (41.0)	3442 (41.6)
Trimethoprim, n (%)	358 (1.7)	349 (8.2)*	1211 (1.6)	1039 (5.7)*	478 (1.2)	152 (1.8)
NSAIDs, n (%)	1444 (6.8)	423 (10.0)*	5767 (7.4)	1802 (9.9)	3286 (7.9)	747 (9.0)
Digoxin, n (%)	1649 (7.8)	494 (11.7)*	4995 (6.4)	1533 (8.4)	2167 (5.2)	595 (7.2)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; LTC, long-term care; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs.

* Standard difference >0.10.

† Past 3 years prior to index date assessed by database codes.

‡ β-Blocker.

whom these outcomes developed during the course of hospitalization. The date of hospitalization served as the index date for all analyses. Only the first instance was considered for patients with more than 1 such admission during the study period. Patients were excluded if they had a history of end-stage renal disease, including patients with kidney transplants in the previous 5 years or any dialysis code in 120 days preceding the hospitalization date.

From the cohort of patients receiving an ACEi or an ARB, we selected up to 5 controls for each case, using incidence density sampling.[22] Controls were matched to their corresponding case on age at the index date (within 3 years), sex, and any history in the past 3 years of chronic kidney disease, diabetes, or congestive heart failure. Chronic kidney disease was defined by physician claims, hospitalization records, and receipt of inpatient or outpatient dialysis.[16] We excluded cases who could not be matched to at least 1 control.

We compared the baseline demographic and clinical characteristics of cases and controls using standardized differences; values less than 0.1 indicate good balance for a given covariate.[23] We conducted 3 prespecified analyses examining the risk of hyperkalemia, AKI, and stroke associated with aliskiren use in the 60 days preceding the index date, with no aliskiren exposure as the reference group. In all groups, we replicated our analyses using amlodipine prescriptions as a neutral comparator, since amlodipine is commonly used to treat hypertension and is not classically associated with hyperkalemia, AKI, or stroke.

For each analysis, conditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for the association between the end point and aliskiren use. Multivariable conditional logistic regression was used to adjust for concomitant medical conditions and other drugs that might modify the risk of these end points.[24] All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC). This project was approved by the Research Ethics Board of the Sunnybrook Health Sciences Centre.

Results

During the 28-month study period, we identified 903,346 patients newly treated with an ACEi or ARB. Within this cohort, we performed 3 separate case-control studies. We identified 4235 case subjects admitted to hospital with hyperkalemia, 8283 admitted with stroke, and 18,231 admitted with AKI. The characteristics of cases and controls are shown in Table 1. As a result of the matching process, cases and controls were similar with respect to age, income quintile, and history of chronic kidney disease, diabetes mellitus, and congestive heart failure in all analyses.

Table 2. Aliskiren use and hospitalization for hyperkalemia, stroke, or acute kidney injury

	Exposure (n, %)			
	Case	Control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Hyperkalemia				
Aliskiren	30 (0.7)	120 (0.6)	1.3 (0.87-1.94)	1.14 (0.74-1.74)
Amlodipine	904 (21.4)	3956 (18.7)	1.18 (1.09-1.28)	1.09 (1.00-1.19)
Stroke				
Aliskiren	47 (0.6)	182 (0.4)	1.3 (0.94-1.79)	1.18 (0.85-1.63)
Amlodipine	1392 (16.8)	6837 (16.5)	1.02 (0.96-1.09)	0.94 (0.88-1.00)
Acute kidney injury				
Aliskiren	115 (0.6)	431 (0.6)	1.21 (0.98-1.49)	1.08 (0.87-1.34)
Amlodipine	3669 (20.1)	14001 (18.0)	1.12 (1.08-1.17)	0.99 (0.94-1.03)

CI, confidence interval; OR, odds ratio.

In the primary analysis, aliskiren was not associated with a significant increase in the risk of hospitalization for any of the outcomes of interest (Table 2). After multivariable adjustment, patients hospitalized with hyperkalemia (adjusted OR, 1.14; 95% CI, 0.74-1.74), AKI (adjusted OR, 1.08; 95% CI, 0.87-1.34), or stroke (adjusted OR, 1.18; 95% CI, 0.85-1.63) were found to be no more likely than controls to have received a prescription for aliskiren in the preceding 60 days. We found consistent results in analyses stratified by diabetes, chronic kidney disease, and heart failure (Table 3).

In our tracer analyses, amlodipine use was weakly associated with hyperkalemia (adjusted OR, 1.09; 95% CI, 1.00-1.19). Amlodipine use was also weakly associated with a reduced risk of hospitalization for stroke (adjusted OR, 0.94; 95% CI, 0.88-1.00) but not for AKI (adjusted OR, 0.99; 95% CI, 0.94-1.03).

Discussion

In 3 population-based studies of more than 1.5 million community-dwelling patients aged 66 years and older, we found, among patients receiving an ACEi or ARB, no association between hospitalization for severe hyperkalemia, AKI, or stroke and a recent aliskiren prescription. These results were unchanged in stratified analyses of patients with diabetes mellitus, chronic kidney disease, and congestive heart failure. Our findings suggest that despite a biologically plausible association between aliskiren and these end points, the risk of hospitalization with severe hyperkalemia, AKI, or stroke is low when the drug is used together with an ACEi or ARB in routine practice.

It is important to note that while these findings offer some reassurance regarding aliskiren's safety, the lack of an association between the drug and these outcomes may reflect limitations of our study design. Specifically, we focused on patients hospitalized for the outcomes of interest, and we had no direct measure of potassium or creatinine levels. Patients admitted with minor increases in potassium or creatinine may not have been identified in our databases. As noted, a recent meta-analysis suggested that aliskiren was associated with an increased risk of moderate hyperkalemia, but no significant difference in the risk of severe hyperkalemia.[12]

The recently published Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes, or ALTITUDE, trial was terminated prematurely because of lack of efficacy and an increase in adverse events, specifically hyperkalemia and renal impairment. We speculate that the divergent findings of ALTITUDE and our study are explained by several observations. First, by design, the ALTITUDE study included patients at higher risk (all of them had type 2 diabetes mellitus) than was the general population we studied. Second, as an observational study, we cannot account for unmeasured differences between patients who received aliskiren and those who did not. Finally, our study does not include patients with minor cases of hyperkalemia or renal impairment who are not hospitalized and are managed in an outpatient setting.

Furthermore, a reduction in levels of angiotensin II has been postulated as a potential mechanism of renal impairment and hyperkalemia with the use of ACEi's and ARBs. This reduction leads to dilation of the efferent arteriole and reduced glomerular perfusion pressure (and potentially acute renal failure), particularly in patients with severe bilateral renal

Table 3. Analyses stratified by previous history of diabetes, kidney disease, or stroke

Exposure	Case, n (%)	Control, n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Diabetes				
Hyperkalemia	22 (0.8)	91 (0.7)	1.26 (0.79-2.01)	1.17 (0.71-1.92)
Acute kidney injury	92 (0.9)	300 (0.7)	1.39 (1.09-1.76)	1.29 (1.01-1.65)
Stroke	26 (0.7)	119 (0.6)	1.09 (0.71-1.68)	1.04 (0.68-1.6)
Chronic kidney disease				
Hyperkalemia	22 (0.9)	84 (0.7)	1.38 (0.86-2.22)	1.43 (0.87-2.33)
Acute kidney injury	77 (0.7)	294 (0.7)	1.14 (0.89-1.47)	1.09 (0.83-1.42)
Stroke	18 (0.9)	73 (0.7)	1.24 (0.74-2.09)	1.22 (0.72-2.07)
Heart failure				
Hyperkalemia	9 (0.5)	38 (0.5)	1.24 (0.6-2.56)	1.46 (0.69-3.07)
Acute kidney injury	28 (0.4)	69 (0.4)	1.16 (0.74-1.82)	1.19 (0.72-1.97)
Stroke	*	23 (0.4)	0.66 (0.2-2.2)	0.72 (0.21-2.42)

CI, confidence interval; OR, odds ratio.

*Cell sizes lower than 6 suppressed in accordance with institutional privacy policy.

artery stenosis. This mechanism has been described as "kicking the back door out of the glomerulus."[25] Patients with heart failure may be at risk of renovascular impairment and as such, patients in the ALTITUDE trial would be at higher risk for this complication.

Some limitations of our work also merit emphasis. We used administrative data and therefore had no knowledge of medication adherence or use of nonprescription medications that may have influenced the risk of hyperkalemia, AKI, or stroke. However, these limitations apply equally to patients receiving aliskiren or amlodipine. We could not identify instances of hyperkalemia or AKI that were mild and treated in the outpatient setting, or severe cases leading to death in the prehospital setting. In addition, our findings derive from an older patient population, and the generalizability to younger patients is unknown. However, younger patients will generally have fewer risk factors for these end points. Finally, discharge coding for AKI and stroke have been validated.[26-28] Although the accuracy of hospital discharge coding for hyperkalemia has not been validated, the same limitation applies to our previous research regarding drug interactions resulting in hyperkalemia.[10,17,29] It should also be noted that perhaps Ontario physicians prescribe low doses of an ACEi or ARB and then add a low dose of aliskiren, limiting the adverse events. This possibility cannot be recognized by the methods used.

It is important to note that because aliskiren is a relatively new drug that has not yet enjoyed widespread clinical use, our study had limited power to detect a major increase in the outcomes of interest. Indeed, post hoc power calculations for aliskiren exposure indicate that our study had a 41% power to detect a 1.36-fold risk of hyperkalemia, a 50% power to detect a 1.19-fold increased risk of AKI, and a 59% power to detect a 1.35-fold increase in the risk of stroke, relative effect sizes suggested by an interim analysis of the ALTITUDE study.[13] This is a key interpretive caution.

Despite the above limitations, observational studies such as this have theoretical advantages over randomized control trials because they include patients in routine clinical practice, rather than in the setting of a clinical trial. In general, community-dwelling patients are likely to be less closely monitored and at higher risk of adverse drug events than are those in clinical trials.

It is also interesting to note that in our hyperkalemia group, patients taking aliskiren were more likely to be on potassium-retaining medications such as potassium-sparing diuretics, potassium supplements, and trimethoprim. Despite this factor, there was still no significant increase in the risk of hospitalization for severe hyperkalemia. This lack of association may further attest to the drug's safety, or it may reflect the selective use of the drug in patients who are at lower risk for other reasons.

Interestingly, we observed a weak but marginally significant association between amlodipine use and hospitalization for hyperkalemia, unexpected in light of the drug's established neutral effects on potassium. This association most likely reflects either a spurious finding or amlodipine's use in patients with other risk factors for hyperkalemia, coupled with the drug's popularity and the resulting increase in statistical precision. While a causal association seems unlikely, 1 case report describes mild hyperkalemia in a patient taking benipidine, a related dihydropyridine.[30] Additionally, in vivo potassium-induced aldosterone secretion is reduced by calcium channel blockade.[31] Whether or not the observed amlodipine association represents cause and effect, the finding does not vitiate our primary observations regarding aliskiren.

In conclusion, we found that the use of aliskiren with an ACEi or an ARB was not associated with an increased risk of hospitalization with severe hyperkalemia, AKI, or stroke among Ontarians aged 66 years and older. While this finding offers a measure of reassurance regarding the drug's safety in routine practice, our study may not have been adequately powered to detect clinically important increases in the risk of these adverse events.

The benefits of dual RAAS blockade continue to be the subject of much research. There is increasing evidence that such an approach may be harmful. A recent meta-analysis of dual blockade with ACEi's and ARBs failed to show benefit in reducing mortality.[32] In addition, the **On**going **T**elmisartan **A**lone and in Combination With **R**amipril **G**lobal **E**ndpoint **T**rial (ONTARGET) study (Telmisartan, Ramipril or both in high-risk patients) failed to show any benefit with dual blockade and also showed an increase in adverse events.[1] Based on the results of the CHARM study, which showed that dual blockade improved left ventricular function and reduced hospital admissions,[33] 2 ongoing trials of aliskiren plus another renin–angiotensin system blocker in patients with heart failure are ongoing.[34,35]

At present, there does not appear to be a clear indication for aliskiren's use in combination with another RAAS blocking agent. Although our data suggest that in the general population, there does not appear to be an increased risk of these adverse events, there is mounting evidence that combination therapy imparts few benefits. If a clinician elects to prescribe aliskiren in combination with another RAAS blocking agent, close monitoring and follow-up should be arranged, and other medications that may increase the risk of adverse effects, such as potassium-sparing diuretics or nonsteroidal anti-inflammatory drugs, should be avoided.

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Disclosures

Dr Mamdani has sat on the advisory board of the following pharmaceutical companies: Astra Zeneca, Bristol-Myers Squibb, Eli Lilly and Company, Glaxo Smith Kline, Hoffman La Roche, Novartis, Novo Nordisk, and Pfizer. The other authors have no conflicts of interest to disclose.

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