Venous Thromboembolism Among Elderly Patients Treated With Atypical and Conventional Antipsychotic Agents

Rosa Liperoti, MD, MPH; Claudio Pedone, MD, PhD, MPH; Kate L. Lapane, PhD; Vincent Mor, PhD; Roberto Bernabei, MD; Giovanni Gambassi, MD

Background: Some antipsychotic agents have been indicated as a possible risk factor for venous thromboembolism (VTE) in adult patients with psychiatric disorders. The aim of this study was to estimate the effect of atypical and conventional antipsychotic agents on the risk of hospitalization for VTE among elderly patients.

Methods: We conducted a retrospective cohort study on nursing home residents in 5 states. We used data from the Minimum Data Set to identify 19 940 new users of antipsychotic agents and 112 078 nonusers. Hospitalization with VTE as primary discharge diagnosis was determined during a 6-month follow-up period using Medicare inpatient claims. Cox proportional hazards models provided estimates of effect adjusted for confounders.

Results: The rate of hospitalization for VTE was 0.91 per 100 person-years. Venous thrombosis accounted for 77.6% of events and 22.4% were pulmonary embolisms. Relative to nonusers, the rate of hospitalization for VTE was increased for users of atypical antipsychotic agents, including risperidone (adjusted hazard ratio [HR], 1.98; 95% confidence interval [CI], 1.40-2.78), olanzapine (adjusted HR, 1.87; 95% CI, 1.06-3.27), and clozapine and quetiapine fumarate (adjusted HR, 2.68; 95% CI, 1.15-6.28). No increased rate was associated with phenothiazines (adjusted HR, 1.03; 95% CI, 0.60-1.77) or other conventional agents (adjusted HR, 0.98; 95% CI, 0.52-1.87).

Conclusions: Atypical antipsychotic agents appear to increase the risk of VTE. However, these events are rare, and in clinical practice the absolute risk should be weighed against the effectiveness of these medications in the elderly population.

Arch Intern Med. 2005;165:2677-2682

Author Affiliations: Centro di Medicina dell'Invecchiamento, Dipartimento di Scienze Gerontologiche, Geriatriche e Fisiatriche, Università Cattolica del Sacro Cuore (Drs Liperoti, Bernabei, and Gambassi), and Unit of Geriatrics, Università Campus Bio-Medico (Dr Pedone), Rome, Italy; and Department of Community Health, Center for Gerontology and Health Care Research (Dr Mor), Department of Community Health, Center for Gerontology and Health Care Research, Brown Medical School (Drs Lapane, Mor, and Gambassi), Providence, RI.

A POSSIBLE ASSOCIATION BETWEEN venous thromboembolism (VTE) and the use of antipsychotic agents was first suggested in the 1950s after the introduction of phenothiazines.[1] Since then, several case studies[2-4] have supported the notion of an increased risk of VTE with conventional antipsychotic agents. Recently, Zornberg and Jick[5] documented a 7-fold increase in the risk of idiopathic VTE among users of conventional antipsychotic agents who were younger than 60 years and free of major risk factors. A similar thromboembolic effect of conventional antipsychotic agents has been observed also among individuals with risk factors for VTE.[6]

Atypical antipsychotic agents represent a newer class of drugs characterized by a distinct pharmacologic and clinical profile. They are more effective for the treatment of negative symptoms and confer a lower risk of extrapyramidal adverse effects compared with conventional agents.[7] To date, information on the risk of VTE is almost exclusively limited to clozapine.[8-11] This association is primarily supported by results of a large record-linkage study[8] in which a 5-fold increase in lethal pulmonary embolism was found. More recently, 3 cases of VTE have been reported among elderly patients treated with olanzapine[12] and 1 case in a young man with a psychotic disorder.[13] Finally, a possible association between risperidone and massive pulmonary thromboembolism has been suggested from a review of autopsy records in a Japanese population.[14]

Despite these suggestions, clear evidence of a possible thromboembolic effect of antipsychotic agents is lacking. Most studies have been conducted on small samples with inadequate control for confounders. Moreover, elderly patients, who are among the most common recipients of antipsychotic medications, have been systematically excluded from research in this field. A single study[15] among adults 65 years and older compared the effect of antipsychotic agents on the risk of VTE rela-

tive to that of thyroid replacement therapy and found only a slightly increased risk with butyrophenones. We conducted a retrospective cohort study to estimate the effect of atypical and conventional antipsychotic agents on the risk of hospitalization for VTE among elderly patients living in nursing homes in 5 states.

METHODS

DATA SOURCE

We used the Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE) database, which contains data from the Minimum Data Set (MDS).[16,17] The MDS is a standardized, clinically based instrument that collects information on each resident's demographic, functional, medical, psychological, and cognitive status. Each Medicare- or Medicaid-certified nursing home conducts an MDS assessment of all residents on admission and quarterly thereafter. Since 1998, the Centers for Medicare and Medicaid Services has maintained a centralized repository of all MDS data, and these data are used for administrative and research purposes. The SAGE database links MDS data to the Medicare inpatient claim files (part A), which contain information on residents' hospitalizations. The Medicare inpatient claim data provide the admission diagnosis and up to 10 discharge diagnoses for each hospitalization, recorded by the *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes.

STUDY POPULATION

Data collected in the nursing homes of 5 states (Kansas, Maine, Mississippi, Ohio, and South Dakota) between January 1, 1998, and December 31, 1999, were used in this study. Eligible candidates were residents 65 years or older. Residents with a diagnosis of schizophrenia were excluded from the study population because they might have presented noticeable differences in their cardiovascular risk profile compared with the general nursing home population.[18]

EXPOSURE ASSESSMENT

Nursing home staff recorded the name, dose, frequency, route of administration, and national drug code for up to 18 medications administered to the resident in the 7 days before the assessment. Exposed residents were "new" users of antipsychotic agents. To select them, we initially identified residents for whom antipsychotic drug use was reported at any MDS assessment during the study period (n=50 405). Then, we selected the first assessment in which residents reported any antipsychotic drug use (index assessment). Residents were considered new users if the MDS assessment documented no use of antipsychotic agents before the index assessment (n=19 940). Among exposed residents we distinguished between users of risperidone (n=7811), olanzapine (n=2825), other atypical antipsychotic agents (clozapine and quetiapine fumarate) (n=977), phenothiazines (chlorpromazine hydrochloride, fluphenazine hydrochloride, mesoridazine besylate, perphenazine-amitriptyline, promazine hydrochloride–hydroCort, thioridazine hydrochloride, trifluoperazine hydrochloride, and trifluprom azine hydrochloride) (n=4127), other conventional agents (chlorprothixene, haloperidol, loxapine succinate, molindone hydrochloride, and thiothixene) (n=3525), and more than 1 antipsychotic agent (n=675). These were the only antipsychotic medications available during the study period. Nonusers of antipsychotic agents were residents for whom at least 2 consecutive MDS assessments were available and no antipsychotic drug use was reported during the study period (n=112 078). We chose the first available assessment as the index assessment. The final sample consisted of 19 940 exposed and 112 078 unexposed residents.

OUTCOME ASSESSMENT

Based on previous reports,[5,6] the thromboembolic effect of antipsychotic agents may be manifest within 3 months of the initiation of therapy. We defined the length of follow-up to be 6 months. The outcome of this study was defined as any hospitalizations for VTE that occurred during that time. We identified all hospitalizations in which the primary discharge diagnosis was one of the following: deep venous thrombosis (*ICD-9* code 453.8), femoral vein thrombi (*ICD-9* code 451.11), popliteal vein thrombi (*ICD-9* code 451.19), iliac vein thrombi (*ICD-9* code 451.81), deep vessels of lower extremity thrombophlebitis (*ICD-9* code 451.1), and pulmonary embolism and infarction (*ICD-9* code 415.1). We used the first hospitalization for VTE among persons with multiple events (n=29).

POTENTIAL CONFOUNDERS

Risk and protective factors for VTE, including body mass index, indicators of functional and cognitive status, history of deep venous thrombosis, history of hip fracture, chronic obstructive pulmonary disease, cancer, and use of anticoagulants, aspirin or antiplatelets, and estrogens, were considered potential confounders in this study. We also identified as confounders those variables that altered the estimate of effect by more than 10% after being included in the multivariate model. These variables included age, sex, dementia, depression, peripheral vascular disease, cerebrovascular disease, heart failure, and diabetes mellitus.

To evaluate functional status, we used the activities of daily living scale (ADL), a 7-item, 5-level score based on the resident's performance in 7 areas: dressing, eating, toileting, bathing, locomotion, transferring, and incontinence.[19] We classified the degree of dependence as mild (ADL score 0-1), moderate (ADL score 2-3), or severe (ADL score 4-5). The Cognitive Performance Scale (CPS) was used to measure cognitive status.[20] The CPS is a validated scale embedded in the MDS with scores that range from 0 (intact cognition) to 6 (severe dementia). The CPS has a good correlation with the Mini-Mental State Examination.[20] We categorized cognitive impairment as follows: minimal (CPS score 0-1), moderate (CPS score 2-3), and severe (CPS score 4-6).

STATISTICAL ANALYSIS

We used methods described by Kaplan and colleagues to estimate event-free survival curves and compared these curves using Mantel-Haenszel tests. The effect of antipsychotic agents on the risk of hospitalization for VTE was estimated using Cox proportional hazards models, with users of no antipsychotic agents as the reference category. Residents were censored at their time of death to adjust for the competing risk. We calculated person-time as number of days from the date of the index assessment to hospitalization for VTE, death, or end of follow-up. Because structural factors of facilities may affect the rates and pattern of hospitalization,[21] we stratified the analysis by facility and calculated pooled estimates to minimize this potential confounding effect. To rule out departures from the proportionality assumption for each model, we examined the log-log survival function. From these models, we derived crude and adjusted estimates of effect and corresponding 95% confidence intervals (CIs). Finally, to rule out the confounding effect of major risk and protective factors for VTE, we conducted a

Table 1. Principal Sociodemographic, Functional, and Clinical Characteristics of the Study Population by Antipsychotic Drug Use

Characteristic	Users, % (n = 19 940)	Nonusers, % (n = 112 078)
Age group, y		
≤74	16.0	14.0
75-84	40.6	36.7
≥85	43.4	49.3
Female	70.5	74.3
Race/ethnicity		
White, not of Hispanic origin	90.0	90.6
Black, not of Hispanic origin	9.1	8.6
Other	0.9	0.8
BMI		
<18.5	14.7	17.6
18.5-24.9	49.2	45.5
25.0-29.9	24.4	23.9
≥30.0	11.7	13.0
Functional impairment (ADL score)		
Mild (0-1)	11.4	14.5
Moderate (2-3)	54.4	53.0
Severe (4-5)	34.2	32.5
Cognitive deficit (CPS score)		
Mild	16.9	34.6
Moderate	52.0	40.9
Severe (4-6)	31.2	24.5
History of deep venous thrombosis	2.2	1.7
Hypertension	52.0	50.8
Heart failure	27.1	27.0
Ischemic heart disease	17.8	17.4
Cardiac arrhythmias	16.2	16.9
History of CVE	25.7	26.7
Peripheral vascular disease	11.4	11.0
Diabetes mellitus	24.1	22.8
History of hip fracture	7.1	6.0
Cancer	10.2	10.5
COPD	18.5	16.2
Alzheimer disease	23.0	13.6
Other dementia	49.8	30.8
Parkinson disease	7.6	6.4
Anxiety disorder	20.1	11.5
Depression	44.7	29.8

Abbreviations: ADL, activities of daily living scale; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); COPD, chronic obstructive pulmonary disease; CPS, Cognitive Performance Scale; CVE, cerebrovascular events.

subgroup analysis that restricted the sample to those residents without a history of deep venous thrombosis, without a history of hip fracture, without cancer, and being treated with neither anticoagulant agents nor estrogens (n = 88 441). Similarly, based on the hypothesis that severe cognitive impairment (CPS score 4-6) may limit mobility, therefore representing a risk factor for VTE, we conducted a second subgroup analysis on a restricted sample of residents with minimal or moderate cognitive impairment (n = 98 370). Statistical analysis was performed using SAS statistical software, version 8 (SAS Institute Inc, Cary, NC).

RESULTS

The sociodemographic characteristics, indicators of functional and cognitive status, and comorbid conditions of antipsychotic users and nonusers are given in **Table 1**.

Table 2. Medication Use in the Study Population by Antipsychotic Drug Use

Medication	Users, % (n = 19 940)	Nonusers, % (n = 112 078)
Diuretics	40.4	43.0
β-Blockers	15.9	15.4
ACE inhibitors	20.3	21.8
Calcium channel blockers	18.8	19.7
Vasodilators	17.3	17.3
Centrally acting antihypertensive drugs	3.5	3.3
Antiarrhythmic drugs	25.1	26.3
Lipid-lowering drugs	9.7	9.3
Oral hypoglycemic agents	9.9	9.7
Insulin	10.3	10.3
Anticoagulants	10.9	12.8
Aspirin or antiplatelets	30.0	30.0
NSAIDs	9.1	9.7
Antidepressants	45.3	30.7
Estrogens	4.5	4.4

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

Users were younger and more cognitively impaired than nonusers. No major differences were evident between the 2 groups with respect to all other variables considered. Only neuropsychiatric conditions were more prevalent among users of antipsychotics, with noticeable differences in the case of Alzheimer disease (23.0% vs 13.6%), dementia other than Alzheimer disease (49.8% vs 30.8%), and depression (44.7% vs 29.8%). Consistently, no differences occurred in concomitant medication use between the 2 groups except that users of antipsychotic agents were more likely to use antidepressants (45.3% vs 30.7% among nonusers) (**Table 2**).

Among antipsychotic users, 40% were receiving risperidone, 14% were receiving olanzapine, and nearly 18% were receiving haloperidol. Residents taking multiple antipsychotic agents (4%) were treated with a combination of 2 antipsychotic medications, mostly risperidone and either haloperidol or thioridazine or olanzapine and haloperidol. Among atypical agents, risperidone accounted for nearly 70% of prescriptions, whereas among conventional antipsychotic agents, haloperidol was the most commonly used medication (nearly 40% of prescriptions) followed by thioridazine. Daily doses for antipsychotic agents were in accordance with recommendations for use in elderly people. The mode of the daily dose was 1 mg for risperidone, 5 mg for olanzapine, 20 mg for thioridazine hydrochloride, and 1 mg for haloperidol.

We identified 539 hospitalizations for VTE; the rate of hospitalization for VTE was 0.91 per 100 person-years. Venous thrombosis accounted for 77.6% and pulmonary embolism for 22.4% of all VTE hospitalizations. The median follow-up time was 180 days for both antipsychotic users and nonusers. The **Figure** shows the event-free survival curve by antipsychotic use. Survival curves for the 2 groups differed at the Mantel-Haenszel test ($P = .02$). The occurrence of VTE hospitalizations started early (30-60 days) and was distributed throughout the entire follow-up time.

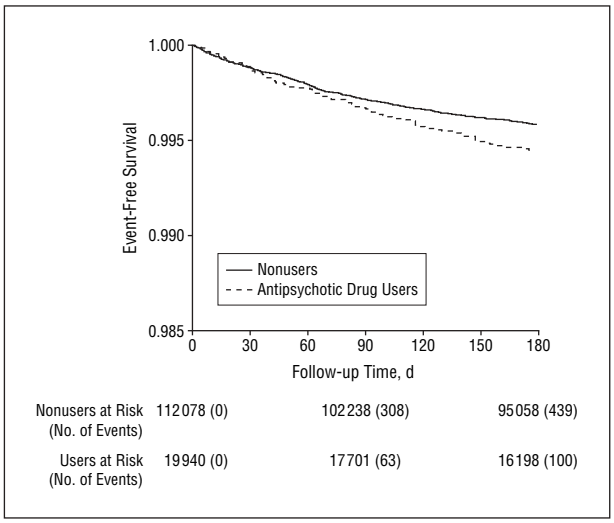

Figure. Unadjusted survival curve for venous thromboembolic events among residents by antipsychotic drug use.

After adjusting for all potential confounders, the rate of hospitalization for VTE was increased for users of atypical antipsychotic agents, including risperidone (adjusted hazard ratio [HR], 1.98; 95% CI, 1.40-2.78), olanzapine (adjusted HR, 1.87; 95% CI, 1.06-3.27), and clozapine and quetiapine (adjusted HR, 2.68; 95% CI, 1.15-6.28) (**Table 3**). No increased rate of hospitalization for VTE was associated with phenothiazines (adjusted HR, 1.03; 95% CI, 0.60-1.77) or other conventional medications (adjusted HR, 0.98; 95% CI, 0.52-1.87). Residents who were receiving more than 1 antipsychotic agent were hospitalized for VTE at a rate much greater than nonusers (adjusted HR, 4.80; 95% CI, 2.28-10.10). When we restricted the study sample to residents without major risk and protective factors for VTE and to residents with minimal or moderate cognitive impairment, estimates of effect did not change remarkably, although they appeared less precise because of the reduced size of samples (**Table 4**).

COMMENT

The findings of our study document that atypical antipsychotic agents, including risperidone, olanzapine, clozapine, and quetiapine, increase the likelihood of deep venous thrombosis or pulmonary embolism among elderly patients. An association between atypical antipsychotic agents and VTE has been previously suggested for clozapine among young adults with psychiatric disorders.[8-11] More recently, an increased risk of VTE was suspected for olanzapine or risperidone.[12-14] A single study[15] among elderly patients under an insurance plan in Ontario found no excess risk of VTE associated with atypical antipsychotic agents compared with thyroid replacement therapy.

In the current study, we found that no increased risk of VTE was associated with the use of phenothiazines or other conventional agents. The results for phenothiazines are apparently in contrast with previous reports.[5,6] However, residents in the current study were receiving phenothiazines at doses substantially lower than those previously associated with the occurrence of thromboembolic events.[1-6]

The mechanisms by which antipsychotic medications may contribute to VTE remain to be established conclusively. Although conventional agents have been associated with enhanced aggregation of platelets,[22] atypical antipsychotic agents have not been tested systematically. Recent in vitro data coming from the maker of risperidone do not support a direct effect of risperidone on human platelet function, plasma coagulation, and fibrinolysis.[23] However, atypical agents possess a high affinity for the serotonin receptor type 2A, and serotonin-induced platelet aggregation may be affected.[24] Evidence also exists that lupus anticoagulant and anticardiolipin antibody levels may be raised in patients taking conventional antipsychotic agents[25] and clozapine.[26] Venous stasis can be exacerbated by excessive sedation.[10] Moreover, a recent meta-analysis[27] has suggested a nearly 3-fold increased risk of peripheral edema associated with risperidone. Metabolic abnormalities (dyslipidemia, increased plasma levels of leptin and glucose, hyperhomocysteinemia) observed among users of atypical antipsychotic agents,[28] and known to be associated with decreased fibrinolytic activity,[29] are unlikely to be etiologic factors in the early thromboembolic occurrence.

This study investigates a topic of high public health significance. In fact, behavioral disturbances and psychosis are increasingly recognized as significant mental health issues for older people. It has been shown that 15% of all residents in US nursing homes receive antipsychotic agents.[30] Prescriptions are increasingly being written for atypical agents. At the time of this study, nearly 60% of users were receiving atypical agents,[30] which is owing to their purported superior extrapyramidal side effect profile compared with conventional agents. Atypical antipsychotic agents have been approved by the US Food and Drug Administration for the treatment of schizophrenia only. Regardless, evidence exists that more than 70% of atypical prescriptions are for off-label indications, including depression and psychosis associated with dementia.[31] Despite this widespread clinical acceptance, evidence supporting the efficacy and safety of atypical antipsychotic agents is still limited, especially among patients with dementia.[32] Recently, other serious complications have been associated with the use of atypical antipsychotic agents, including an increased risk of cerebrovascular events and death, especially in persons with dementia and preexisting risk factors.[33] This finding has led to restrictions in their use. In the current study, we documented an increased relative rate for an event that is rare and associated with an extremely low absolute risk. In clinical practice, physicians should judge, on an individual basis, whether or not the magnitude of this risk outweighs the benefits that can be expected from the use of antipsychotic agents. This seems especially true in the case of behavioral disturbances and psychotic symptoms of dementia, which can be distressing for patients and caregivers and are known to be associated with early institutionalization and increased morbidity and mortality.[34]

Table 3. Effect of Antipsychotic Drug Use on the Risk of Hospitalization for Venous Thromboembolism

Agent	No. of Events	Total Follow-up, Person-Years	Crude Incidence Rate per 100 Person-Years	Crude HR	Adjusted HR (95% CI)†
Atypical agents	64	5173	1.24	1.57	2.01 (1.50-2.70)
Risperidone	43	3451	1.25	1.52	1.98 (1.40-2.78)
Olanzapine	15	1279	1.17	1.54	1.87 (1.06-3.27)
Clozapine–quetiapine fumarate*		443	1.35	2.08	2.68 (1.15-6.28)
Conventional agents	28	3318	0.84	0.93	1.02 (0.67-1.55)
Phenothiazines	15	1813	0.83	0.95	1.03 (0.60-1.77)
Other	13	1505	0.86	0.91	0.98 (0.52-1.87)
>1 Antipsychotic agent*		286	2.80	3.42	4.80 (2.28-10.10)
Nonusers	439	50 604	0.87	Referent	Referent

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Number of events was less than 11; we are unable to report the actual number under our data use agreement with the Centers for Medicare and Medicaid Services.
†Adjusted for age, sex, body mass index, activities of daily living score, Cognitive Performance Scale score, history of deep venous thrombosis, history of hip fracture, chronic obstructive pulmonary disease, cancer, dementia, depression, peripheral vascular disease, cerebrovascular disease, heart failure, diabetes mellitus, and concomitant drug, use including anticoagulants, aspirin or antiplatelets, and estrogens.

Table 4. Effect of Antipsychotic Drug Use on the Risk of Hospitalization for VTE Among Residents Without Major Risk and Protective Factors for VTE Among Residents With Minimal or Moderate Cognitive Impairment

	Adjusted HR (95% CI)	
Agent	Residents Without Main Risk and Protective Factors for VTE (n = 88 441)*	Residents With Minimal or Moderate Cognitive Impairment (CPS Score ≤3) (n = 98 370)†
Atypical agents	2.43 (1.69-3.49)	1.94 (1.33-2.58)
Risperidone	2.54 (1.69-3.82)	1.83 (1.23-2.72)
Olanzapine	1.71 (0.96-3.45)	1.95 (1.06-3.62)
Clozapine–quetiapine fumarate	4.88 (2.03-11.72)	2.79 (1.09-7.13)
Conventional agents	1.00 (0.57-1.78)	0.90 (0.56-1.44)
Phenothiazines	0.96 (0.56-2.02)	1.00 (0.56-1.79)
Other	1.04 (0.45-2.40)	0.77 (0.36-1.64)
>1 Antipsychotic agent	5.29 (2.05-13.66)	2.82 (1.01-7.90)
Nonusers	Referent	Referent

Abbreviations: CI, confidence interval; CPS, Cognitive Performance Scale; HR, hazard ratio; VTE, venous thromboembolism.
*Main risk factors for VTE included history of deep venous thrombosis, history of hip fracture, cancer, use of anticoagulants, and use of estrogens. These HRs were adjusted for age, sex, body mass index, activities of daily living score, CPS score, chronic obstructive pulmonary disease, dementia, depression, peripheral vascular disease, cerebrovascular disease, heart failure, diabetes mellitus, and use of aspirin or antiplatelets.
†These HRs were adjusted for age, sex, body mass index, activities of daily living score, CPS score, history of deep venous thrombosis, history of hip fracture, chronic obstructive pulmonary disease, cancer, dementia, depression, peripheral vascular disease, cerebrovascular disease, heart failure, diabetes mellitus, and concomitant drug use, including anticoagulants, aspirin or antiplatelets, and estrogens.

This study has some limitations. Thromboembolic events were selected on the basis of Medicare claims data; therefore, the potential for misclassification of the outcome exists. We documented an incidence of VTE of 0.91 per 100 person-years, which is somewhat lower than that observed in previous studies.[35] Our study was restricted to events that could be confirmed by hospital diagnosis; thus, we have missed all events that resulted in a fatality before hospital referral and all events for which hospitalization was deemed unnecessary. Most antipsychotic prescriptions among patients with dementia are for atypical agents.[30] Dementia, especially in the advanced stage, may predispose patients to immobility. Although findings were confirmed after excluding residents with severe cognitive decline from the sample, confounding by indication is possible. We have no information on whether the users were taking antipsychotic agents at the time of hospitalization, which introduces a potential for misclassification of the exposure. With respect to dosages, we observed low variability among drug regimens, and we were not able to investigate dose-response relationships. Finally, although we have taken due care to address numerous potential confounders, residual confounding is always possible.

In conclusion, our study documented that atypical antipsychotic agents may increase the risk of VTE among elderly patients. It seems advisable to be cautious when prescribing antipsychotic agents to elderly patients. However, the therapeutic choice should be individualized based on a careful evaluation of the benefits and risks of both classes of antipsychotic agents and patients' risk profiles.

Accepted for Publication: June 9, 2005.
Correspondence: Rosa Liperoti, MD, MPH, Centro di Medicina dell'Invecchiamento, Dipartimento di Scienze Gerontologiche, Geriatriche e Fisiatriche, Università Cattolica del Sacro Cuore Largo A. Gemelli, 80168 Rome, Italy (rossella_liperoti@rm.unicatt.it).
Author Contributions: Dr Liperoti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Funding/Support: This study was funded by grant R37 AG11624-06s1 from the National Institute on Aging, National Institutes of Health, Bethesda, Md.
Role of the Sponsor: The funder of this study had no role in the design or conduct of the study; in the collection, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

REFERENCES

1. Grahmann H, Suchenwirth R. Thrombosis hazard in chlorpromazine and reserpine therapy of endogenous psychoses [in German]. *Nervenarzt*. 1959;30:224-225.
2. Haefner H, Brehm I. Thromboembolic complications in neuroleptic treatment. *Compr Psychiatry*. 1965;58:25-34.
3. Varia I, Krishnan RR, Davidson J. Deep-vein thrombosis with antipsychotic drugs. *Psychosomatics*. 1983;24:1097-1098.
4. Thorogood M, Cowen P, Mann J, Murphy M, Vessey M. Fatal myocardial infarction and use of psychotropic drugs in young women. *Lancet*. 1992;340:1067-1068.
5. Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet*. 2000;356:1219-1223.
6. Parkin L, Skegg DC, Herbison GP, Paul C. Psychotropic drugs and fatal pulmonary embolism. *Pharmacoepidemiol Drug Saf*. 2003;12:647-652.
7. Kapur S, Remington G. Atypical antipsychotics. *BMJ*. 2000;321:1360-1361.
8. Walker AM, Lanza LL, Arellano F, Rothman KJ. Mortality in current and former users of clozapine. *Epidemiology*. 1997;8:671-677.
9. Ihde-Scholl T, Rolli ML, Jefferson JW. Clozapine and pulmonary embolus. *Am J Psychiatry*. 2001;158:499-500.
10. Hägg S, Spigset O, Söderström TG. Association of venous thromboembolism and clozapine. *Lancet*. 2000;355:1155-1156.
11. Knudson JF, Kortepeter C, Dubitsky GM, Ahmad SR, Chen M. Antipsychotic drugs and venous thromboembolism. *Lancet*. 2000;356:252-253.
12. Hägg S, Tatting P, Spigset O. Olanzapine and venous thromboembolism. *Int Clin Psychopharmacol*. 2003;18:299-300.
13. Waage IM, Gedde-Dahl A. Pulmonary embolism possibly associated with olanzapine treatment. *BMJ*. 2003;327:1384.
14. Hamanaka S, Kamijo Y, Nagai T, et al. Massive pulmonary thromboembolism demonstrated at necropsy in Japanese psychiatric patients treated with neuroleptics including atypical antipsychotics. *Circ J*. 2004;68:850-852.
15. Ray JG, Mamdani MM, Yeo EL. Antipsychotic and antidepressant drug use in the elderly and the risk of venous thromboembolism. *Thromb Haemost*. 2002;88:205-209.
16. Bernabei R, Gambassi G, Lapane K, et al. SAGE (Systematic Assessment of Geriatric drug use via Epidemiology) Study Group. Characteristics of the SAGE database: a new resource for research on outcomes in long-term care. *J Gerontol A Biol Sci Med Sci*. 1999;54:M25-M33.
17. Gambassi G, Landi F, Peng L, et al; SAGE (Systematic Assessment of Geriatric drug use via Epidemiology) Study Group. Validity of diagnostic and drug data in standardized nursing home resident assessments: potential for geriatric pharmacoepidemiology. *Med Care*. 1998;36:167-179.
18. McCreadie RG; Scottish Schizophrenia Lifestyle Group. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. *Br J Psychiatry*. 2003;183:534-539.
19. Morris JN, Fries BE, Morris SA. Scaling ADLs within the MDS. *J Gerontol A Biol Sci Med Sci*. 1999;54:M546-M553.
20. Hartmaier SL, Sloane PD, Guess HA, Koch GG. The MDS Cognition Scale: a valid instrument for identifying and staging nursing home residents with dementia using the minimum data set. *J Am Geriatr Soc*. 1994;42:1173-1180.
21. Intrator O, Castle NG, Mor V. Facility characteristics associated with hospitalization of nursing home residents: results of a national study. *Med Care*. 1999;37:228-237.
22. Boullin DJ, Woods HF, Grimes RP, Grahame-Smith DG. Increased platelet aggregation responses to 5-hydroxytryptamine in patients taking chlorpromazine. *Br J Clin Pharmacol*. 1975;2:29-35.
23. De Clerck F, Somers Y, Mannaert E, Greenspan A, Eerdekens M. In vitro effects of risperidone and 9-hydroxy-risperidone on human platelet function, plasma coagulation, and fibrinolysis. *Clin Ther*. 2004;26:1261-1273.
24. Love RC. Novel versus conventional antipsychotic drugs. *Pharmacotherapy*. 1996;16:6-10.
25. Canoso RT, de Oliveira RM, Nixon RA. Neuroleptic-associated autoantibodies: a prevalence study. *Biol Psychiatry*. 1990;27:863-870.
26. Davis S, Kern HB, Asokan R. Antiphospholipid antibodies associated with clozapine treatment. *Am J Hematol*. 1994;46:166-167.
27. Katz IR, Mintzer J, Brodaty H, De Deyn PP, Greenspan A. Risperidone in the treatment of psychosis of Alzheimer's disease (PAD): a meta-analysis of 4 controlled trials. Paper presented at: 2005 Annual Scientific Meeting of the American Geriatrics Society; May 13, 2005; Orlando, Fla.
28. Nasrallah H. A review of the effect of atypical antipsychotics on weight. *Psychoneuroendocrinology*. 2003;28(suppl 1):83-96.
29. Doggen CJ, Smith NL, Lemaitre RN, et al. Serum lipid levels and the risk of venous thrombosis. *Arterioscler Thromb Vasc Biol*. 2004;24:1970-1975.
30. Liperoti R, Mor V, Lapane KL, Pedone C, Gambassi G, Bernabei R. The use of atypical antipsychotics in nursing home. *J Clin Psychiatry*. 2003;64:1106-1112.
31. Glick ID, Murray SR, Vasudevan P, Marder SR, Hu RJ. Treatment with atypical antipsychotics: new indications and new populations. *J Psychiatr Res*. 2001;35:187-191.
32. Lee PE, Gill SS, Freedman M, Bronskill SE, Hillmer MP, Rochon PA. Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. *BMJ*. 2004;329:75-78.
33. US Food and Drug Administration. FDA public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. Available at: http://www.fda.gov/cder/drug/advisory/antipsychotics.htm. Accessed April 11, 2005.
34. Finkel SI. Behavioral and psychologic symptoms of dementia. *Clin Geriatr Med*. 2003;19:799-824.
35. Gomes JP, Shaheen WH, Truong SV, Brown EF, Beasley BW, Gajewski BJ. Incidence of venous thromboembolic events among nursing home residents. *J Gen Intern Med*. 2003;18:934-936.