

Predictors of Direct Oral Anticoagulants Utilization for Thromboembolism Prevention in Atrial Fibrillation

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ABSTRACT - PURPOSE: Several factors have been associated with the prescription of direct oral anticoagulants (DOAC) over warfarin such as younger age, fewer concomitant medications, and lower CHADS₂ or bleeding scores. The primary objective of this study was to identify predictors of DOAC choice compared with warfarin for patients who are starting a new oral anticoagulant (OAC) for atrial fibrillation (AF). The secondary objective was to describe the proportion of DOAC prescriptions in new users of OAC for AF. **METHODS:** A retrospective cross-sectional study was conducted in a teaching hospital in Canada. Medical records of adult patients hospitalized in any medical units between October 1st, 2011 and October 1st, 2014, who were newly prescribed an OAC for non valvular AF were systematically reviewed. Baseline characteristics of warfarin and DOAC users were compared and a multivariate logistic regression analysis was completed to identify predictors of DOAC use. Variables included in the multiple regression analysis were: age, hypertension, diabetes, history of stroke or transient ischemic attack, coronary artery disease, peripheral arterial disease, CHADS₂ score of 2 or more, creatinine clearance 30mL/min or more, polypharmacy, concomitant use of ASA or clopidogrel, and prescription by a neurologist. **RESULTS:** Among OAC users (144 patients on DOAC and 295 patients on warfarin), older age (odds ratio [OR] 0.97; 95%CI 0.95-0.98), peripheral arterial disease (OR: 0.41;95%CI: 0.21-0.82), polypharmacy (OR: 0.30;95%CI:0.10-0.89), and concomitant use of clopidogrel (OR: 0.19;95%CI:0.07-0.56) decreased the probability of DOAC use. Prescription by a neurologist (OR: 2.77;95%CI:1.34-5.76) and an estimated creatinine clearance of at least 30mL/min (OR: 3.53;95%CI:1.18-10.57) increased the likelihood of DOAC prescription. **CONCLUSION:** To the best of our knowledge, this is the first observational study finding that concomitant use of clopidogrel reduced the likelihood of DOAC utilization while prescription by a neurologist increased the probability of receiving a DOAC over warfarin in patients with AF.

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INTRODUCTION

Oral anticoagulants (OAC) are the cornerstone of therapy to prevent thromboembolic events associated with atrial fibrillation (AF).¹ Direct oral anticoagulants (DOAC) such as apixaban, dabigatran, edoxaban and rivaroxaban have been shown to be non inferior^{2,3} or superior^{4,5} in terms of efficacy when compared to warfarin in randomized clinical trials. All were associated with a lower risk of intracranial haemorrhage²⁻⁵, but a greater risk of gastrointestinal bleeding was found with the higher doses of dabigatran² and rivaroxaban³. Several real-

world studies conducted in North America have described patterns and predictors of DOAC use in AF.⁶⁻¹² DOACs were prescribed in proportions of 33.9%¹⁰ and 42.2%¹¹ among new users of OAC for AF. Factors associated with the prescription of a DOAC over warfarin were younger age⁹⁻¹², male gender^{10,11}, prior ischemic stroke¹⁰, lower scores for the risk of stroke^{8,9,11,12} or bleeding^{8,11,12}, fewer comorbidities⁸ or comedications^{8,11}, a higher

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calculated creatinine clearance⁹, having a private medical insurance⁹, and prescription by a cardiologist¹⁰. Most studies focused on dabigatran, only a few assessed predictors in new users of OAC^{10,11}, and several were based on data retrieved from administrative databases only^{7,8,10,11}. The main objective of this study was to assess clinical predictors associated with the use of DOACs over warfarin among new users of OAC for AF in a hospital based population.

METHODS

Design

A retrospective, cross-sectional study was conducted in a single teaching hospital in Canada, the Centre Hospitalier Universitaire de Sherbrooke (CHUS). The CHUS offers specialized and over-specialized care and services, including cardiology, neurosurgery, oncology and neonatology. The scientific and ethics committees of the CHUS's research center approved the conduct of this study.

Objectives

The primary objective of this study was to identify predictors of DOAC choice compared with warfarin for patients who are starting a new anticoagulation therapy for AF. The secondary objective was to describe the proportion of DOAC prescriptions in new users of OAC for AF.

Inclusion/Exclusion criteria

We included subjects who were hospitalized in all medical units between October 1st, 2011 and October 1st, 2014, who were at least 18 years old, who had a documented diagnosis of non valvular AF, who had a complete hospital discharge prescription documented in their medical chart, and an OAC prescribed during hospital admission and at discharge. Subjects were excluded if they were prescribed an OAC prior to hospital admission, moderate to severe mitral stenosis, heart valve repair or replacement, congenital heart disease, hypercoagulability, transient AF (i.e. lasting less than 48 hours), another indication for anticoagulation (e.g. venous thromboembolism), uncontrolled hyperthyroidism, illicit drug use (amphetamines, cocaine, crack), admission for drug intoxication (eg. tricyclic antidepressant) or perioperative AF.

Data collection and outcomes

A medical archivist identified charts of hospitalized subjects who had a documented diagnosis of AF (using ICD-10 codes I48X, I48.XN-001 and I48.XN-002), and apixaban, dabigatran, rivaroxaban or warfarin (edoxaban was not available during the study period) on the pharmacologic profile's field. We selected the first eligible hospitalization between October 1st, 2011 and October 1st, 2014.

Data were collected from individual electronic medical records (EMRs). More than one evaluator completed data collection. Therefore, all data collectors used the same form developed for the purpose of this study and it was pretested on ten medical charts for standardization. The information collected corresponds to the one available any time during admission, but when several values were available, the one that was closest to OAC prescription was documented. Demographic data collected included age, gender, weight, and body mass index. Medical history data included: heart failure, hypertension, diabetes, stroke or transient ischemic attack, coronary artery disease (CAD), peripheral artery disease (PAD), dementia, history of fall, and history of major bleeding.¹³ The CHADS₂ score was calculated based on the information retrieved from the discharge summary. Laboratory data included serum creatinine (to estimate creatinine clearance using the Cockcroft-Gault formula) and liver enzymes (i.e., aspartate transaminase [AST] and alanine transaminase [ALT], reporting the proportion of subjects who had values higher than twice the upper limit of normal). Number of drugs at discharge, concomitant use of ASA and other antiplatelets (i.e., clopidogrel, prasugrel, ticagrelor) were documented. Polypharmacy was defined as the prescription of at least five chronic medications. We also collected the medical specialty of the OAC's prescriber.

Predictors of DOAC prescription, compared to warfarin, were assessed among incident users of OACs. Incident users were subjects who were not prescribed an OAC at the time of admission (i.e. OAC was initiated during hospitalization). By selecting only incident users, we avoided the potential bias associated with different length of oral anticoagulant use in prevalent users. Variables related to demographics, medical history, laboratory data, and concomitant medications described previously were considered as potential predictors of DOAC use.

STATISTICAL ANALYSIS

Baseline characteristics are described using proportions for categorical variables and means with standard deviations for continuous variables. To identify predictors of DOAC prescription over warfarin, univariate logistic regressions were completed to estimate the crude odds ratio (OR) for each potential predictor (i.e. demographic, medical history, and laboratory data along with concomitant medications described above). Variables that reached statistical significance ($\alpha = 0.05$) in the univariate analysis were included in a multiple logistic regression analysis (with forward selection of the variables). Variables included in the multiple regression analysis were: age (continuous variable), hypertension, diabetes, history of stroke or TIA, CAD, PAD, CHADS₂ score of 2 or more, creatinine clearance 30mL/min or more, polypharmacy, concomitant use of ASA or clopidogrel, and prescription by a neurologist. The log-linearity of the continuous variables was tested with the 4-Tidwell transformation before integration in the multivariate logistic regression model.¹⁴ Based on the log-linear analysis, the CHADS₂ score, creatinine clearance and number of medications (i.e., polypharmacy) were included as dichotomous variables. Adjusted ORs were estimated for the variables that were included in the final regression model. Data analyses were conducted using SPSS version 20.

RESULTS

Screening

A total of 3849 medical charts were screened and 2958 were excluded because they were from prevalent users of OAC (2401 on warfarin, 41 on apixaban, 259 on dabigatran, and 257 on rivaroxaban). From the 891 incident users of OAC, 349 on warfarin and 103 on a DOAC (total of 452) were excluded (see figure 1). The main reason for exclusion was because of the unavailability or incomplete discharge prescription. A total of 439 incident users of OAC were included in this study; 295 on warfarin (67.2%) and 144 (32.8%) on a DOAC (29 apixaban, 38 dabigatran and 77 rivaroxaban).

Baseline characteristics

Characteristics of incident users of OACs are shown in Table 1. About half of the subjects were females, mean age was of 79,6 years old in the warfarin group

and 73,9 in DOAC users. Mean CHADS₂ scores were of 2.63 and 2.44 in the warfarin and DOAC groups, respectively. The most common comorbidity was hypertension. The proportions of subjects: who were 75 years of age or older, with hypertension, with diabetes, with CAD, with PAD, on ASA, on clopidogrel, with polypharmacy, were lower in the DOAC group. The mean CHADS₂ score and the mean number of drugs were lower for subjects on DOAC. The percentage of subjects with a stroke or TIA history and the mean estimated creatinine clearance were higher in the DOAC group. Overall, cardiologists mostly prescribed OAC. Furthermore, neurologists were more likely to prescribe a DOAC over warfarin.

Predictors of DOAC utilization

Predictors of DOAC use are presented in Table 1. In the univariate analysis, older age (crude OR for age ≥ 75 years: 0.38;95%CI: 0.25-0.58), hypertension (crude OR:0.62;95%CI:0.38-0.99), diabetes (crude OR 0.61; 95%CI: 0.40-0.96), CAD (crude OR 0.45; 95%CI:0.30-0.69), PAD (crude OR 0.30; 95%CI: 0.16-0.58, CHADS₂ score of 2 or more (crude OR 0.53; 95%CI: 0.32-0.88), polypharmacy (crude OR 0.14; 95%CI: 0.05-0.39), concomitant use of ASA (crude OR 0.41; 95%CI:0.25-0.69) or clopidogrel (crude OR 0.17; 95%CI: 0.06-0.49) reduced the likelihood of DOAC prescription. History of stroke or TIA (crude OR:1.76; 95%CI: 1.13-2.72), creatinine clearance of 30mL/min or more (crude OR 5.05; 95%CI: 1.76-14.46), and prescription by a neurologist (crude OR 3.32; 95%CI: 1.69-6.50) increased the probability of DOAC prescription. In the multivariate analysis, six predictors of DOAC use reached statistical significance. Younger patients (adjusted OR for mean age: 0.97; 95%CI: 0.95-0.98), no PAD (adjusted OR for PAD: 0.41; 95%CI: 0.21-0.82), having a creatinine clearance at least 30mL/min (adjusted OR: 3.53; 95%CI:1.18-10.57), no polypharmacy (adjusted OR for polypharmacy: 0.30; 95%CI: 0.10-0.89), not prescribed clopidogrel at discharge (adjusted OR for clopidogrel use: 0.19; 95%CI:0.07-0.56), and who were prescribed the OAC by a neurologist (adjusted OR: 2.77; 95%CI:1.34-5.76) were more likely to receive a DOAC.

DISCUSSION

This study describes predictors of DOAC utilization in new users of OAC. DOACs were prescribed in

32.8% of incident users. This proportion is similar to the one described by AbuDagga et al., which reported that 33.9% of OAC naïve subjects were prescribed dabigatran (OAC prescription claims from October 2010 to October 2011 in the Integrated Research Database, USA).¹⁰ It is lower than the proportion reported by Desai et al., which was of 42.2%, but this study included outpatients covered

by a health care benefits company (Aetna, USA) with OAC prescriptions between 2010 and 2013.¹¹

Unsurprisingly, DOACs were more likely prescribed in younger patients, such as reported by others.⁹⁻¹¹ We also found that subjects with fewer concomitant medications (based on the variable “polypharmacy”) and no PAD (which could be an indicator of less comorbidities) were more likely prescribed a DOAC, similar to others.^{8,11}

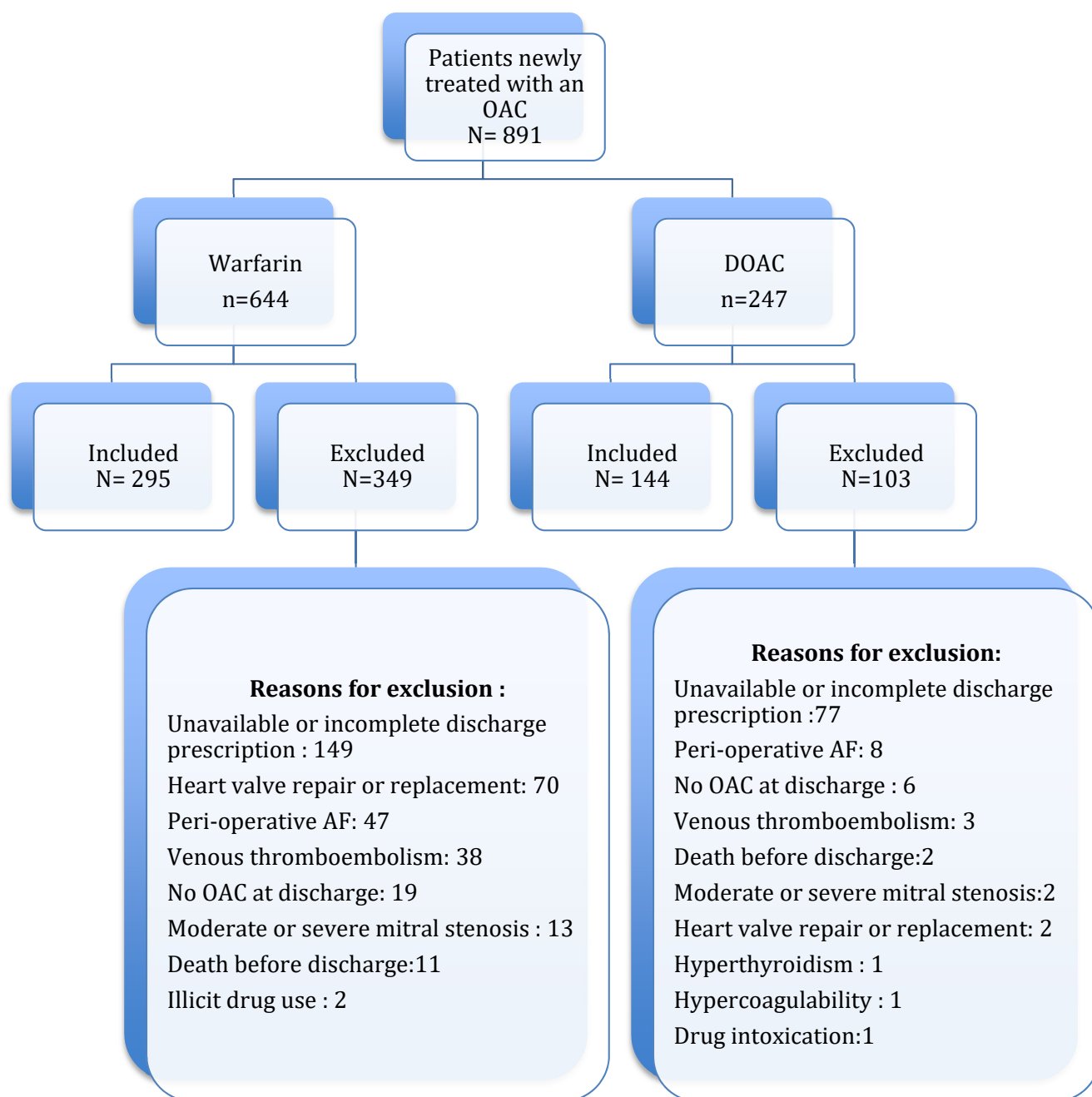


Figure 1. Study flow diagram - AF: atrial fibrillation; DOAC: direct oral anticoagulants; OAC: oral anticoagulants.

Table 1. Baseline characteristics and predictors of DOAC use over warfarin

Characteristics	Warfarin N=295	DOAC N=144	Crude OR (95%CI)	Adjusted OR (95%CI)
Mean age \pm sd	79.6 \pm 10.2	73.9 \pm 12.5	0.96 (0.94-0.97)	0.97 (0.95-0.98)
Age \geq 75 years, n(%)	215 (72.9)	73 (50.7)	0.38 (0.25-0.58)	-
Female, n(%)	160 (54.2)	72 (50.0)	0.84 (0.57-1.26)	-
Mean BMI (kg/m ²) ¹ , \pm sd	28.5 \pm 7.6	29.6 \pm 8.3	1.02 (0.99-1.04)	-
BMI >30 (kg/m ²) ¹	98 (34.8)	52 (36.6)	1.09 (0.71-1.65)	-
Heart failure, n(%)	79 (26.8)	37 (25.7)	0.95 (0.60-1.49)	-
Hypertension, n(%)	243 (82.4)	107 (74.3)	0.62 (0.38-0.99)	-
Diabetes, n(%)	104 (35.3)	36 (25.0)	0.61 (0.40-0.96)	-
Stroke or TIA, n(%)	67 (22.7)	49 (34.0)	1.76 (1.13-2.72)	-
Coronary artery disease, n(%)	146 (49.5)	44 (30.6)	0.45 (0.30-0.69)	-
Peripheral artery disease, n(%)	68 (23.1)	12 (8.3)	0.30 (0.16-0.58)	0.41 (0.21-0.82)
Dementia, n(%)	49 (16.6)	14 (9.7)	0.54 (0.29-1.02)	-
Fall, n(%)	13 (4.4)	3 (2.1)	0.46 (0.13-1.65)	-
Major bleeding, n(%)	7 (2.4)	0	-	-
Mean CHADS ₂ score \pm sd	2.63 \pm 1.18	2.44 \pm 1.30	0.88 (0.75-1.04)	-
CHADS ₂ score \geq 2, n(%)	255 (86.4)	111 (77.1)	0.53 (0.32-0.88)	-
Mean creatinine clearance (mL/min) ² \pm sd	63.2 \pm 39.0	82.9 \pm 42.6	1.01 (1.00-1.02)	-

Table 1. Baseline characteristics and predictors of DOAC use over warfarin, continued

Characteristics	Warfarin N=295	DOAC N=144	Crude OR (95%CI)	Adjusted OR (95%CI)
Creatinine clearance \geq 30 mL/min ³ , n(%)	251 (87.2)	137 (97.2)	5.05 (1.76-14.46)	3.53 (1.18-10.57)
AST \geq 2 times the upper limit ⁴ , n(%)	7 (3.2)	1 (1.0)	0.32 (0.04-2.61)	-
ALT \geq 2 times the upper limit ⁵ , n(%)	7 (3.2)	2 (2.0)	0.63 (0.13-3.10)	-
Mean number of medications at discharge \pm sd	11.9 \pm 4.6	9.6 \pm 4.5	0.89 (0.85-0.94)	-
ASA, n(%)	90 (30.5)	22 (15.3)	0.41 (0.25-0.69)	-
Clopidogrel, n(%)	42 (14.2)	4 (2.8)	0.17 (0.06-0.49)	0.19 (0.07-0.56)
Polypharmacy	290 (98.3)	128 (88.9)	0.14 (0.05-0.39)	0.30 (0.10-0.89)
Speciality of prescribing physician, n(%)				
Cardiology	108 (36.6)	61 (42.4)	1.27 (0.86-1.91)	-
Internal Medicine	107 (36.3)	40 (27.8)	0.68 (0.44-1.04)	-
Family Medicine	19 (6.4)	8 (5.6)	0.85 (0.37-2.00)	-
Neurology	16 (5.4)	23 (16.0)	3.32 (1.69-6.50)	2.77 (1.34-5.76)
Other	45 (15.3)	12 (8.3)	0.50 (0.26-0.99)	-

1. Data missing for 15 subjects.

2. Data missing for 10 subjects. Estimated glomerular filtration rate calculated with Cockcroft-Gault formula.

3. Data missing for 10 subjects.

4. Data missing for 122 subjects.
5. Data missing for 118 subjects.
6. Variables included in the multiple regression analysis were: age (continuous variable), hypertension, diabetes, history of stroke or TIA, CAD, PAD, CHADS₂ score of 2 or more, creatinine clearance 30mL/min or more, polypharmacy, concomitant use of ASA or clopidogrel, and prescription by a neurologist. Based on the log-linear analysis, the CHADS₂ score, creatinine clearance and number of medications (i.e., polypharmacy) were included as dichotomous variables. Adjusted OR are presented for the variables that were included in the final regression model.

Table 1 Legend:

ALT: alanine aminotransferase

AST: aspartate aminotransferase

BMI: body mass index

DOAC: direct oral anticoagulants

TIA: transient ischaemic attack.

Interestingly, subjects on clopidogrel were more likely prescribed warfarin rather than a DOAC. This could be explained by limited evidence on the safety of the DOAC-clopidogrel association. Furthermore, at the beginning of the study period, the 2010 Canadian Cardiovascular Society Atrial Fibrillation Guidelines recommended warfarin over dabigatran in patients with AF and coronary artery disease requiring an OAC and antiplatelet therapy¹⁵, while more recent guidelines favors DOACs based on limited evidence.¹⁶ This result suggests that clinicians are cautious about the use of DOACs in subjects on antiplatelet therapy.

Moreover, subjects on DOACs had better renal function than the ones on warfarin, which was also reported by Steinberg et al.⁹ This result is reassuring considering that DOACs are contraindicated when kidney function is severely reduced. This advocates the appropriate use of DOACs in our population of subjects with AF.

A new finding was that neurologists were more likely to prescribe a DOAC. This results could be explained by the fact that DOACs are associated with a lower risk of intracranial haemorrhage, and because they are effective in stroke prevention.²⁻⁵ Therefore, quality improvement projects on DOACs should not only target cardiologists who regularly prescribe OAC for AF, but also neurologists.

Our study has several limitations. First, data were collected retrospectively and relevant information could have been missed (eg. the presence of a comorbidity if it was not documented in the EMR). Secondly, a high number of patients were excluded, mostly because of incomplete discharge prescriptions. Thirdly, this study was conducted in a single teaching hospital. Finally,

there are reimbursement restrictions for DOAC prescriptions in subjects covered by the public medication insurance plan in the province of Quebec, which limits the generalization of the results.

Our study supports previous findings, but it differs from others by the inclusion of subjects on rivaroxaban and apixaban, and collection of laboratory data (i.e., serum creatinine, AST and ALT) to take into account renal and liver impairments, which are associated with higher risks of bleeding in users of OAC. To the best of our knowledge, this is the first study finding that prescription by a neurologist increased the likelihood while concomitant use of clopidogrel reduced the probability of DOAC prescription over warfarin. Results from this study add to the currently limited research on DOAC predictors of use among OAC naive patients. It allowed us to identify subjects who are more likely to be prescribed a DOAC, and thus target interventions to promote the proper use of these drugs.

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