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Short Report

Incidence of neurodegenerative and cerebrovascular diseases associated with antihypertensive drug classes

Paul J. Harrison, Lucy Colbourne and Sierra Luciano

Antihypertensive drugs (AHTs) are associated with lowered risks of neurodegenerative diseases and stroke. However, the relative risks associated with different AHT classes are unclear. Using an electronic health record network with 34 million eligible patients, we compared rates of these disorders over a 2-year period, in propensity score-matched cohorts of people taking calcium channel blockers (CCBs) compared with those taking other AHT classes. CCBs were associated with a higher incidence of all disorders compared with renin-angiotensin system agents, and a higher incidence of dementia and cerebrovascular disease compared with diuretics. CCBs were associated with a lower incidence of movement disorders and cerebrovascular disease compared with beta-blockers. The data show that AHT classes confer differential risks of neurodegenerative and cerebrovascular diagnoses.

Keywords

Epidemiology; dementia; antihypertensive drugs; calcium channel blockers; electronic health records.

Antihypertensive drugs (AHTs) have been associated with lowered risks of dementia,[1,2] Parkinson's disease[3] and stroke.[4] However, the picture remains unclear. Relevant issues include concerns over residual confounding and lack of matching for blood pressure and other factors.

There is also uncertainty as to the diagnostic specificity of the associations and, importantly, whether one AHT class differs from another. We addressed these issues by studying patients who were free of any of the disorders, and who were then prescribed a calcium channel blocker (CCB) or one of the other major AHT classes (diuretics, renin-angiotensin system [RAS] agents, or beta-blockers). CCBs were used as the reference AHT class based on their potential therapeutic use for neuropsychiatric disorders.[5]

Method

Our study followed Strengthening the Reporting of Observational Studies in Epidemiology guidelines. We used the TriNetX Analytics network, part of TriNetX (www.trinetx.com), a global federated cloud-based network providing access to electronic medical records from multiple healthcare organisations. Details have been described elsewhere.[6,7] Briefly, the network allows patient cohorts to be created based on defined inclusion and exclusion criteria. Two cohorts can then be compared for other characteristics and outcomes. There is a built-in capability to propensity score match cohorts for any variables of interest;[8] TriNetX uses greedy nearest neighbour matching with a calliper distance of 0.1, to produce 1:1 matching. TriNetX has a waiver from the Western Institutional Review Board because only aggregated counts and statistical summaries of de-identified information are used.

We excluded patients younger than 50 years. We also excluded anyone with a history of any of the diagnoses of interest, or with conditions that may be prodromal to them (ICD-10 codes shown in Supplementary Table 1 available at https://doi.org/10.1192/bjp.2020.249).

From the eligible population (~34 million), we created cohorts of people receiving their first prescription of each AHT class. The exposure and outcome period was 2 years; exposure was proxied by requiring prescriptions for the assigned AHT class, separated by at least 2 years. As predicted based on clinical AHT guidelines, the initial cohorts were not matched for factors such as age, gender, race or blood pressure (Supplementary Table 2), and also differed in some other variables that could contribute to confounding. Hence, we used propensity score matching to produce cohorts matched for age, gender, race, blood pressure and body mass index, as well as for a range of prior diagnoses and treatments that are risk factors for neurodegeneration or stroke (Supplementary Table 1). A variable with a standard difference between groups of <0.1 is considered matched.[8]

The outcomes of interest were a first diagnosis of dementia, movement disorder or cerebrovascular disease. We also measured dementia subtypes, Parkinson's disease, stroke and cerebral haemorrhage. Additionally, we measured 12 negative control outcomes; these help identify residual confounding.[9] Cohort comparisons were made with odds ratios and 95% confidence intervals.

Results

Propensity score matching successfully produced cohorts matched for the wide range of demographic factors, prior diagnoses and exposures, noted above. The main findings are shown in Fig. 1. The cohort characteristics and detailed results are provided in Supplementary Table 3.

CCBs versus diuretics

CCBs were associated with higher rates of dementia (odds ratio 1.19, 95% CI 1.13–1.26) and cerebrovascular disease (odds ratio 1.17, 95% CI 1.14–1.21), as well as with dementia subtypes, mild cognitive impairment, stroke and cerebral haemorrhage. Movement disorders were less common with CCBs than diuretics (odds ratio 0.92, 95% CI 0.88–0.96), but Parkinson's disease was not (odds ratio 1.01, 95% CI 0.91–1.13). The mean odds ratio for the negative control outcomes was lower in the CCB group (odds ratio 0.89, 95% CI 0.84–0.93).

CCBs versus RAS agents

Compared to RAS agents, CCBs were associated with increases in all three diagnostic categories: dementia (odds ratio 1.24, 95% CI 1.17–1.32), movement disorders (odds ratio 1.21, 95% CI 1.16–1.28) and

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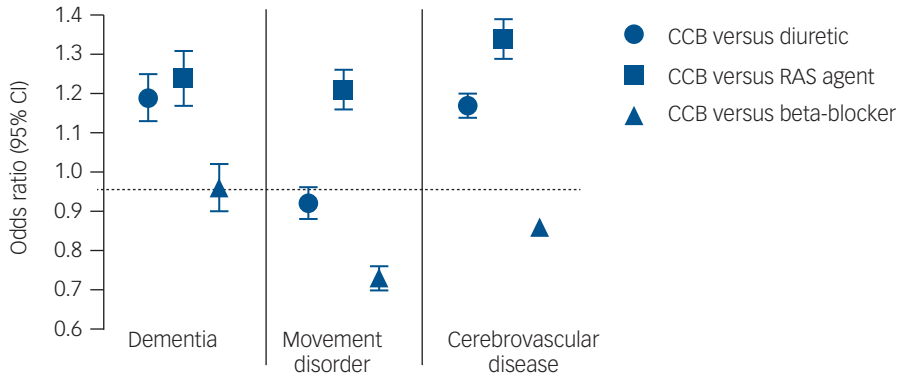

Fig. 1 Incidence of dementia, movement disorders and cerebrovascular disease during a 2-year exposure to CCBs compared with diuretics (circles; 231 764 in each cohort), RAS agents (squares; 181 495 in each cohort) and beta-blockers (triangles; 234 015 in each cohort). Results are shown as odds ratios with 95% confidence intervals. See Supplementary Table 3 for full details of each cohort, and results for subtypes of dementia and for Parkinson's disease, stroke and cerebral haemorrhage. CCB, calcium channel blocker; RAS, renin-angiotensin system.

cerebrovascular disease (odds ratio 1.34, 95% CI 1.29–1.28); odds ratio for Alzheimer's disease and Parkinson's disease showed similar trends (Supplementary Table 4). Negative control outcomes were not different between groups (odds ratio 1.04, 95% CI 0.97–1.11).

CCBs versus beta-blockers

CCBs were associated with a lower incidence of cerebrovascular disease (odds ratio 0.86, 95% CI 0.84–0.89) and movement disorders (odds ratio 0.73, 95% CI 0.70–0.76), including Parkinson's disease (odds ratio 0.73, 95% CI 0.66–0.81). There was no difference in dementia between the groups (odds ratio 0.96, 95% CI 0.90–1.01), and a marginal increase in negative control outcomes (odds ratio 1.06, 95% CI 1.00–1.13).

Discussion

Using a federated electronic health records network, we examined rates of dementia, movement disorders and cerebrovascular disease in people free of these conditions at baseline who were then exposed to CCBs or other AHT classes over a 2-year period. The size of the cohorts, and the use of propensity score matching and negative control outcomes, suggest that our results are relatively robust.

The association of AHTs with reduced risk of these disorders is well established.[1–4] The present results strengthen the evidence that not all AHT classes are the same in this respect, and also show that their benefits differ across the disorders measured. Since cohorts were matched at baseline for blood pressure, and remained so during the 2-year period, the results are not merely a result of differences in control of hypertension.

Regarding the comparisons between AHTs, there was no evidence that CCBs have particular benefits, as we had anticipated.[5] Indeed, the incidence of dementia and cerebrovascular disease was greater with CCBs than with RAS agents or diuretics. Instead, it was RAS agents that were associated with a lower incidence of all outcomes, extending the evidence that they may be neuroprotective, perhaps through effects on central angiotensin receptors.[10]

The only clear benefits of CCBs were when compared with beta-blockers for risk of movement disorders and cerebrovascular disease. The association of beta-blockers with Parkinson's disease has been controversial, with a recent review concluding that much of the reported association is probably a result of reverse causation (beta-blockers are used to treat tremor) and confounded by differential rates of smoking.[11] However, our data cannot readily be explained in this way, because all patients at baseline were free of movement disorder, including tremor, and cohorts were matched for rates of nicotine dependence. We confirmed earlier findings that CCBs are more effective than beta-blockers in prevention of stroke,[4] likely because CCBs decrease blood pressure variability, whereas beta-blockers increase it.

The negative control outcomes showed no difference between CCBs and RAS agents, reducing the likelihood of residual confounding. In contrast, their incidence was lower in users of CCBs compared with diuretics, and equivocally higher in users of CCBs compared with beta-blockers. These differences may reflect overall health, or healthcare usage. Either way, differences of similar magnitude and direction that are seen for outcomes of interest are likely to be non-specific correlates. Equally, where outcomes of interest are in the opposite direction to the negative control outcomes (e.g. the higher rate of dementia seen with CCBs versus diuretics), the findings are arguably of greater significance.

Despite its size and methodological strengths, our study has limitations. Residual confounding can never be eliminated from an observational study. We did not control for concurrent medication use during the outcome period. It is possible that subjects stopped and restarted treatment during the exposure period. Neither do we know about dosage, nor whether compliance was the same between AHT classes.

It is notable that the results are observed after only 2 years of exposure. Given that neurodegenerative and cerebrovascular disorders have a pathogenesis thought to begin many years before diagnosis, this suggests that AHTs differ in their ability to retard the disease process soon before it manifests clinically, rather than (or as well as) having a direct causal role. Longer-term exposures and outcomes would be of interest. They are more difficult to assess because cohort sizes become much smaller, but we find comparable results for 4 years of AHT exposure, except for a lower incidence of dementia with CCBs than with beta-blockers (data not shown).

The results extend the evidence that AHT classes are associated with differential risks of neurodegenerative and cerebrovascular disease. Future research should explore risk differences between drugs within an AHT class, and examine the mechanisms by which AHTs affect the brain and its disorders.

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1192/bjp.2020.249

Data availability

Access to TriNetX's de-identified patient data is available for the purpose of healthcare research, with an approved user license.

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Author contributions

P.J.H. and L.C. designed the study. P.J.H. conducted the analyses, assisted by S.L. P.J.H. wrote the paper, with input from L.C. and S.L. All authors revised and approved the submission.

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Declaration of interest

P.J.H. and L.C. were granted unrestricted access to the TriNetX Analytics network for the purposes of research relevant to psychiatry, and with no constraints on the analyses performed nor the decision to publish. S.L. is an employee of TriNetX Inc.

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EXTRA CONTENT ONLINE

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