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Risk of Dementia During Antihypertensive Drug Therapy in the Elderly

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ABSTRACT

BACKGROUND Evidence exists that lowering high blood pressure reduces the risk of dementia. However, the generalizability of this evidence to old patients from the general population remains uncertain.

OBJECTIVES This study sought to evaluate the effect of antihypertensive drug treatment on the risk of dementia in a heterogeneous group of new users of antihypertensive drugs.

METHODS A nested case-control study was carried out by including the cohort of 215,547 patients from Lombardy, Italy, aged ≥65 years, who started taking antihypertensive drugs between 2009 and 2012. Cases were the 13,812 patients (age 77.5 ± 6.6 years; 40% men) who developed dementia or Alzheimer's disease during follow-up (up to 2019). For each case, 5 control subjects were selected to be matched for sex, age, and clinical status. Exposure to drug therapy was measured by the proportion of the follow-up covered by antihypertensive drugs. Conditional logistic regression was used to model the outcome risk associated with exposure to antihypertensive drugs.

RESULTS Exposure to treatment was inversely associated with the risk of dementia. Compared with patients with very low exposure, those with low, intermediate, and high exposure exhibited a 2% (95% CI: −4% to 7%), 12% (95% CI: 6%-17%), and 24% (95% CI: 19%-28%) risk reduction, respectively. This was also the case for very old (aged ≥85 years) and frail patients (ie, those characterized by a high mortality risk at 1 year).

CONCLUSIONS In the old fraction of the general population, antihypertensive drug treatment is associated with a lower risk of dementia. This was also the case in very old and frail patients. (J Am Coll Cardiol 2024;83:1194–1203)

Several epidemiologic and clinical studies have shown that hypertension in midlife or old age is associated with a greater risk of cognitive decline, vascular dementia, and Alzheimer's disease.[1,2] This risk can be explained by the detrimental effect of blood pressure (BP) elevation on the structure of the brain (white matter lesions, microbleeding episodes, and lacunar infarcts)[3,4] through remodeling of the small cerebral vessels,[5] although more direct brain damage caused by the increased arterial stiffness and enhanced blood flow pulsatility associated with hypertension is probably also involved.[6]

The protective effect of antihypertensive treatment on the risk of dementia has been uncertain for a long time. However, more recently, evidence that antihypertensive drug treatment lowers the risk of dementia has grown considerably. First, systolic BP reduction to <130 mm Hg has been shown to reduce the progression of white matter lesions.[7] Second, in a substudy of SPRINT (Systolic Blood Pressure Intervention Trial), a delay of mild cognitive impairments was observed with systolic BP reductions to <130 or 120 mm Hg compared with standard BP control.[8] Third, although the SPRINT data failed to show

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a delay of dementia with intensive BP reductions (presumably because of the early trial termination),[9] an individual-based meta-analysis of 5 randomized trials in patients aged >65 years showed that an antihypertensive treatment that lowered systolic BP by 10 mm Hg was accompanied by a 13% reduction in the risk of dementia over a follow-up of slightly >4 years.[10] This finding has led recent hypertension guidelines to include protection against dementia among the benefits of antihypertensive treatment.[11]

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However, several aspects of the now available trial-based evidence of the beneficial effect of antihypertensive treatment on the risk of dementia remain to be clarified. For example, the available trials and their meta-analysis are based on a relatively short follow-up, which is not ideal for the characterization of the effect of antihypertensive treatment on a disease that may have slow development and require more prolonged exposure to its causative factors.[12] Furthermore, the generalizability of trial findings to the general population may be problematic because of the demographic and clinical heterogeneity of the general population compared with the group recruited in trials,[13] in which patients with a greater risk of dementia (eg, very old patients, frail patients, patients with a high cardiovascular risk, and patients with a short survival) have a limited representation.[14-16]

The foregoing limitations can be addressed by analyzing the risk of dementia associated with antihypertensive treatment over a long follow-up and in a large and heterogeneous general population. This was the aim of the present study, which made use of the entire old population of Lombardy, Italy to investigate, over a follow-up of up to 11 years (average 7.3 years), whether in new users of antihypertensive drugs who were aged ≥65 years antihypertensive drug treatment was associated with a reduction in the risk of dementia. The effect of antihypertensive treatment on the risk of dementia was assessed by comparing different exposures to antihypertensive drugs as a result of different levels of adherence. Data were extended to the analysis of very old patients and patients with a different clinical status (including frail patients) on the basis of the lower or greater risk of early mortality.

METHODS

SETTING. The present study included data from the health care utilization databases of Lombardy, a region of Italy that accounts for approximately 16% of the country's population (approximately 10 million individuals, mostly White). In Italy, the whole population is covered by the National Health Service (NHS), which in each region relies on an automated system of databases collecting a variety of information, including demographic and administrative data of residents, up to 6 diagnoses at discharge from public or private hospitals (coded according to the International Classification of Diseases-9th Revision-Clinical Modification [ICD-CM-9] classification system), and health services or drugs (coded with the Anatomical Therapeutic Chemical [ATC] classification system) partially or totally reimbursed by the NHS on prescription by physicians and delivered to the patients by community and hospital pharmacies. The databases also include the date when a patient was exempted from the copayment of drugs and other health services for their disease, the cost of which was then covered entirely by the NHS. Because a unique identification code was used for all databases, their linkage provided information on the complete care pathway supplied to residents for years. To preserve privacy, each individual identification code was automatically deidentified, the inverse process being allowed only to the Regional Health Authority on request from judicial authorities. A detailed description of the health care utilization databases of the Lombardy region in the cardiovascular field is available in previous studies.[16,17]

According to the rules issued by the Italian Medicines Agency,[18] retrospective studies using administrative databases do not require protocol approval by ethics committees.

COHORT SELECTION AND FOLLOW-UP. The target population included Lombardy residents aged 65 years or older. Of these, residents who started therapy with antihypertensive drugs between 2009 and 2012 were identified, and the date of the first prescription during this period was defined as the index date. Excluded were patients who: 1) were not resident in Lombardy for at least 5 years before the index date; 2) had received antihypertensive drug prescriptions within 5 years before the index date; and 3) already had dementia or Alzheimer's disease on the basis of a hospital diagnosis, prescriptions for antidementia drugs (see later), or exemption of copayment for drugs or health services related to dementia or Alzheimer's disease within the 5 years before the index date. The remaining patients were included in the final cohort, whose members accumulated person-years of follow-up from the index

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

NHS = National Health Service

PDC = proportion of days covered

date until the earliest date among the onset of dementia or Alzheimer's disease, death, emigration, or December 31, 2019.

SELECTION OF CASES AND CONTROL SUBJECTS. A case-control study was nested into the cohort of antihypertensive drug users. Cases were members of the cohort who experienced the outcome during the follow-up. The outcome of interest was the diagnosis of dementia or Alzheimer's disease, whose date of onset was defined as the date corresponding to the first event among the following: 1) hospitalization with a diagnosis of dementia or Alzheimer's disease; 2) prescription of antidementia drugs (galantamine, rivastigmine, donepezil, and memantine); and 3) exemption from the copayment for drugs and other health services for dementia or Alzheimer's disease.

For each case patient, control subjects were identified from the cohort as individuals of the same sex, age at cohort entry (±3 years), clinical status (see later), and index date (±30 days) of the corresponding case patient. In addition, control subjects had to be at risk of the outcome when the matched case had it. For each case patient, up to 5 control subjects were randomly selected.

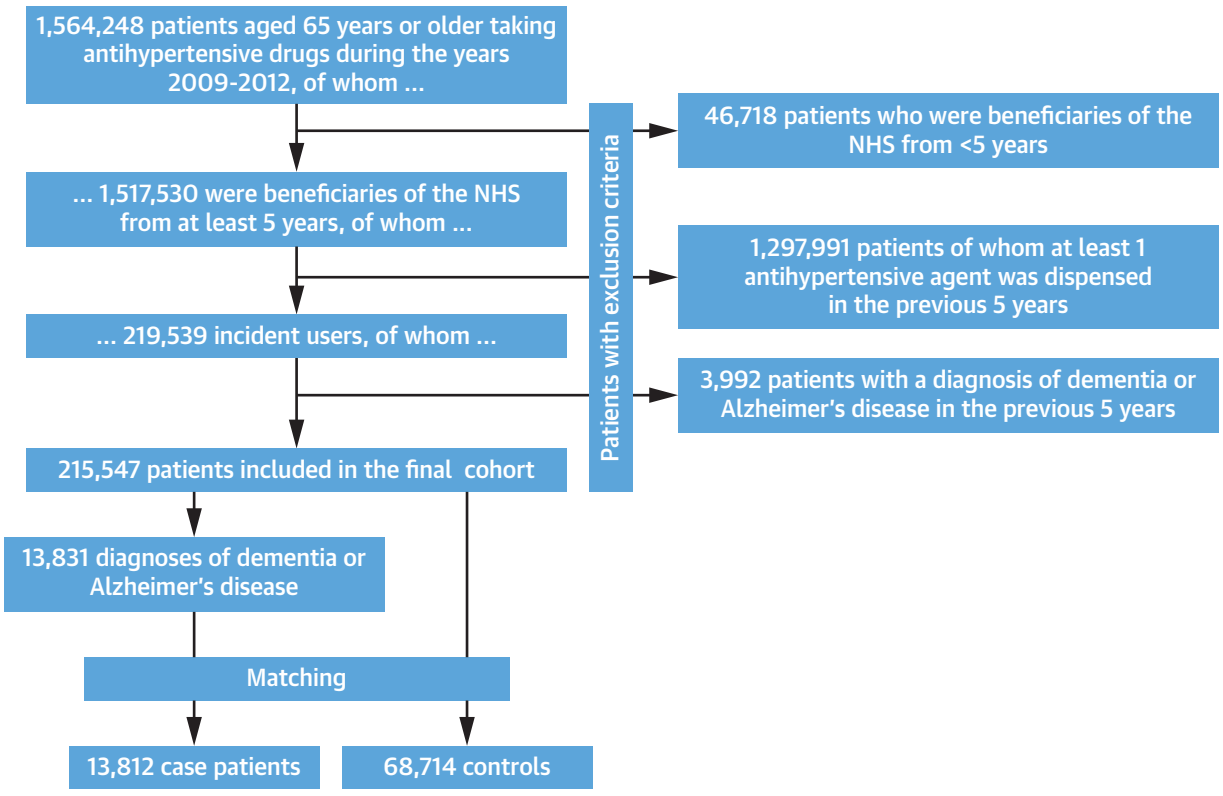
EXPOSURE TO ANTIHYPERTENSIVE DRUG THERAPY. For each patient included in the cohort, all antihypertensive drugs dispensed during the follow-up were identified. The period covered by a prescription was calculated by dividing the total amount of the drug prescribed by the defined daily dose. For overlapping prescriptions, the patient was assumed to have taken all the drugs contained in the first prescription before starting the second prescription. Adherence to treatment, and thus exposure to antihypertensive drugs, was assessed by the ratio between the number of days in which the antihypertensive drug therapy was available and the days of follow-up, a measure defined as the "proportion of days covered" (PDC) by prescriptions.[19] Because information on drug therapies dispensed during hospitalizations was not available, the antihypertensive drug therapy was assumed to be prescribed during a hospitalization period.[20] Four categories of adherence or exposure to antihypertensive drugs were considered: very low (PDC ≤25%), low (26%-50%), intermediate (51%-75%), and high (>75%).

COVARIATES. Baseline characteristics included sex, age, use of other drugs (statins, antidiabetic agents, antithrombotic drugs, antiarrhythmic agents, and antidepressant drugs, digitalis, nitrates, nonsteroidal anti-inflammatory drugs, and drugs for pulmonary diseases), and comorbidities (heart failure, myocardial infarction, stroke, diabetes, respiratory disease, kidney disease, and cancer). Comedications and comorbidities were identified from out-of-hospital prescriptions as well as from diagnoses at discharge from any hospitalization within the 5 years before the index date. In addition, the clinical status was assessed by the Multisource Comorbidity Score, a prognostic score that has been shown to predict all-cause death of Italian people more accurately than other widely used scores.[21] Four categories of clinical status were considered: good (score = 0), intermediate (score ≤1 to ≤4), poor (score ≤5 to ≤14), and very poor (score ≥15). Because in a previous study old hypertensive patients with very poor clinical status were associated with very low survival,[16] this category was regarded as representing frail individuals.

DATA ANALYSIS. The standardized mean differences were used to compare differences between cases and control subjects. Standardized mean differences <0.10 were considered negligible.[22] Conditional logistic regression models were fitted to estimate the OR (and its 95% CI) of dementia or Alzheimer's disease in relation to the categories of drug exposure, by using the lowest category (PDC ≤25%) as the reference. Adjustments were made for the previously reported covariates (ie, use of other drugs, comorbidities). No demographic adjustment was necessary because of the age and sex matching between cases and control subjects. The analyses were repeated after stratification of patients for sex, age, and clinical status.

SENSITIVITY ANALYSES. To verify the robustness of our findings, 5 additional analyses were performed. First, to avoid the inclusion of individuals for which antihypertensive drug treatment may have been occasional and not really needed, analyses were repeated by excluding patients who did not receive 2 antihypertensive drug prescriptions during the 6 months after the index date. Second, analyses were repeated by modifying the definition of exposure to antihypertensive drug therapy. Namely, exposure was measured by the cumulative number of days during which the drug was available and classified into 4 categories: <6 months, 6 months to 1 year, 1 to 2 years, and >2 years. Third, we investigated the association between adherence or exposure to antihypertensive drug therapy and outcomes that were causally unrelated to antihypertensive drugs.[23] The unrelated outcomes were the composite of hospital admissions for malignant melanoma, burns, injury,

FIGURE 1 Flowchart of Inclusion and Exclusion Criteria



The inclusion and exclusion criteria used to select the final cohort. NHS = National Health Service.

traumatic complications, and railway, motor vehicle, water, or air transport accidents. We thought that a reduction of these events with increased drug adherence or exposure would raise the possibility that a lower risk of dementia with better drug adherence or exposure did not reflect a protective effect of antihypertensive drugs but rather a health-seeking behavior of the adherent patients (ie, the so-called healthy user bias). Fourth, outcomes were decomposed and considered separately (ie, dementia or Alzheimer's disease). Finally, because cognitive impairment affects the patient's ability to manage medications,[24] onset of the disease before its detection and recording could affect exposure to drug therapy and lead to reverse causation (ie, low exposure to antihypertensive drugs caused by dementia rather than the reverse). This issue was addressed by reanalyzing the data after the exclusion of the last year from the evaluation of the overall drug exposure.

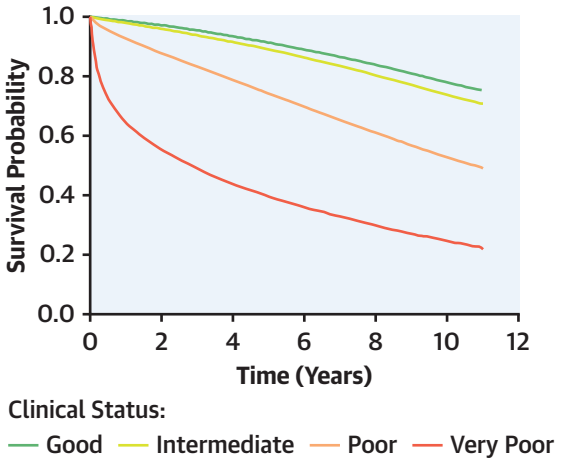
All analyses were performed using SAS software version 9.4 (SAS Institute). The random selection of control subjects was performed using the PROC SURVEYSELECT.

RESULTS

PATIENTS. Among the 1,564,248 patients aged 65 years or older who were treated with antihypertensive drugs between 2009 and 2012, 215,547 subjects met the inclusion criteria and were included in the study (Figure 1). Approximately 80% of patients started treatment with 1 drug, and the most frequent monotherapy was by far a renin-angiotensin system blocker, whereas the most frequent 2-drug combination was a renin-angiotensin system blocker and a diuretic agent (Supplemental Table 1).

Among the whole cohort, the death incidence increased progressively from the group of patients

FIGURE 2 Survival Probabilities in Old Patients According to Their Clinical Status



The clinical status was assessed by the Multisource Comorbidity Score (MCS) according to the hospital admission and the drugs prescribed before the index admission. Four categories of clinical status were considered: good (score = 0), intermediate (score ≤1 to ≤4), poor (score ≤5 to ≤14), and very poor (score ≥15). The 11-year survival decreased from 75% in the group of patients with good clinical status to 22% in the group of patients with very poor clinical status.

with good clinical status to the group of patients with very poor clinical status (Figure 2). The cohort subjects accumulated 1,566,520 person-years of observation and generated 13,831 diagnoses of dementia or Alzheimer's disease over an average follow-up of 7.3 years. The incidence of dementia showed a progressive increase with age, whereas the incidence of Alzheimer's disease showed the highest incidence among patients aged 80 to 84 years (Figure 3).

Among the 13,831 case patients, 13,812 were matched with 68,714 control subjects. The characteristics of cases and control subjects are shown in Table 1. At the index date, 2 in 5 patients were men, 1 in 6 patients was aged ≥85 years, and 1 in 3 patients had a poor or very poor clinical status. More case patients than control subjects were receiving treatment with antidepressant drugs or had been hospitalized for stroke.

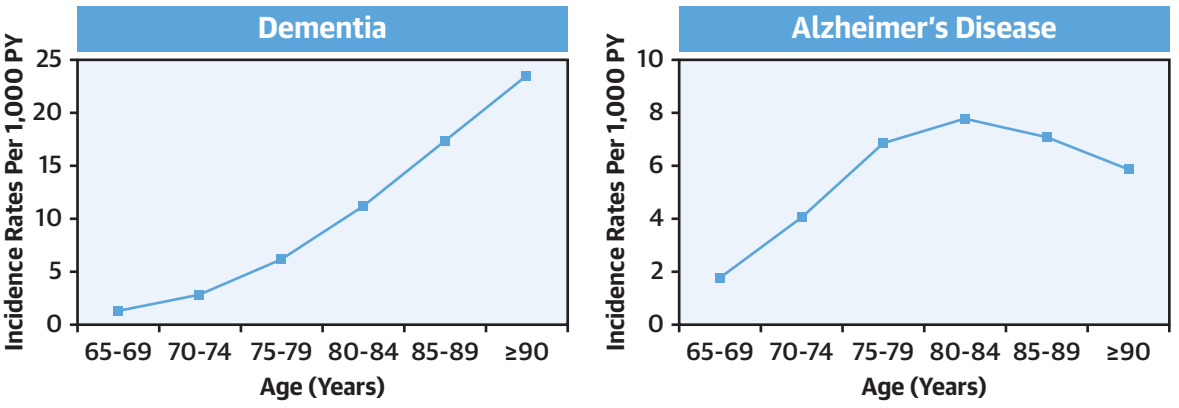
EXPOSURE TO ANTIHYPERTENSIVE DRUG THERAPY AND RISK OF DEMENTIA OR ALZHEIMER'S DISEASE. As shown in the Central Illustration in the whole cohort, the risk of dementia or Alzheimer's disease exhibited a significant inverse association with the exposure to antihypertensive drug treatment. Compared with patients with very low exposure, those with low, intermediate, and high exposure showed a 2% (95% CI: −4% to 7%), 12% (95% CI: 6%-17%), and 24% (95% CI: 19%-28%) risk reduction, respectively. This was the case in each stratum of sex, age, and clinical status (Central Illustration, Figure 4, Supplemental Figure 1), although the risk reduction associated with the highest level of exposure became lower among the oldest patients (ie, it was −32% among patients aged 65 to 74 years and −17% among patients aged 85 years or older; P interaction = 0.012).

SENSITIVITY ANALYSES. The results of the sensitivity analyses are reported in Figure 5 and Supplemental Table 2. Figure 5 shows that the effect of exposure to antihypertensive drugs on the risk of dementia was substantially similar to the effect of exposure to antihypertensive drugs on the risk of Alzheimer's disease. Supplemental Table 2 shows that the main findings did not change substantially by excluding occasional users, modifying the definition of exposure, or removing the last year in the assessment of drug exposure. Furthermore, exposure to antihypertensive drugs did not bear any association with the outcomes that have no relationship with hypertension and antihypertensive drug treatment.

DISCUSSION

This large real-world investigation that was based on more than 200,000 patients and almost 14,000 events shows that, in old hypertensive patients, greater adherence, and thus exposure, to antihypertensive drug treatment was associated with a lower risk of dementia or Alzheimer's disease than lower exposure to antihypertensive drug treatment. It further shows that: 1) the treatment-related benefit was not marginal because, compared with patients with the lowest exposure (antihypertensive drugs available for ≤25% of the follow-up time), those with the highest exposure (antihypertensive drugs available for >75% of the follow-up time) exhibited a 24% reduction in the risk of dementia or Alzheimer's disease; 2) the association between exposure and a reduced risk of dementia or Alzheimer's disease was observed regardless of the patient's sex and baseline clinical status, including patients characterized by a very high risk of early mortality (ie, 36% at 1 year); and 3) the favorable effect of exposure to antihypertensive treatment in delaying the onset of dementia extended to a considerably more advanced age than that reported by previous studies[10,25,26]

FIGURE 3 Incidence Rates of Dementia and Alzheimer's Disease According to Age



The plots show the incidence of dementia and Alzheimer's disease according to age. The incidence of dementia showed a progressive increase with age, whereas the incidence of Alzheimer's disease showed the highest incidence among patients aged 80 to 84 years. PY = person-years.

(ie, to patients aged 85 years or older [mean: 88 years]). Taken together, these findings confirm and extend the available evidence that antihypertensive drug treatment has a protective effect on the progression of cognitive dysfunction that leads to dementia.[10,25,26] According to the large body of evidence provided by the present data, this protective effect is documentable in the general old population and can be extended to a wide range of demographic and clinical conditions.

Several other findings of our study deserve to be mentioned. First, although the use of antihypertensive drugs was associated with a reduced risk of dementia in all age groups, the reduction in the risk of dementia was less pronounced in patients aged 85 years or older than in those aged 65 to 74 years. This observation, which has also been made in previous studies,[10,26] does not have an evidence-based explanation, although greater irreversibility of the brain damage and/or greater inability to reach the target BP values that maximize the protective effects of treatment at very old ages may be plausible factors. With regard to our data, however, another possible explanation is that the quantification of drug exposure may be less accurate in patients aged 85 years or older who may use antihypertensive drugs at lower doses, thus making the duration of a canister longer and the level of drug exposure higher than that calculated using the defined daily doses. This misclassification may have reduced the outcome difference between patient categories with low and high exposure, thereby underestimating the benefit of drug treatment among patients aged 85 years or older. Second, in line with a previous study that found a lower risk of dementia after 1.5 years of drug treatment,[27] in our study a significant reduction in the risk of dementia was observed only after 2 years of therapy, thus confirming that the benefit of antihypertensive treatment takes some time before becoming clinically manifest and that studies on the relationship between BP-lowering treatment and dementia need the observations to cover an adequate follow-up. Third, the protective effects of antihypertensive treatment were similarly visible when patients with a diagnosis of Alzheimer's disease and those with a diagnosis of other dementias were separately analyzed. This finding is in line with those of previous studies that showed that hypertension increases the risk of both Alzheimer's disease and other dementias,[28] both of which are beneficially affected by antihypertensive treatment. The most likely explanation is that in either condition neural damage of vascular origin is common[29] (that is, the prevalence of mixed vascular and Alzheimer's disease is high[30]). Fourth, the greater risk of dementia in patients with the lowest drug adherence or exposure could reflect a generalized impairment of the patient's clinical status that led to the inability to receive drug dispensation. However, this is unlikely because the relationship between exposure to antihypertensive drug treatment and dementia was detected in different old age strata

TABLE 1 Characteristics of the Case Patients and the Corresponding Control Subjects

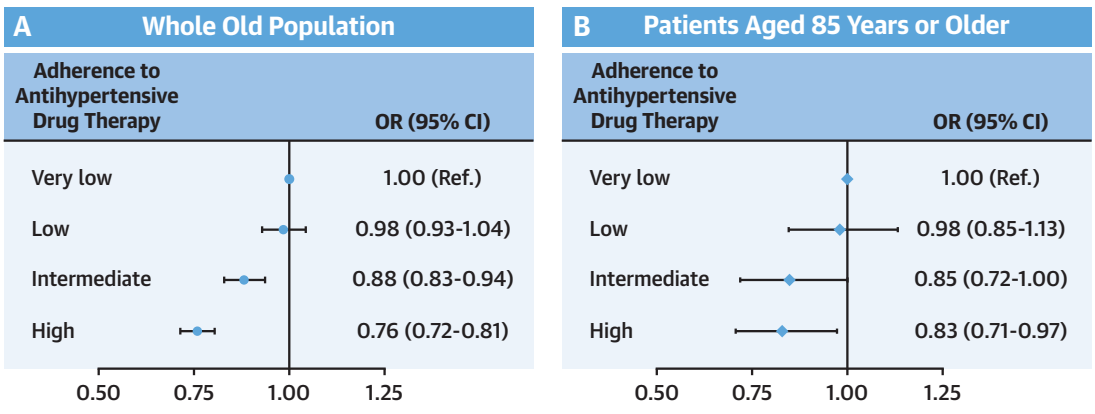
	Case Patients (n = 13,812)	Control Subjects (n = 68,714)	Standardized Differences
Baseline			
Men	5,580 (40.4)	27,727 (40.4)	MV
Age, y			MV
65-74	4,857 (35.2)	24,285 (35.3)	
75-84	6,833 (49.5)	34,134 (49.7)	
≥85	2,122 (15.3)	10,295 (15.0)	
Clinical status[a]			MV
Good	3,565 (25.8)	17,774 (25.9)	
Intermediate	5,166 (37.4)	25,770 (37.5)	
Poor	4,149 (30.0)	20,694 (30.1)	
Very poor	932 (6.8)	4,476 (6.5)	
Other drugs			
Lipid-lowering drugs	2,263 (16.4)	11,065 (16.1)	0.008
Antidiabetic drugs	1,422 (10.3)	5,932 (8.6)	0.057
Antithrombotic drugs	4,906 (35.5)	21,666 (31.5)	0.085
Digitalis	143 (1.0)	788 (1.2)	−0.011
Nitrates	253 (1.8)	1,220 (1.8)	0.004
Antiarrhythmic drugs	404 (2.9)	2,258 (3.3)	−0.021
NSAIDs	6,168 (44.7)	31,713 (46.2)	−0.030
Antigout drugs	307 (2.2)	1,768 (2.6)	−0.023
Drugs for pulmonary diseases	1,910 (13.8)	10,312 (15.0)	−0.034
Antidepressant drugs	2,984 (21.6)	8,190 (11.9)	0.262
Previous hospitalizations			
Stroke	1,274 (9.2)	4,140 (6.0)	0.121
Heart failure	427 (3.1)	2,095 (3.1)	0.002
Myocardial infarction	734 (5.3)	3,891 (5.7)	−0.015
Diabetes	617 (4.5)	2,229 (3.2)	0.064
Respiratory disease	1,126 (8.2)	4,729 (6.9)	0.048
Kidney disease	161 (1.2)	656 (1.0)	0.021
Cancer	1,310 (9.5)	8,214 (12.0)	−0.080
During follow-up			
Exposure to antihypertensive drugs			0.068
Very low	4,769 (34.5)	22,351 (32.5)	
Low	2,416 (17.5)	10,995 (16.0)	
Intermediate	2,408 (17.4)	11,886 (17.3)	
High	4,219 (30.6)	23,482 (34.2)	

Values are n (%) and standardized differences. [a]4 categories were considered for clinical status according to the Multisource Comorbidity Score: good (0), intermediate (1≤ to ≤4), poor (5≤ to ≤14), and very poor (≥15).
MV = matching variable; NSAID = nonsteroidal anti-inflammatory drug.

as well as in a wide range of clinical conditions, not only the most compromised ones. Fifth, high drug adherence or exposure may reflect overall "health-seeking behavior" (better adherence to healthy lifestyle advice, better use of medical facilities, better precautions against diseases in general), which may account for the antidementia effect. However, according to one of our sensitivity analyses, exposure to antihypertensive drugs did not have any effect on diseases or conditions unrelated to antihypertensive treatment, and this makes it likely that greater use of antihypertensive drugs in people more adherent or more exposed to antihypertensive drugs was responsible for the beneficial effects on dementia. Finally, our study provides collateral findings of clinical interest such as the overall low adherence to antihypertensive drug treatment in clinical practice.[16,31] For example, in the control group the proportion of patients who had antihypertensive drugs available for use in more than 75% of the follow-up time was only 34%, whereas in patients who developed dementia it was 31%. Low adherence to antihypertensive drug treatment is known to: 1) be a worldwide phenomenon that accounts for the generalized poor rate of BP control in hypertensive persons as well as for the persisting importance of hypertension as cause of death and burden of disease[32]; and 2) depend on a large number of factors[32] whose investigation was not part of the design of our study. It is also of interest that, in Lombardy hypertensive patients aged 65 years or more, dementia showed a progressive steep increase,[33] and this was also the case for the Alzheimer's disease, although with a peak between 80 and 84 years and then a decline.[34] Finally, although in Italy hypertension accounts for more than 70% of their use,[35] antihypertensive drugs are also prescribed for coronary heart disease, heart failure, and chronic kidney disease, in persons with but also without hypertension. Thus, our findings may reflect an antidementia effect of BP-lowering agents in a larger range of diseases than hypertension.

Our study has several strengths. First, the investigation was based on a large and unselected population, which was made possible because the health care utilization databases of Lombardy involve virtually all citizens.[17] Second, huge numbers of cases of dementia were identified, which allowed data analysis to be adequately performed in several important subgroups, such as very old patients, patients with different clinical statuses, and patients characterized by a very high risk of early mortality. Third, the drug-dispensing database provided accurate data because pharmacists are required to report prescriptions in detail to obtain reimbursement, and incorrect reports have legal consequences.[17] In addition, because under the NHS antihypertensive drugs are given free or almost free of charge, only 6% of the drugs used for cardiovascular diseases are outside the NHS.[36] Fourth, the adoption of the "user-only" design (ie, comparison among patients with the same indication at baseline but with a different level of exposure to the drug of interest), as well as of the

CENTRAL ILLUSTRATION **Association Between Dementia or Alzheimer's Disease and Antihypertensive Drugs**



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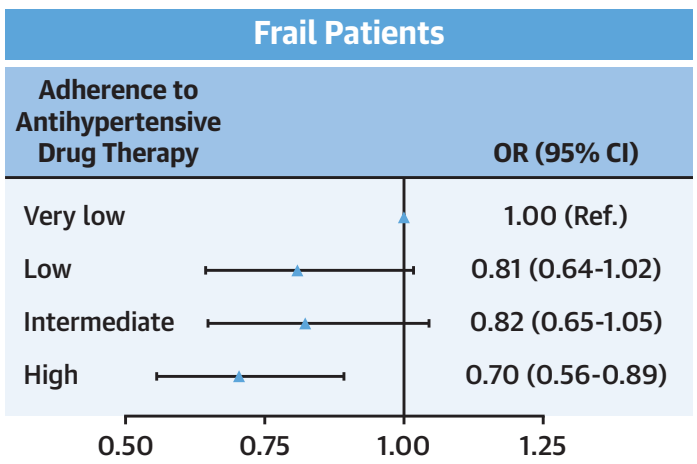
Conditional logistic regression models were fitted to estimate the OR and its 95% CI of dementia or Alzheimer's disease in relation to the drug exposure categories, by using the lowest category (proportion of days covered by drug ≤25%) as the reference, in (A) the whole population and among (B) patients aged 85 years or older. Covariates included in the model were the use of other drugs (lipid-lowering drugs, antidiabetic drugs, antithrombotic drugs, digitalis, nitrates, antiarrhythmic drugs, nonsteroidal anti-inflammatory drugs, antigout drugs, drugs for pulmonary diseases, antidepressant drugs) and comorbidities (heart failure, myocardial infarction, stroke, diabetes, respiratory disease, kidney disease, and cancer). Compared with patients with very low exposure, those with low, intermediate, and high exposure showed a 2% (95% CI: −4% to 7%), 12% (6%-17%), and 24% (19%-28%) risk reduction, respectively.

"new-user" approach (ie, prevalent users were excluded from the analysis), reduced the potential for selection bias and confounding.[37,38] Finally, the robustness of our main findings was confirmed by several sensitivity analyses.

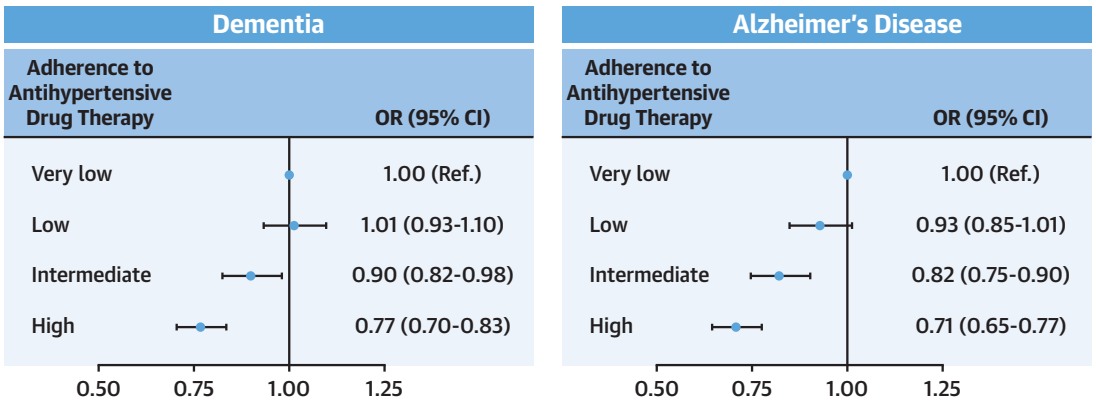
STUDY LIMITATIONS. First, adherence or exposure to antihypertensive drugs was derived from drug dispensing (ie, a widely used method in population studies[19]), which requires, however, the assumption that drug prescription reflects drug consumption by the patient.[17] This may not have been the case in all patients. Second, dementia could have been present before its diagnostic discovery, thus affecting drug adherence or exposure and causing outcome misclassification. However, our findings were not affected by excluding from analysis the last year of follow-up, which makes this possibility unlikely. Third, the so-called new-users design is a widely adopted approach for reducing the potential for confounding in observational studies.[38] However, this design requires the exclusion of a large fraction of the patient population, in the present case patients with long-standing antihypertensive drug treatment. This issue deserves future investigations. Fourth, our database does not include information on BP (as well as on other clinical variables). It is thus impossible for our paper to discuss at which BP levels the antidementia effect is more prominent. Finally, some studies have shown greater protection against dementia by some antihypertensive drugs,[39,40] an issue that was not addressed by our study.

FIGURE 4 **Association Between Dementia or Alzheimer's Disease and Antihypertensive Drugs**



Conditional logistic regression model was fitted to estimate the OR and its 95% CI of dementia or Alzheimer's disease in relation to the drug exposure categories, by using the lowest category (proportion of days covered by drug ≤25%) as the reference, in frail patients.

FIGURE 5 Association Between Outcomes (Dementia and Alzheimer's Disease) and Antihypertensive Drugs



Two conditional logistic regression models were fitted to estimate the OR and its 95% CI, of (left) dementia and (right) Alzheimer's disease in relation to the drug exposure categories. Covariates included in the model were use of other drugs (lipid-lowering drugs, antidiabetic drugs, antithrombotic drugs, digitalis, nitrates, antiarrhythmic drugs, nonsteroidal anti-inflammatory drugs, antigout drugs, drugs for pulmonary diseases, antidepressant drugs) and comorbidities (heart failure, myocardial infarction, stroke, diabetes, respiratory disease, kidney disease, and cancer). The effect of drug exposure on the risk of dementia was substantially similar to the effect of drug exposure on the risk of Alzheimer's disease.

CONCLUSIONS

Exposure to antihypertensive drug treatment reduced the risk of dementia in old hypertensive patients. This was the case regardless of the old age strata, sex, and patients' baseline clinical condition, and the effect extended to an age above 85 years and to clinical conditions characterized by a very high risk of early mortality.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Adherence to antihypertensive drug therapy reduces the risk of dementia even in very old patients at risk of mortality.

TRANSLATIONAL OUTLOOK: More studies are needed to evaluate differences in antihypertensive drugs in preventing or delaying cognitive impairment.

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KEY WORDS Alzheimer's disease, antihypertensive drugs, dementia, old patients, population-based cohort study

APPENDIX For supplemental tables and a figure, please see the online version of this paper.

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