CLINICAL CONTEXT

Clinicians can face a difficult choice in deciding what class of antihypertensive medication to prescribe for their patients. However, all medications used to treat hypertension are not equal in their effects on important cardiovascular outcomes. A review by De Caterina and Leone, which appeared in the May 15, 2010, issue of The American Journal of Cardiology, concluded that beta-blockers are associated with worse results in the prevention of stroke compared with the use of other antihypertensive medications. Moreover, beta-blockers may not prevent coronary artery disease when used to treat patients with hypertension. They fail to lower central blood pressure to the degree of other antihypertensive drugs, and they have negative metabolic effects, which might contribute to higher rates of cardiovascular disease.

Beta-blockers have also been associated with worsened cognitive outcomes compared with angiotensin II receptor blockers (ARBs). It is possible that both angiotensin-converting enzyme (ACE) inhibitors and ARBs can reduce the risk for incident dementia. The current study by Kehoe and colleagues examines this possibility in a large cohort of patients.

STUDY SYNOPSIS AND PERSPECTIVE

Controlling blood pressure with an ARB rather than other antihypertensive agents may significantly reduce the risk for Alzheimer's disease (AD) and vascular dementia (VaD), suggest results of a large observational study from the United Kingdom.

In the study, the risk for AD was 53% lower in older adults prescribed an ARB compared with those prescribed other antihypertensive agents. The risk was 24% lower in those prescribed an ACE inhibitor.

Patrick G. Kehoe, PhD, coleader of the Dementia Research Group at Frenchay Hospital, Bristol, and colleagues report their study in the October issue of the Journal of Alzheimer's Disease.

Dr. Kehoe and colleagues say their findings support those of a recent study in a predominantly male population from the United States. In that study, reported previously by Medscape Medical News, men prescribed ARBs had a lower incidence and rate of progression of AD than those prescribed ACE inhibitors or other cardiovascular drugs.

The accumulating observational and biological evidence in favor of ARBs protecting against dementia "strengthens the need for them to be studied more rigorously in the future," Dr. Kehoe and colleagues conclude.

Although "interesting, these are not conclusive findings," coauthor Richard M. Martin, PhD, from the University of Bristol, notes in a statement. "We now need to do the clinical trials to properly test our observations."

Accumulating Evidence

The study was a nested case-control study within the UK general practice research database. It was designed to see whether ARBs and ACE inhibitors are more strongly associated with AD, VaD, and other dementias relative to other antihypertensive drugs such as calcium channel blockers, beta-blockers, or thiazide diuretics.

Although both ARBs and ACE inhibitors reduce angiotensin II signaling, "now believed to be involved in the pathology of AD, ARBs are unlikely to interrupt ACE-mediated [amyloid-beta] degradation," unlike ACE inhibitors, the researchers note in their article. "These mechanisms of action suggest that ARBs may have benefits over [ACE inhibitors] in the etiology of AD," they write.

Included in the analysis were 5197 patients, aged 60 years and older, who were diagnosed between 1997 and 2008 with probable or possible AD (n = 5797), VaD (n = 2168), or unspecified other dementia (n = 1214). Each case patient was matched by age, general practice, and sex to up to 4 control patients (n = 36,166).

The researchers observed that patients ever prescribed either ARBs or ACE inhibitors were less likely to develop AD, VaD, or other dementia than patients ever prescribed other antihypertensive medications. The associations were stronger for ARBs than for ACE inhibitors.

Table. Dementia Outcomes With ARBs and ACE Inhibitors vs Other Agents

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ARBs, OR (95% CI)</th>
<th>ACE inhibitors, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD</td>
<td>0.47 (0.37 - 0.58)</td>
<td>0.76 (0.69 - 0.84)</td>
</tr>
<tr>
<td>Probable VaD</td>
<td>0.70 (0.57 - 0.85)</td>
<td>0.82 (0.75 - 0.91)</td>
</tr>
<tr>
<td>Unspecified/other dementia</td>
<td>0.62 (0.47 - 0.81)</td>
<td>0.85 (0.75 - 0.96)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
These associations did not differ by age, comorbidities, or blood pressure, suggesting little confounding by observed comorbidities, the researchers say. There was also evidence of a dose–response relationship between ARBs and AD (P = .009).

In analyses restricted to patients exposed either to ARBs or ACE inhibitors as their only therapy, there was an inverse association of ARB sole therapy (OR, 0.63; 95% CI, 0.45 - 0.88), but not ACE inhibitor sole therapy (OR, 1.01; 95% CI, 0.91 - 1.12).

"Preaching to the People"

Reached for comment, Gustavo C. Román, MD, medical director of the Nantz National Alzheimer Center at the Methodist Neurological Institute in Houston, Texas, who was not involved in the study, said it “reaffirms the need to control blood pressure, and the sooner, the better.”

Dr. Román said he has been “preaching to the people that you need to keep your blood pressure under good control because it really seems that vascular disease, and especially hypertension, opens the gate to the amyloid-beta changes, although the mechanism is not very clear.

"Whatever the mechanism, it has been demonstrated over and over that vascular disease, in particular hypertension, is a risk factor for the development of [AD],” he added.

The study was supported by the North Bristol National Health Service Trust. The authors and Dr. Román have disclosed no relevant financial relationships.


STUDY HIGHLIGHTS

- Researchers used the UK General Practice Research Database to investigate their hypothesis. This database contains clinical and prescription records for 10.6 million patients in 593 general practices.
- The study authors found cases of AD, VaD, or other dementia based on diagnosis codes. These cases were compared with up to 4 control participants matched by age, practice site, and sex.
- The primary variable was the use of ACE inhibitors or ARBs. Individuals taking both classes of medication were excluded from study analysis.
- The main study outcome was the relationship between treatment with ACE inhibitors or ARBs and the prevalence of dementia. Researchers adjusted for demographic, disease, and healthcare utilization data in their analysis of this result.
- 20,021 case patients were compared vs 77,475 control participants. The mean age of study participants was 82 years, and two thirds of patients were women.
- Among patients receiving antihypertensive treatment, 2227 were categorized as having probable AD; 3570 with possible AD; 2166 with probable VaD; and 1214 with unspecified dementia.
- The mean blood pressure was not significantly different based on the presence of dementia.
- After multivariable adjustment, treatment with ARBs was significantly protective against AD (adjusted OR, 0.47; 95% CI, 0.37 - 0.66). ACE inhibitors were less so but were still significantly protective against AD (adjusted OR, 0.76; 95% CI, 0.68 - 0.84).
- ARBs appeared less protective against VaD (OR, 0.70; 95% CI, 0.57 - 0.85) or nonspecific dementia (OR, 0.62; 95% CI, 0.47 - 0.81) compared with their protective effects against AD. However, ACE inhibitors appeared more similarly protective against AD, VaD, or any dementia.
- There was evidence of a dose–response relationship between the dose of ACE inhibitors and the prevalence of AD and VaD. There was a dose–response relationship between ARBs and the risk for AD (P = .009), but not VaD.
- Reverse causation (more ARBs prescribed because of cognitive problems) did not appear likely in examining the association between ARBs and AD.

CLINICAL IMPLICATIONS

- Beta-blockers should generally be avoided as first-line therapy for patients with uncomplicated hypertension. They do not reduce central blood pressure or the risk for stroke to the same degree as other antihypertensive medications.
- In the current study by Kohce and colleagues, treatment with either ACE inhibitors or ARBs was associated with a lower risk for AD, with a stronger reduction associated with ARBs.