Association of Selected Antipsychotic Agents With Major Adverse Cardiovascular Events and Noncardiovascular Mortality in Elderly Persons

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Background—Data from observational studies have raised concerns about the safety of treatment with antipsychotic agents (APs) in elderly patients with dementia, but this area has been insufficiently investigated. We performed a head-to-head comparison of the risk of major adverse cardiovascular events and noncardiovascular mortality associated with individual APs (ziprasidone, olanzapine, risperidone, quetiapine, levomepromazine, chlorprothixen, flupentixol, and haloperidol) in Danish treatment-naïve patients aged ≥70 years.

Methods and Results—We followed all treatment-naïve Danish citizens aged ≥70 years that initiated treatment with APs for the first time between 1997 and 2011 (n=91 774, mean age 82±7 years, 35 474 [39%] were men). Incidence rate ratios associated with use of different APs were assessed by multivariable time-dependent Poisson regression models. For the first 30 days of treatment, compared with risperidone, incidence rate ratios of major adverse cardiovascular events were higher with use of levomepromazine (3.80, 95% CI 3.43 to 4.21) and haloperidol (1.85, 95% CI 1.67 to 2.05) and lower for treatment with flupentixol (0.54, 95% CI 0.45 to 0.66), ziprasidone (0.31, 95% CI 0.10 to 0.97), chlorprothixen (0.76, 95% CI 0.61 to 0.95), and quetiapine (0.68, 95% CI 0.58 to 0.80). Relationships were generally similar for long-term treatment. The majority of agents were associated with higher risks among patients with cardiovascular disease compared with patients without cardiovascular disease (*P* for interaction <0.0001). Similar results were observed for noncardiovascular mortality, although differences in associations between patients with and without cardiovascular disease were small.

Conclusions—Our study suggested some diversity in risks associated with individual APs but no systematic difference between first- and second-generation APs. Randomized placebo-controlled studies are warranted to confirm our findings and to identify the safest agents. (*J Am Heart Assoc*. 2015;4:e001666 doi: 10.1161/JAHA.114.001666)

Key Words: antipsychotic medications • cardiovascular risks • elderly

The estimated worldwide prevalence of dementia was 35.6 million in 2010 and is expected to almost double within the next 20 years.[1] Dementia may be accompanied by

physical aggression, anxiety, hallucinations, and behavioral problems, which are referred to as behavioral and psychological symptoms of dementia.[2] For management of these symptoms, antipsychotic agents (APs) are frequently prescribed.[3,4] Because the second-generation APs are considered to have fewer side effects than first-generation APs, they are now more widely used in patients with behavioral and psychological symptoms of dementia than first-generation APs.[5,6] In recent years, however, data from observational studies have raised concerns about the safety of this practice.[7–11] Of particular note, it has been suggested that the risk of sudden cardiac death associated with second-generation APs may be at least as high as that for first-generation APs.[12] Moreover, use of APs in people with dementia has been associated with increased risk of stroke and acute myocardial infarction, but prior studies did not differentiate between first- and second-generation APs.[13,14]

In addition to using APs to treat behavioral problems in elderly patients with dementia, elderly persons without

dementia are often prescribed APs for conditions such as anxiety, depression, or insomnia; however, the outcomes associated with AP use in this particular group have not been well investigated, and it is not known if risks differ for patients with and without dementia. Moreover, several APs are considered to pose greater risk of adverse outcomes for patients with established cardiovascular disease (CVD) than for patients without CVD, but head-to-head comparisons of individual APs in patients with and without CVD are sparse.[15] To further address these issues, we investigated the risk of major adverse cardiovascular events (MACE) and noncardio-vascular mortality associated with individual APs in a Danish population with and without diagnosed dementia and with and without CVD.

Methods

The study was approved by the Danish Data Protection Agency (2007-58-0015/local j.nr. GEH-2014-012 I-Suite nr: 02720). Register-based studies in which persons cannot be identified do not need ethics approval in Denmark. All Danish citizens are medically covered by a tax-financed system that provides each citizen with equal health care free of copayment. For administrative purposes, the government has kept records of all hospitalizations (in-hospital and outpatient visits) since 1978 (in the Danish National Patient Registry) and records of all prescription claims from Danish pharmacies since 1995 (in the Danish Register of Medicinal Product Statistics). Furthermore, registration of all births and deaths, including dates of occurrence, has been complete for all citizens since 1968 (in the National Population Register). Because all Danish citizens are given a permanent personal civil registration number at time of birth or immigration, they can be followed up by individual-level linkage of the registers.

Population and Comorbidities

For the present study, we included all persons in Denmark between 1997 and 2011 who were aged ≥70 years at the time when they claimed their first prescription of antipsychotic medication and who had previously been treatment-naïve (ie, allowing for a look back to 1995, when the Danish Register of Medicinal Product Statistics was established). We identified comorbidities throughout the whole observational period by continuous screening of the Danish National Patient Register. Because most diagnoses were for chronic conditions, people were classified as having the disease from the first day of diagnosis. For all diagnoses but dementia, schizophrenia, and Parkinson's disease, only validated in-hospital diagnoses were considered.[16] In addition to previously validated chronic comorbid diagnoses, we retrieved

information on acute delirium based on in-hospital diagnoses. Because the diagnoses of dementia, Parkinson's disease, and schizophrenia are often based on outpatient visits, diagnoses from both in-hospital and outpatient visits were considered for these comorbidities.

Outcomes

The primary outcomes were MACE, comprising the first occurring nonfatal acute myocardial infarction (*International Classification of Diseases, 10th revision* [ICD-10] code I21) or nonfatal ischemic stroke (ICD-10 codes I63 and I64 ["I64" denotes unspecified stroke, of which the majority are of ischemic origin])[17] and cardiovascular mortality (ICD-10 codes I00 to I99) and non–cardiovascular-related mortality (causes of mortality were obtained from the Danish Causes of Death Register).

Pharmacotherapy

From the National Register of Medicinal Product Statistics, we identified exposure to the individual APs outlined in Table 1. For these agents and for vitamin K antagonists (B01AA03), clopidogrel (B01AC04), low-dose aspirin (B01AC06), and loop diuretics (C03CA01, C03CA02), treatment was updated continuously, that is, patients were considered to be exposed only while covered by claimed prescriptions. To determine treatment length and average daily dosages, up to 3 consecutive prescriptions were considered in a retrospective manner. We created an algorithm for each agent in which minimum, maximum, and typical daily dosages of used medication were defined. For patients' first claimed prescriptions, the typical daily dosage was assigned, and treatment length was calculated by dividing the amount of claimed medications by that daily dosage. For patients who were covered by a previous prescription at the time of claiming a new prescription, the daily dosage was reset, and a new daily dosage was calculated as the amount of claimed medications during the previous period divided by time between prescription claims (based on up to 3 previous prescriptions without treatment breaks). If calculated dosages exceeded the predefined highest daily dosages, patients were assigned the maximum dosages, and exceeding tablets were assumed to be stored and consumed during the immediate period following the end of the last prescription.

For other medications (ie, dementia medications [ATC code N06DA], beta blockers [C07], thiazides [C03A], calcium channel blockers [C08], digoxin [C01AA], renin-angiotensin system inhibitors [C09], aldosterone blockers [C03D], and statins [C10AA]), treatment status was updated every 30 days for the whole observational period. Persons were considered to be in treatment with the different medications if

Table 1. Classification of the Different Antipsychotic Agents

Name	ATC Code	Generation
Chlorprothixen	N05AF03	First
Flupentixol	N05AF01	First
Haloperidol	N05AD01	First
Levomepromazine	N05AA02	First
Olanzapine	N05AH03	Second
Risperidone	N05AX08	Second
Quetiapine	N05AH04	Second
Ziprasidone	N05AE04	Second

they claimed at least 1 prescription during the preceding 4 months (this pragmatic method was applied because of computational limitations).

Statistics

All patients were followed from the date of first claimed prescription until date of death, emigration, or December 31, 2011. The incidence rate ratios (IRRs) associated with exposure to APs were analyzed using multivariable Poisson regression models. The following variables were included as time-dependent variables: treatment with antipsychotic medications; all comorbidities (schizophrenia, Parkinson's disease,

dementia, acute delirium, prior cerebrovascular disease, heart failure, acute myocardial infarction, peripheral vascular disease, chronic obstructive pulmonary disease, atrial fibrillation, moderate or severe renal disease, diabetes, cancer, and cancer with metastases; for ICD-10 codes, see Table 2); age; and use of warfarin, aspirin, clopidogrel, loop diuretics, thiazides, renin-angiotensin system blockers, aldosterone antagonists, statins, beta blockers, calcium channel blockers, or digoxin. All models were adjusted for the aforementioned variables and for actual calendar year and sex. Use of antipsychotic medications was included as a time-dependent multilevel categorical variable for which people using >1 medication for a given time were grouped in a separate *use of multiple medication* category. People who were not covered by a claimed prescription were assigned to a *no treatment* category. For all comparisons, use of risperidone as monotherapy served as the referent group (because this group was the largest quantitatively). We performed 2 separate types of analyses. In the first, we created 3 different categorical variables for antipsychotic use according to time elapsed since first treatment because time dependency for risks was present (*P* for interaction between time elapsed and associated risks <0.0001; use of medications was split into the first 30 days, 31 to 365 days, and >365 days after treatment initiation). After having explored the IRRs among different medications in different time periods, the differences appeared to be rather small between the periods; therefore, in subsequent models, we included a variable reflecting only

Table 2. ICD-10 Codes for Various Medical Conditions

Condition	ICD-10
Dementia	F00, F01, F02, F03, F05.1, G30
Schizophrenia	F20
Parkinson's disease	G20
Acute delirium	F05
Ischemic heart disease	I20, I23, I24, I25
Cerebrovascular disease	I60 to I69, G45, G46
Acute myocardial infarction	I21, I22, I23
Heart failure	I50, I42, I110, I13.0, I13.2
Atrial fibrillation	I48
Peripheral artery disease	I70 to I74
Chronic obstructive pulmonary disease	J40 to 47, J60 to 67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Cancer	C00 to C75, C81 to 96
Metastases	C76 to C80
Renal disease	N00 to 06, N07, N11, N17 to 19, R34, I12, I13, Q61
Diabetes	Treatment with glucose-lowering medication (ATC code A10)

ICD-10 indicates *International Classification of Diseases, 10th Revision*.

Table 3. Baseline Characteristics of Study Population

	Haloperidol (n=20 873)	Flupentixol (n=10 807)	Levopromazine (n=16 127)	Chlorprothixen (n=7762)	Quetiapine (n=12 854)	Risperidone (n=28 161)	Olanzapine (n=16 102)	Ziprasidone (n=500)
Age, y (SD)	83 (7)	79 (6)	80 (7)	79 (7)	82 (6)	84 (7)	82 (7)	81 (7)
Sex, male (%)	9122 (44)	3081 (29)	7105 (44)	2843 (37)	5149 (40)	10 268 (36)	5589 (35)	170 (34)
Cerebrovascular disease (%)	5193 (25)	2544 (24)	3266 (20)	1647 (21)	3338 (26)	7241 (26)	4050 (25)	123 (25)
Heart failure (%)	3378 (16)	1763 (16)	3227 (20)	1203 (16)	1554 (12)	4064 (14)	2357 (15)	76 (15)
Acute myocardial infarction (%)	1837 (9)	1091 (10)	1557 (10)	680 (9)	995 (8)	2144 (8)	1203 (7)	32 (6)
Peripheral arterial disease (%)	1428 (7)	705 (7)	1336 (8)	529 (7)	660 (5)	1460 (5)	818 (5)	24 (5)
Chronic obstructive pulmonary disease (%)	2737 (13)	1822 (17)	4369 (27)	1381 (18)	1377 (11)	2855 (10)	1795 (11)	51 (10)
Cancer (%)	6097 (29)	2072 (19)	4826 (30)	1447 (19)	1731 (13)	3292 (12)	2344 (15)	48 (10)
Cancer with metastases (%)	1948 (9)	384 (4)	1348 (8)	238 (3)	199 (2)	416 (1)	452 (3)	5 (1)
Atrial fibrillation (%)	3432 (15)	768 (7)	1860 (11)	750 (9)	1799 (13)	1065 (4)	1866 (12)	50 (10)
Parkinson's disease (%)	483 (2)	298 (3)	335 (2)	197 (3)	1516 (12)	889 (3)	1050 (7)	15 (3)
Acute delirium (%)	1357 (7)	212 (2)	210 (1)	175 (2)	902 (7)	1473 (5)	720 (4)	15 (3)
Schizophrenia (%)	71 (0.3)	25 (0.2)	45 (0.3)	60 (1)	128 (1)	287 (1)	288 (2)	15 (3)
Diabetes (%)	2226 (11)	785 (7)	1552 (10)	720 (9)	1309 (10)	2728 (10)	1435 (9)	45 (9)
Renal disease (%)	1044 (5)	501 (5)	854 (5)	409 (5)	525 (4)	1073 (4)	689 (4)	23 (5)
Dementia diagnosis (%)	1638 (8)	154 (1)	374 (2)	235 (3)	2394 (19)	3357 (12)	1718 (11)	83 (17)
Treatment with dementia medications (%)	3058 (15)	813 (8)	903 (6)	669 (9)	4625 (36)	6688 (24)	3550 (22)	163 (33)
Statin treatment (%)	2051 (10)	939 (9)	1194 (7)	977 (13)	2057 (16)	2488 (9)	1224 (8)	44 (9)
RAS inhibitors (%)	3832 (18)	1945 (18)	2811 (17)	1604 (21)	2801 (22)	4869 (17)	2426 (15)	68 (14)
Calcium channel blockers (%)	3095 (15)	1816 (17)	2589 (16)	1277 (16)	1908 (15)	3862 (14)	2104 (13)	73 (15)
Beta blockers (%)	3411 (16)	1673 (15)	2098 (13)	1185 (15)	2242 (17)	4256 (15)	2125 (13)	57 (11)
Digoxin (%)	2839 (14)	869 (8)	2117 (13)	608 (8)	1146 (9)	3231 (11)	1699 (11)	38 (8)
Thiazides (%)	3445 (17)	1929 (18)	2596 (16)	1286 (17)	2283 (18)	4715 (17)	2642 (16)	86 (17)
Aldosterone blockers (%)	1269 (6)	361 (3)	1224 (8)	259 (3)	546 (4)	1326 (5)	699 (4)	17 (3)
Aspirin (%)	6874 (33)	2850 (26)	4525 (28)	2187 (28)	4678 (36)	9746 (35)	5151 (32)	168 (34)
Clopidogrel (%)	355 (2)	86 (1)	152 (1)	100 (1)	286 (2)	370 (1)	186 (1)	2 (0.4)
Warfarin (%)	834 (4)	286 (3)	538 (3)	256 (3)	557 (4)	994 (4)	471 (3)	13 (3)

Baseline characteristics for different antipsychotic medication users. Numbers are presented as counts (%) for discrete variables and means (SD) for continuous variables. Characteristics were obtained at first day of treatment; thus groups are not exclusive. RAS indicates renin-angiotensin system.

time since first treatment initiation to account for time dependency in risks. In the second models, we tested for effect modification between the different treatment groups and prevalent dementia (diagnosis or use of dementia medications) and CVD (myocardial infarction, congestive heart failure, stroke, or peripheral vascular disease) by inclusion of an interaction term between the categorical treatment variable and CVD or dementia, respectively. Because these were highly significant, we created a categorical dummy variable stratifying use of medications by the prevalence of the different diseases. All analyses were done in SAS version 9.4 (SAS Institute). A 2-sided $P<0.05$ was considered statistically significant.

Results

We identified 91 774 persons (mean age 82±7 years, 35 474 [39%] were men). Numbers of those ever exposed to the different APs are presented in Table 3, along with the baseline characteristics for different exposure groups. The different exposure groups had comparable age, sex, and comorbidity burdens, although patients receiving levomepro-

Table 4. Numbers of Major Adverse Cardiovascular Events, Exposure Time, and Crude Incidence Rates for Different Antipsychotic Agents

|	Events/Person-Years	Unadjusted Incidence Rate (Per 100 Person-Years)
Associated risks for the first 30 days after initiation		
Risperidone	842/1765	47.7 (44.6 to 51.0)
Flupentixol	142/859	16.5 (14.0 to 19.5)
Chlorprothixen	132/460	28.7 (24.2 to 34.0)
Levomepromazine	1162/717	162 (153 to 172)
Haloperidol	1250/1340	93.3 (88.3 to 98.6)
Ziprasidone	3/30	10.1 (3.2 to 31.2)
Quetiapine	284/952	29.8 (26.5 to 33.5)
Olanzapine	428/1106	38.7 (35.2 to 42.5)
Multiple medications	143/142	101 (85 to 119)
Associated risks for the first 31 to 365 days after initiation		
Risperidone	2294/10 523	21.8 (20.9 to 22.7)
Flupentixol	397/3577	11.1 (10.1 to 12.2)
Chlorprothixen	168/1466	11.5 (9.9 to 13.3)
Levomepromazine	426/2179	19.5 (17.8 to 21.5)
Haloperidol	1471/3834	38.4 (36.5 to 40.4)
Ziprasidone	3/16	19.3 (6.2 to 59.9)
Quetiapine	925/6234	14.8 (13.9 to 15.8)
Olanzapine	1151/6645	17.3 (16.3 to 18.4)
Multiple medications	172/621	27.7 (23.9 to 32.2)
Associated risks for the first >365 days after initiation		
Risperidone	2516/16 231	15.5 (14.9 to 16.1)
Flupentixol	488/5676	5.6 (7.9 to 9.4)
Chlorprothixen	288/3350	8.6 (7.7 to 9.6)
Levomepromazine	515/4603	11.2 (10.3 to 12.2)
Haloperidol	602/2908	20.7 (19.1 to 22.4)
Ziprasidone	31/265	11.7 (8.2 to 16.6)
Quetiapine	1001/8995	11.1 (10.5 to 11.8)
Olanzapine	1635/13 032	12.5 (12.0 to 13.2)
Multiple medications	130/1086	12.0 (10.1 to 14.2)

Table 5. Numbers of Noncardiovascular Mortality, Exposure Time, and Crude Incidence Rates for Different Antipsychotic Agents

|	Events/Person-Years	Unadjusted Incidence Rate (Per 100 Person-Years)
Associated risks for the first 30 days after initiation		
Risperidone	630/1809	34.8 (32.2 to 37.7)
Flupentixol	99/867	11.4 (9.4 to 13.9)
Chlorprothixen	116/469	24.8 (20.6 to 29.7)
Levomepromazine	2052/750	274 (262 to 286)
Haloperidol	2365/1411	168 (161 to 175)
Ziprasidone	12/31	39.1 (22.2 to 68.8)
Quetiapine	281/982	28.6 (25.5 to 32.2)
Olanzapine	472/1136	41.6 (38.0 to 45.5)
Multiple medications	239/148	162 (143 to 184)
Associated risks for the first 31 to 365 days after initiation		
Risperidone	1900/10 949	17.4 (16.6 to 18.2)
Flupentixol	293/3671	8.0 (7.1 to 9.0)
Chlorprothixen	122/1506	8.1 (6.8 to 9.7)
Levomepromazine	580/2292	25.3 (23.3 to 27.4)
Haloperidol	2109/4254	49.6 (47.5 to 51.7)
Ziprasidone	3/18	16.8 (5.4 to 52.0)
Quetiapine	1009/6552	15.4 (14.5 to 16.4)
Olanzapine	1064/6896	15.4 (14.5 to 16.4)
Multiple medications	236/656	36.0 (31.7 to 40.9)
Associated risks for the first >365 days after initiation		
Risperidone	2704/17 604	15.4 (14.8 to 16.0)
Flupentixol	339/6098	5.6 (5.0 to 6.2)
Chlorprothixen	226/3605	6.3 (5.5 to 7.1)
Levomepromazine	481/4992	9.6 (8.8 to 10.5)
Haloperidol	568/3167	18.0 (16.5 to 19.5)
Ziprasidone	49/284	17.3 (13.0 to 22.8)
Quetiapine	1631/9916	16.4 (15.7 to 17.3)
Olanzapine	1850/14 275	13.0 (12.4 to 13.6)
Multiple medications	185/1165	15.9 (13.8 to 18.3)

mazine and haloperidol had higher prevalence of cancers (≈30% versus 10% for the other groups).

Total exposure time, MACE, and noncardiovascular mortality for each treatment group are given in Tables 4 and 5. Crude event rates were lowest for flupentixol and chlorprothixen compared with the other AP groups. As seen in the tables, for all agents, we observed a highly increased incidence rate of MACE and noncardiovascular mortality during the first month after initiation, with a subsequent decline for longer treatment durations. Associated adjusted IRRs were increased for treat-

ment with levomepromazine or haloperidol and treatment with multiple medications, whereas treatment with flupentixol, ziprasidone, chlorprothixen, or quetiapine was associated with a significantly lower IRR compared with treatment with risperidone, as shown in Figure 1 (MACE) and Figure 2 (noncardiovascular mortality). For longer treatment duration, levomepromazine and use of multiple medications were no longer associated with increased risks compared with risperidone monotherapy (Figures 1C and 2C). The risks associated with use of different antipsychotic medications differed for
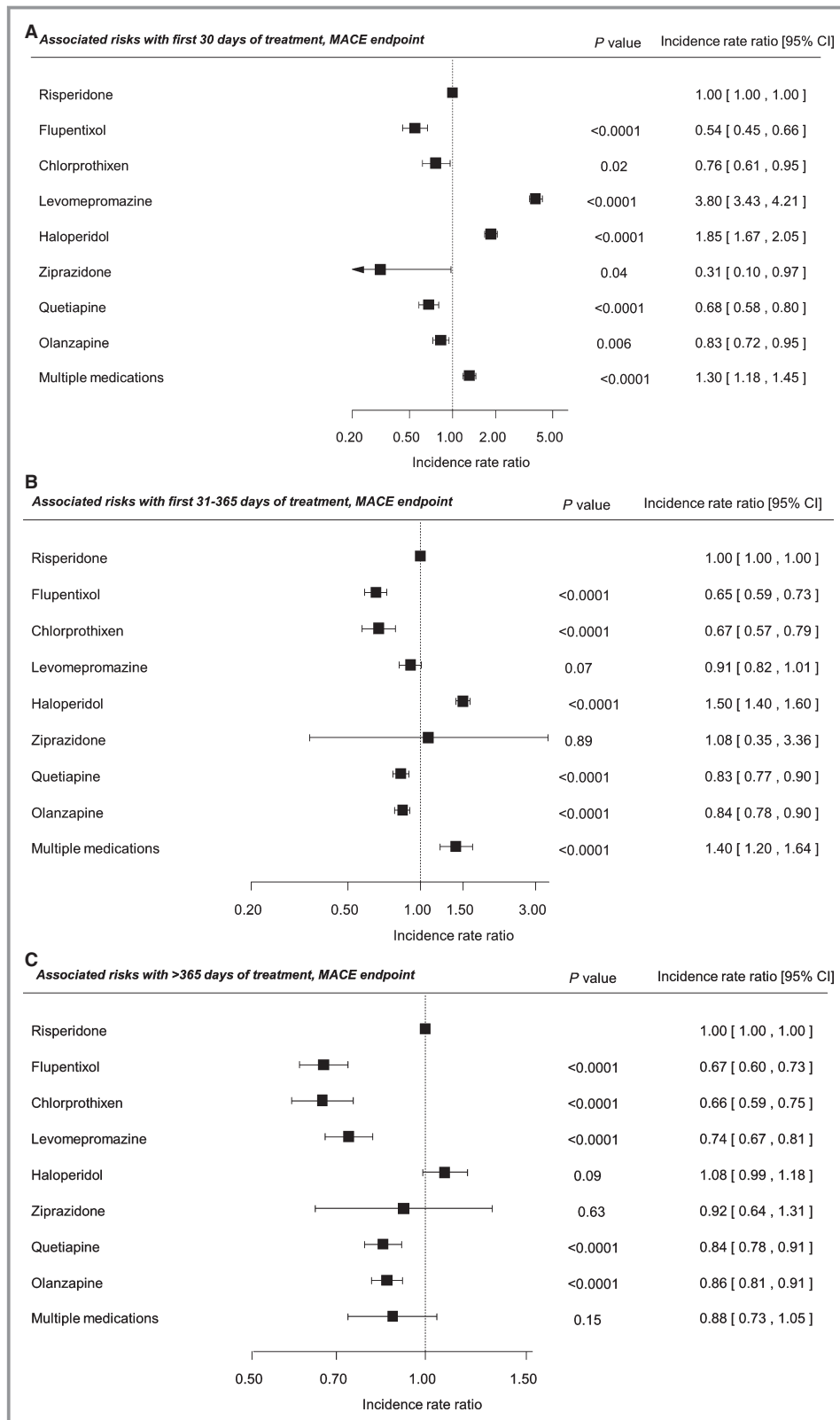
Figure 1. Multivariable-adjusted risks of MACE for different treatment regimens in different time periods after treatment initiation: (A) first 30 days, (B) 31 to 365 days, (C) >365 days. MACE indicates major adverse cardiovascular events.
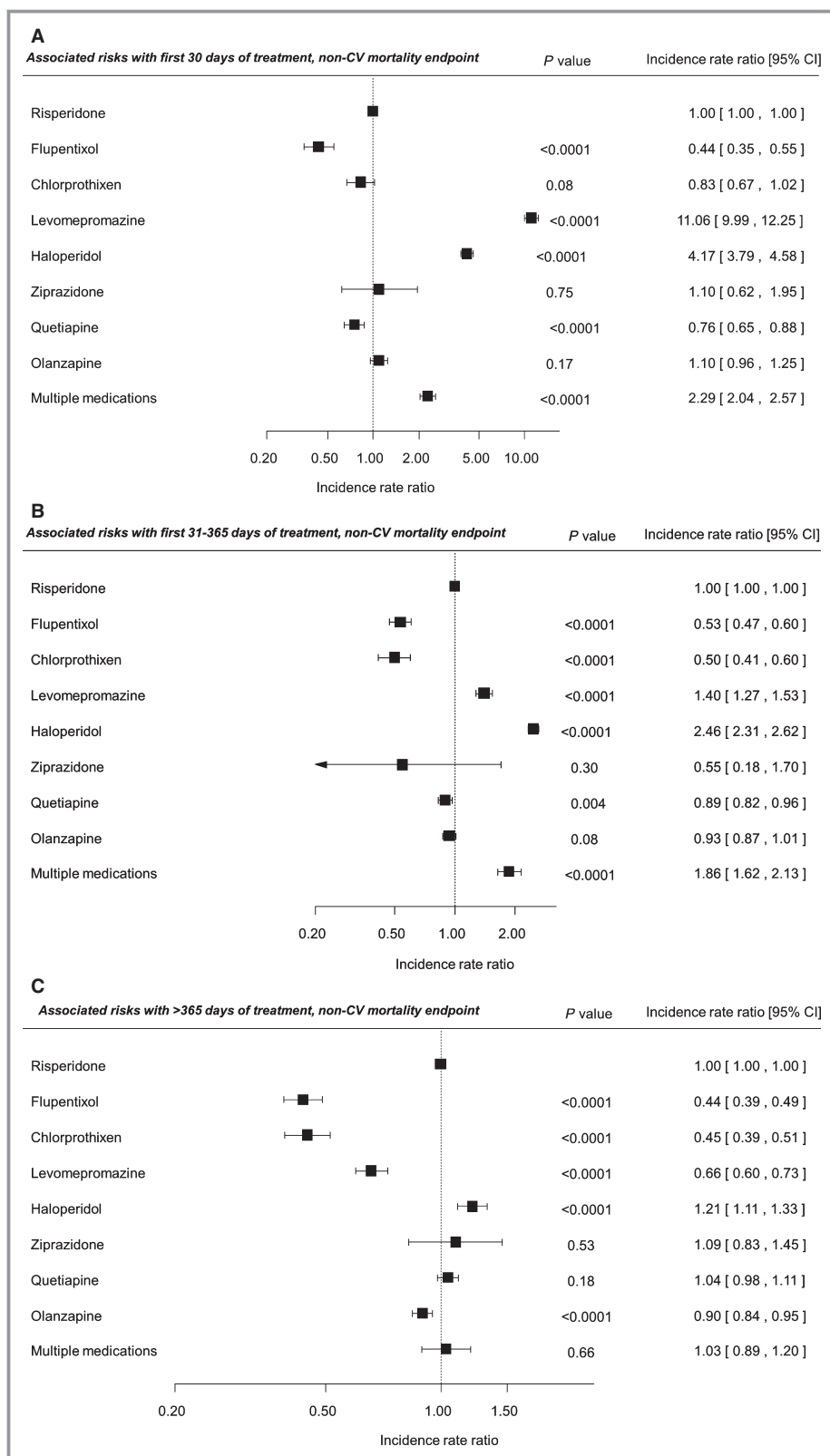
Figure 2. Multivariable-adjusted risks of noncardiovascular mortality for different treatment regimens in different time periods after treatment initiation: (A) first 30 days, (B) 31 to 365 days, (C) >365 days.
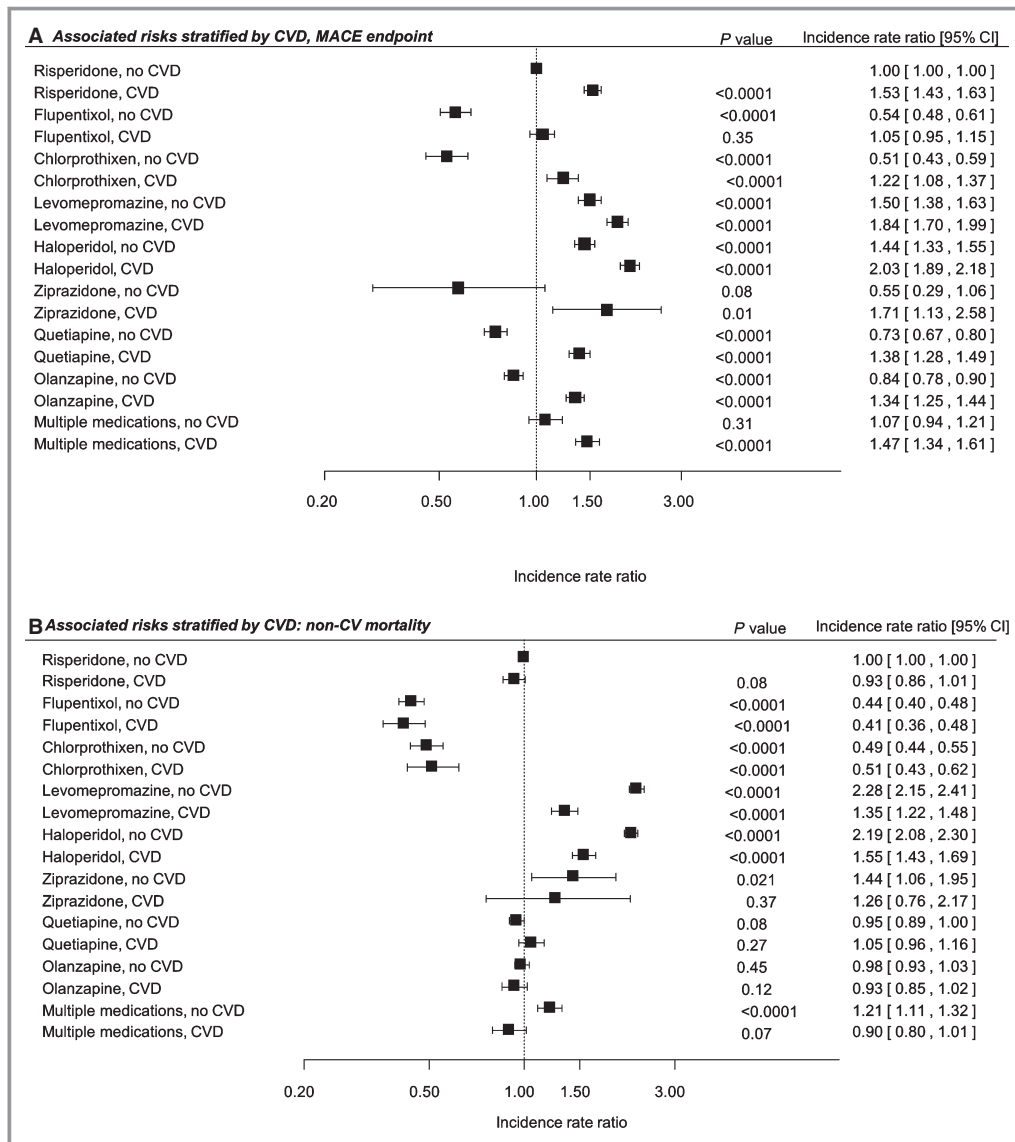
Figure 3. Multivariable-adjusted risks of (A) MACE and (B) noncardiovascular mortality stratified by prevalent CVD. CV indicates cardiovascular; CVD, cardiovascular disease; MACE, major adverse cardiovascular events.

patients with and without CVD and were greater among patients with established CVD (*P* for interaction between treatment group and CVD <0.00001) (Figure 3). Similarly, the risks were slightly higher among patients without established dementia compared with patients with dementia (*P* for interaction between treatment group and dementia <0.0001) (Figure 4).

Discussion

In this Danish study of all persons without prior use of APs who were aged ≥70 years, we investigated the association between different APs and risks of MACE and noncardiovascular mortality. In general, we observed that use of haloperidol or

levomepromazine and treatment with multiple medications were associated with similar or greater IRRs than use of risperidone, whereas treatment with flupentixol, ziprasidone, chlorprothixen, or quetiapine was associated with significantly lower IRRs compared with treatment with risperidone. The absolute event rates were highest shortly after treatment initiation and declined with long-term use.

Safety of APs in Elderly Persons

After findings of increased risk of cerebrovascular events associated with use of second-generation APs,[10,18,19] the US Food and Drug Administration (FDA) issued a warning in 2005
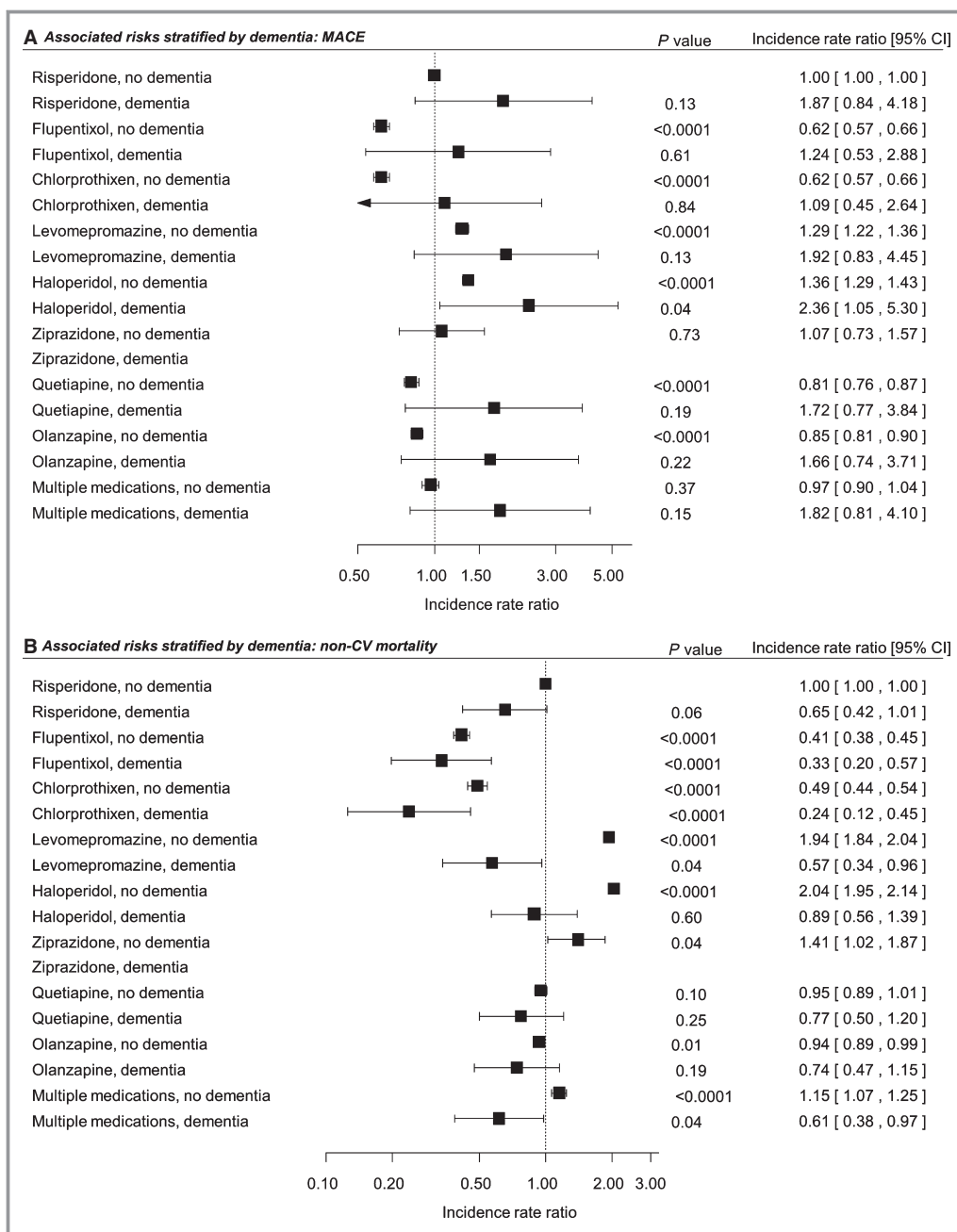
Figure 4. Multivariable-adjusted risks of (A) MACE and (B) noncardiovascular mortality stratified by prevalent dementia. CV indicates cardiovascular; MACE, major adverse cardiovascular events.

against use of second-generation APs in dementia.[18,20] In 2008, the FDA extended this warning to include use of first-generation APs in dementia.[21] Several studies have since demonstrated increased mortality with use of APs in dementia,[8,10,22] and some studies have shown increased mortality in elderly patients regardless of dementia status.[9,11,19] Previous studies have also suggested that the use of APs is associated with increased risk of myocardial infarction among older patients with treated dementia[13] and that exposure to APs may be a trigger for stroke.[11] Furthermore, a Cochrane review estimated the risk of

cerebrovascular events to be >3-fold higher in risperidone- versus placebo-treated elderly patients with dementia.[23] Our observations suggest that medications belonging to the second- and first-generation classes of APs may be associated with more or less comparable risk in elderly patients with or without dementia, although flupentixol, chlorprothixen, and quetiapine may be particularly associated with lower MACE and mortality rates than risperidone.

For all drugs, we found that the incidence rates of MACE and noncardiovascular mortality were highest during the first

30 days of treatment and declined with longer exposure time. This finding is consistent with the findings of other studies.[11,22,24] When elderly patients are prescribed APs, it may be due to neuropsychiatric symptoms in dementia or to delirium as part of a somatic disease that carries a high mortality risk. Because we were unable to accurately control for several diseases in our study, it cannot be excluded that the higher risks observed, especially among nondemented elderly people who were treated, may be partly due to confounding by indication. Delirium, however, is an acute disease with high short-term mortality; therefore, associations with long-term use may be less prone to confounding than the analyses of short-term use. Worth emphasizing in this context is that the relative risk of mortality with levomepromazine and haloperidol shortly after treatment initiation was higher than that observed for other APs. A very high proportion of patients using these drugs had diagnosed cancer; therefore, we cannot rule out that the IRR for the first period after treatment initiation was driven by confounding by indication. Even when excluding patients with a preexisting cancer, haloperidol has been shown to be associated with the highest risk of death among APs users in nursing homes.[24]

First- Versus Second-Generation APs

Second-generation APs have been promoted for having a low risk of extrapyramidal symptoms compared with first-generation APs. Previous studies suggest that both first- and second-generation APs can lower blood pressure, leading to increased risk of falls and to a varying extent to prolonged QT interval, which might lead to arrhythmia and death.[25–28] Another problem related to second-generation APs is adverse influence on glucose metabolism, diabetes, and blood lipid composition, leading to increased cardiovascular risks with long-term use.[29,30]

Several prior observational studies have compared the safety of first- versus second-generation APs[6,8,9,11,19,22,31–33] and generally have indicated that the risk of death and/or MACE when using second-generation APs is at least as high as that for first-generation APs.[21] At least 1 retrospective cohort study has suggested that in older adults with dementia, second- and first-generation APs were associated with comparable risks of ischemic stroke.[31] A larger retrospective cohort study in 2009 also suggested a comparable dose-related increased risk of sudden cardiac death for first- and second-generation APs.[12]

Strengths and Limitations of the Study

The main strength and novelty of this study is that we compared MACE and noncardiovascular mortality risk among individual APs across the first and second generations in a rather large group of patients aged ≥70 years. Moreover, because medical care is offered to all Danish citizens without copayment and because medications are reimbursed by the government, selection bias related to socioeconomic status and, for example, prior participation in the labor market is likely less pronounced compared with many other observational studies. Another strength of our study was the sample size, which allowed us to examine the effect of individual drugs, although it must be acknowledged that we might still have lacked power to firmly conclude anything about some of the individual drugs (particularly ziprasidone). Some limitations, however, merit consideration. We lacked data on several clinical variables including blood pressure, hematological profiles, electrocardiograms, and indication for treatment. All of these variables may have influenced clinicians' decisions of whether to prescribe a particular agent. Our data must be interpreted with great caution, bearing these limitations in mind.

Conclusion and Clinical Implications

There is an important but limited role for antipsychotic treatment of severe neuropsychiatric symptoms.[23] Our study demonstrated high incidence rates of MACE and noncardiovascular mortality associated with use of individual APs in elderly persons with or without dementia and with and without CVD. This underscores that APs should be used with caution in elderly patients, regardless of dementia status, at the lowest possible dose and for shortest possible time. A particular focus on risks and benefits is warranted among people with prevalent CVD because these patients seem to have the highest risks associated with APs. Our study further suggested some diversity in risks associated with individual APs but no systematic differences between first- and second-generation APs. Randomized placebo-controlled studies are warranted to confirm our findings and to identify the safest agents. Until then, the antipsychotic benefit in people with and without dementia must be considered against the risks of adverse events. Finally, in Denmark, restrictions on the use of APs are focused predominantly on people with dementia. Our study warrants a broader focus on elderly people in general.

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Disclosures

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