Occurrence and Progression of Dementia in a Community Population Aged 75 Years and Older

Relationship of Antihypertensive Medication Use

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Objective: To examine whether antihypertensive medication use can affect the occurrence and progression of dementia.

Subjects and Methods: In a community cohort of 1810 persons aged 75 years and older, 225 prevalent cases of dementia were detected. Among the 1301 persons without dementia, 224 incident cases of dementia were identified during an average period of 3 years. Among the 225 prevalent cases of dementia, 79 were suitable for the analysis of cognitive decline. Information on drug use was collected for the 2 weeks preceding the baseline interview.

Results: Subjects taking antihypertensive medication (n = 651, 83.9% of whom took diuretics) had a lower prevalence of dementia than those not taking antihypertensive medication (P < .001). Subjects without dementia who were taking antihypertensive medication at baseline (n = 584) had a reduced incidence of dementia (adjusted relative risk, 0.7; 95% confidence interval, 0.6-1.0; P = .03). Furthermore, subjects taking diuretics (n = 484) had an adjusted relative risk of 0.7 (95% confidence interval, 0.5-1.0; P = .02) for all dementia, and subjects taking diuretic monotherapy (n = 345) had an adjusted relative risk of 0.6 (95% confidence interval, 0.4-0.9; P = .006). The use of other antihypertensive medication (calcium antagonists or β-blockers), however, was related to a reduced risk of Alzheimer disease (adjusted relative risk, 0.6; 95% confidence interval, 0.3-1.2) only in the subpopulation with a higher baseline blood pressure (n = 458). Patients with dementia at baseline who were not taking diuretics had a 2-fold faster rate of decline in the score on the Mini-Mental State Examination than those taking diuretics.

Conclusion: The use of diuretics may protect against dementia in elderly persons.

Arch Neurol. 1999;56:991-996

I F DEMENTIA with a vascular component comprises nearly half of all cases of dementia in persons aged 85 years and older, and a substantial portion of cases of dementia may be prevented in this age group. Among many vascular factors or diseases that may be related to dementia, hypertension has been suggested as the most important vascular risk factor. In fact, hypertension may not only increase the risk of vascular dementia (VaD) by causing ischemic stroke and other cerebrovascular events or lesions, it may also be involved in the pathogenesis of Alzheimer disease (AD). This hypothesis is supported by a recent study showing that brain infarction increases the clinical expression of AD and a report indicating that cerebral infarction in AD is associated with severe amyloid angiopathy and hypertension. Despite these findings, no data are available regarding the possible effects of antihypertensive medication use in decreasing the risk of dementia in the general population, although several clinical trials have examined the effects of these drugs on cognition.

We examine whether antihypertensive medication use affects the occurrence of dementia and cognitive decline in patients with dementia in a community-based cohort aged 75 years and older.

RESULTS

The mean age at baseline of 1810 participants in the Kungsholmen Project was 82.5 years (range, 75-101 years), 76.1% were women, and 53.0% had less than 8 years of education (only 2 persons had less than 4 years of education). The mean (SD) systolic and diastolic blood pressures were 154 (22) and 81 (11) mm Hg, respectively. The prevalence of heart disease, stroke, and dementia was 17.6%, 8.5%, and 12.4%, respectively. The baseline mean MMSE score was 24.5 (6.2).
SUBJECTS AND METHODS

STUDY SUBJECTS

Data for this study came from the baseline and first follow-up examinations of the Kungsholmen Project,17 which is a longitudinal study of aging and dementia. The study was approved by the ethics committee of the Karolinska Institute, Stockholm, Sweden. The study population included all inhabitants of the Kungsholmen district of Stockholm who on October 1, 1987, were aged 75 years or older. At baseline, 1810 subjects were administered the Mini-Mental State Examination (MMSE),18 and then subjects with MMSE scores of less than 24 (n = 314) and a random sample of subjects with MMSE scores of 24 or higher (n = 354) were extensively examined.19 By the 2-phase design, which included a screening phase and a clinical examination phase, 225 prevalent cases of dementia were detected (216 derived from subjects whose dementia was detected during screening and 9 from the examined random sample of subjects whose screening results were normal). One hundred ten persons refused to participate in the baseline clinical examination, and 174 persons (2 with a mental disorder) refused to participate in the follow-up examination or were unavailable during the follow-up period. Of the 1301 subjects without dementia who were eligible for the follow-up evaluation,20 314 died before the follow-up examination. The remaining subjects (n = 987) were administered a comprehensive clinical examination between November 1990 and April 1992.

DIAGNOSING DEMENTIA

The same protocol was used to gather the information for the diagnosis of dementia at baseline and at follow-up. It included the collection of family and personal histories by nurses, clinical examination by physicians, and the administration of psychological tests by trained personnel. The interview by nurses involved social, occupational, functional, and medical aspects and also included an assessment of the performance of activities of daily living. The physicians examined the physical and neurologic conditions, as well as the cognitive and psychiatric states. For the cognitive examination, memory functions were explored by asking facts of general knowledge and past personal information, language functions by assessing subjects’ object-naming ability and comprehension, abstract thinking by assessing subjects’ problem-solving ability and analysis of proverbs, praxis function by examining simple motor activities (dressing and pantomime), and visuospatial orientation by assessing subjects’ performance on copying figures. Psychological tests included the MMSE, episodic and primary memory tasks such as free recall and the recognition of random words, and digit span tests. Diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Revised, Third Edition,21 were used to define dementia. The diagnosis of dementia was given after consensus among 3 independent physicians (L.F., B.W., and M.V.).

Dementia severity was determined according to the Clinical Dementia Rating Scale,22 with some modifications.23 For analysis, we treated severity of the disease as a category variable by artificially coding questionable, mild, moderate, and severe dementia as 1, 2, 3, and 4, respectively. No information regarding drug use was used in the diagnosis of dementia. For the dead subjects during the follow-up period, however, information from medical records and death certificates was used to make dementia diagnoses. Details of the clinical examination and diagnostic procedures have been reported elsewhere.19,20

BASELINE DATA COLLECTION

The baseline interview was conducted by trained nurses from October 1987 to December 1989. Information on drug use was collected for the 2 weeks preceding the baseline interview.24 Both prescription and nonprescription drug use were inquired about; drug containers and drug prescription forms were inspected to verify this information. Drug use was

PREVALENCE OF DEMENTIA

The baseline characteristics of the study population according to the use of antihypertensive medication are shown in Table 1. Subjects taking diuretics were older and had a higher systolic blood pressure; there was also a higher proportion with less than 8 years of education and with a history of heart disease or stroke. They were more likely to be female than those not taking antihypertensive medication.

At baseline, 225 cases of dementia were detected, giving an overall prevalence of 12.4%. Compared with those not taking antihypertensive medication, subjects taking diuretics had a higher score on the MMSE (P = .006) and a lower prevalence of dementia (P < .004). Logistic regression analysis showed that subjects taking diuretics had an odds ratio of 0.4 (95% confidence interval [CI], 0.3-0.6) for dementia, after adjustment for age, sex, education, systolic blood pressure, heart disease, and stroke. Subjects taking other antihypertensive drugs but no diuretics also had a lower prevalence of dementia, with an odds ratio of 0.3 (95% CI, 0.1-0.8).

INCIDENCE OF DEMENTIA

Among the 1301 persons without dementia who participated in the follow-up evaluation, 987 (75.9%) received a comprehensive clinical examination, and 199 were diagnosed as having dementia. Among the 314 subjects who died during the follow-up interval, 25 were diagnosed as having dementia, using data from medical records and death certificates. The mean follow-up of the cohort was 36.7 months, with a maximum of 63.1 months.

Among the 1301 subjects, 584 (44.9%) took at least 1 type of antihypertensive drug at baseline. Subjects taking antihypertensive medication had an adjusted RR of 0.7 (95% CI, 0.6-1.0; P = .03) for dementia.

At baseline, 484 (37.2%) persons took diuretics. Subjects taking diuretics were older (age [mean ± SD], 82.6 ± 3.1 years vs 81.7 ± 4.9 years, respectively), more likely to be female (81.4% vs 70.9%), and had a higher prevalence of heart disease (26.9% vs 8.1%) and stroke (9.5% vs 4.9%) than those not taking antihypertensive medication. There was no difference in the MMSE scores between those taking diuretics and those not taking an-
classified according to the Anatomical Therapeutic Chemical classification system. Antihypertensive drugs included all medicines potentially used for lowering blood pressure (Anatomical Therapeutic Chemical codes C02, C03, and C07). For analysis, we first divided the whole sample into 3 groups: the group using diuretics, regardless of other drug use; the group using other antihypertensive drugs, no diuretics; and the group not using any antihypertensive drugs. A portion of diuretic users took other antihypertensive drugs at the same time. We also checked the subjects receiving diuretic monotherapy separately. The drugs that were used by more than 20 subjects included diuretics (bendroflumethiazide, hydrochlorothiazide, furosemide, spironolactone, and amiloride hydrochloride), calcium channel antagonists (verapamil hydrochloride, nifedipine, and diltiazem hydrochloride), and β-adrenergic blocking agents (metoprolol tartrate, propranolol hydrochloride, alprenolol hydrochloride, and atenolol). Among them, bendroflumethiazide, furosemide, amiloride, and verapamil were used by more than 100 subjects. When the subject was unable to provide reliable information, as assessed by the subject's response to the first few items of the questionnaire and to all items of the MMSE, a proxy respondent (relative, caregiver, or other) was used.

The arterial blood pressure (systolic: Korotkoff phase 1, and diastolic: phase 5) was measured with a mercury sphygmomanometer with the subject in a sitting position after a 5-minute rest. Information regarding the medical history for each participant was obtained from the computerized inpatient register, which covers all hospitals in the Stockholm area. We treated heart disease (coronary heart disease, cardiac dysrhythmia, and heart failure) and stroke as 2 potential confounders.

**DATA ANALYSIS**

The difference of the score on the MMSE and the prevalence of dementia between drug use groups were examined, respectively, by the Student t test and the chi-square test. Logistic regression analysis was used to adjust for potential confounders in the association between the use of antihypertensive medication and prevalent dementia.

The incidence of dementia was calculated by dividing the number of cases by the number of person-years of follow-up. The follow-up time for persons without dementia was determined from the date of the baseline interview to the date of the follow-up examination or death. For the persons with dementia, half of this time was assumed. We used Cox proportional hazards regression analysis to estimate the relative risk (RR) of dementia developing in relation to the use of antihypertensive medication. We performed the analyses in the entire study population (n = 1301), in the subpopulation with a baseline MMSE score of greater than 23 (n = 1212), in the subpopulation who participated in the follow-up clinical examination (n = 987), and in the subpopulation with a baseline systolic blood pressure of greater than 160 mm Hg or a diastolic blood pressure of greater than 95 mm Hg (n = 458). When the age at the onset of dementia was used as the time-scale in the Cox proportional hazards regression model, as suggested by Korn et al, similar results were obtained. Therefore, the results from the models in which the follow-up time was used are presented here.

The rate of decline in the score on the MMSE among patients with dementia at baseline was calculated using the following formula: (baseline score − follow-up score) ÷ baseline score ÷ years of follow-up. A multiple stepwise linear regression analysis was used to identify the significant predictors for the rate of cognitive decline. We also performed other analyses by establishing several generalized models. None of these models identified more predictors than the linear model at the same significant level.

Age, sex, education, systolic (or diastolic) blood pressure, heart disease, and stroke were considered as covariates in all the analyses. Although we reanalyzed our data taking into account the use of estrogens, nonsteroidal anti-inflammatory drugs, aspirin, vitamins E and C, and apolipoprotein E genotypes, we did not present the results in this study because none of these factors changed the results substantially.

In the subpopulation with a baseline MMSE score of greater than 23 (n = 1212), subjects taking diuretics had an adjusted RR of 0.7 (95% CI, 0.5-0.9) for dementia, and subjects receiving diuretic monotherapy had an adjusted RR of 0.6 (95% CI, 0.4-0.8). In addition, the inclusion of baseline MMSE scores in the models produced similar results regarding the use of diuretics.

In the subpopulation who participated in the follow-up clinical examination (n = 987, excluding those who died during the period of follow-up), subjects taking diuretics had an adjusted RR of 0.7 (95% CI, 0.5-0.96), and subjects receiving diuretic monotherapy had an adjusted RR of 0.6 (95% CI, 0.4-0.9).

In the subpopulation with a baseline systolic blood pressure of greater than 160 mm Hg or a diastolic blood pressure of greater than 95 mm Hg (n = 458), subjects receiving diuretic monotherapy (n = 122) had an adjusted RR of 0.7 (95% CI, 0.5-1.2) for dementia, and subjects taking other antihypertensive drugs (n = 94, 42 subjects taking calcium channel antagonists and 43 taking β-blockers; 19 also with diuretics) had an adjusted RR of 0.6 (95% CI, 0.3-1.2).

**COGNITIVE DECLINE AMONG PERSONS WITH DEMENTIA**

Among the 225 subjects with prevalent dementia, 115 died before the follow-up examination. Among the 110 persons who participated in the follow-up evaluation, 28 with a baseline MMSE score of less than 6 were excluded from further analyses. We also excluded 3 persons who did not use diuretics but who took other antihypertensive drugs because the number was too small to be analyzed separately. There was no difference in the baseline MMSE score between those taking and those not taking diuretics. Subjects not taking diuretics had a decline of 17% every year from the baseline score, which was 2 times more than the decline of those taking diuretics.
uretics (Table 3). By using a multiple stepwise linear regression analysis, the use of diuretics was found to be inversely related to the rate of cognitive decline (regression coefficient = −0.07, \( P = .04 \)).

### MAIN FINDINGS

The use of diuretics was related to a lower prevalence of dementia, a reduced incidence of dementia, and slower cognitive decline among patients with dementia. A reduced risk of dementia associated with the use of other antihypertensive drugs (calcium channel antagonists or β-blockers), however, was observed only in the subpopulation with a baseline systolic blood pressure of greater than 160 mm Hg or a diastolic blood pressure of greater than 95 mm Hg. The results were derived from a population-based epidemiological study of 1810 persons aged 75 years and older in which several factors, including possible protectors for AD reported in the literature, were considered.

### POSSIBLE MECHANISMS

The antihypertensive effect of diuretics, especially in the elderly, has been proved. It is, therefore, conceivable that taking diuretics may reduce the risk of dementia or slow the progress of dementia by reducing the number of cerebrovascular events or silent vascular lesions in the brain. We demonstrated that the use of diuretics was related to a 30% reduced risk of dementia in the general population. The result is similar to that of a metaanalysis that reported a 34% reduced risk of major cerebrovascular events with low-dose diuretic therapy in hypertensive patients. Hypertension-related silent vascular lesions in the brain, such as white matter changes, are common in persons with dementia (both AD and VaD), although they can also occur with normal aging. In addition, a recent study showed an increased incidence of senile plaques and neurofibrillary tangles in persons with hypertension. Controlling hypertension may prevent the development and progression of these lesions.

Increasing evidence suggests that cerebrovascular dysfunction and damage may also be involved in the pathogenesis of AD. A recent study found that amyloid β-protein, the major component of amyloid plaques in the AD brain, enhanced vasoconstriction and resistance to the relaxation of endothelial cells in intact rat aorta. In vitro, this toxicity of amyloid β-protein can be partially prevented by the use of verapamil (a com-

### Table 1. Baseline Characteristics of the 1810 Participants in the Kungsholmen Project, by Use of Antihypertensive Medication

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diuretics (n = 651)†</th>
<th>Other (n = 125)‡</th>
<th>None (n = 1034)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>83.1 ± 5.2</td>
<td>81.0 ± 4.3</td>
<td>82.3 ± 5.2</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>81.4</td>
<td>72.8</td>
<td>73.2</td>
</tr>
<tr>
<td>Education &lt; 8 y, %</td>
<td>57.5</td>
<td>41.6</td>
<td>51.5</td>
</tr>
<tr>
<td>Heart disease, %</td>
<td>30.1</td>
<td>19.2</td>
<td>9.6</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>10.1</td>
<td>8.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Blood pressure, mm Hg§</td>
<td>156 ± 23</td>
<td>160 ± 25</td>
<td>153 ± 22</td>
</tr>
<tr>
<td>Systolic</td>
<td>81 ± 11</td>
<td>82 ± 12</td>
<td>80 ± 11</td>
</tr>
<tr>
<td>Diastolic</td>
<td>25.1 ± 5.2</td>
<td>26.5 ± 3.6</td>
<td>23.9 ± 7.1</td>
</tr>
<tr>
<td>Score on the MMSE</td>
<td>9.4</td>
<td>4.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Dementia, %</td>
<td>4.8</td>
<td>4.8</td>
<td>15.3</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD except where noted. MMSE indicates Mini-Mental State Examination.
†Of this group, 70% were receiving diuretic monotherapy; 14.4% were also taking calcium channel antagonists, and 10.6% were taking β-blockers.
‡Of this group, 52% were taking calcium channel antagonists, and 41.6% were taking β-blockers.
§Values were missing for 63 persons.

### Table 2. Use of Antihypertensive Medication and Incident Rate of Dementia in the First Follow-up of the Kungsholmen Project

<table>
<thead>
<tr>
<th>Antihypertensive Medication Use at Baseline</th>
<th>No. of Dementia Cases</th>
<th>Incident Rate per 1000 Person-Years</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics (n = 484)†</td>
<td>73</td>
<td>56.7</td>
<td>0.7 (0.5-1.0)</td>
</tr>
<tr>
<td>Diuretic monotherapy (n = 345)</td>
<td>48</td>
<td>52.5</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>Other (n = 100)‡</td>
<td>17</td>
<td>56.7</td>
<td>0.9 (0.5-1.5)</td>
</tr>
<tr>
<td>None (n = 717)</td>
<td>134</td>
<td>66.2</td>
<td>1.0 (Reference)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, education, systolic blood pressure, heart disease, and stroke.
†Of this group, 15.1% were also taking calcium channel antagonists, and 11.0% were also taking β-blockers.
‡Of this group, 50% were taking calcium channel antagonists, and 45% were taking β-blockers.

### Table 3. Characteristics and Mini-Mental State Examination Score of 79 Patients With Dementia at Baseline, by Diuretic Use

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diuretic Use†</th>
<th>No Antihypertensive Medication Use‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>85.3 ± 5.9</td>
<td>84.1 ± 5.5</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>77 (49)</td>
<td>80 (50)</td>
</tr>
<tr>
<td>Education &lt; 8 y, %</td>
<td>17 (47)</td>
<td>17 (47)</td>
</tr>
<tr>
<td>Heart disease, %</td>
<td>14 (40)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (13)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Blood pressure, mean ± SD, mm Hg</td>
<td>157 ± 26</td>
<td>144 ± 27</td>
</tr>
<tr>
<td>Systolic</td>
<td>82 ± 18</td>
<td>77 ± 11</td>
</tr>
<tr>
<td>Diastolic</td>
<td>34.5 ± 8.1</td>
<td>34.1 ± 6.3</td>
</tr>
<tr>
<td>Follow-up score</td>
<td>13.4 ± 6.2</td>
<td>9.5 ± 6.8</td>
</tr>
<tr>
<td>Rate of decline§</td>
<td>0.09 ± 0.13</td>
<td>0.17 ± 0.13</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) except where noted.
†Eighteen persons were taking diuretic monotherapy; 3 were also taking calcium channel antagonists, and 2 were also taking β-blockers.
‡According to the Clinical Dementia Rating Scale.
§Calculated as follows: (baseline score – follow-up score) ÷ (baseline score + (years of follow-up).

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monly used calcium channel antagonist),‡ probably through verapamil’s antioxidative activities. Diuretics, especially thiazides, also have direct vasorelaxant effects on vessel wall,§,∥ which may contribute to their antihypertensive properties and may have implications in reducing this toxic effect of amyloid β-protein.

A faster rate of decline of cognition among those not taking antihypertensive medication could be due to the poorer control of blood pressure during the follow-up. Furthermore, other unknown mechanisms may explain the possible protection of diuretics. This should be explored further.

LIMITATIONS OF THE STUDY

Information on the duration of antihypertensive medication use was not available. The classification of drug use was made only at baseline. Persons taking diuretics at baseline may take other antihypertensive drugs later, such as calcium channel antagonists. Unlike a clinical trial, our study is not designed specifically to assess the effects of antihypertensive medication. The group using antihypertensive medication in our cohort differs inherently from the group not using antihypertensive medication in a number of factors, such as heart disease, stroke, and hypertension, that may be related to the risk of dementia. Generally, these limitations may decrease the power to detect a given association or lead to an underestimation of the association. These limitations may particularly affect the results regarding the use of other antihypertensive medication because this group was relatively small.

In cross-sectional studies,41,42 patients with dementia often have a lower blood pressure level than those without dementia. Therefore, current use of antihypertensive medication could be lower in those with clinically manifest dementia. This may explain the much lower RRs of dementia associated with the use of antihypertensive medication estimated from prevalence data than those from incidence data. In addition, subjects with cognitive impairment may underestimate their use of medication, although we tried to get information from proxy informants on drug use of the subjects with possible cognitive impairment. There was no difference, however, in the use of cardiac glycosides between those with dementia (18.2%) and those without dementia (19.2%). This may suggest that the recall bias is minimal in this study. In addition, similar results were obtained when subjects with a baseline MMSE score of less than 24 were excluded.

Although we cannot definitely rule out the possibility that our findings are the results of combined effects of antihypertensive medication and lifestyle modifications for manifest dementia. This may explain the much lower RRs of dementia associated with the use of antihypertensive medication could be due to the poorer control of blood pressure during the follow-up. Furthermore, other unknown mechanisms may explain the possible protection of diuretics. This should be explored further.

CONCLUSIONS

To our knowledge, this is the first large-scale prospective study that examined the relationship between antihypertensive medication use and dementia in a general population. Taking diuretics appears to protect against dementia. The main mechanism is probably that diuretics can significantly reduce the number of cerebrovascular events or lesions, which are now thought to be important in the pathogenesis of both AD and VaD; other mechanisms are, however, possible. Because of the nature of an observational study, the findings need to be replicated in further studies, particularly clinical trials.

Accepted for publication October 27, 1998.

This study was supported by grants from the Swedish Medical Research Council, the Swedish Council for Social Research, the Swedish Municipal Pension Institute, the National Corporation of Swedish Pharmacies’ Fund for Research and Studies in Health Economics and Social Pharmaceutics, the Torsten and Ragnar Söderbergs Foundation, the SHMF (Stiftelsen Hjälp till Medicinsk Forskning) Foundation, and the Gun and Bertil Stohne Foundation.

We thank Margaret Maytan, MD, for revision of the manuscript and our colleagues at the Kungsholmen Project, Stockholm, Sweden, for their collaboration in collecting and managing data.

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