Original Contribution

Use of Calcium Channel Blockers and Parkinson’s Disease

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Experimental evidence and case-control studies suggest that dihydropyridine calcium channel blockers (DiCCBs) may protect against Parkinson’s disease. The authors conducted a historical cohort study in Denmark to investigate the association between DiCCB use and risk of Parkinson’s disease (1998–2006). Individual-level data on filled drug prescriptions, diagnostic information, and covariates were linked between nationwide registries. Among DiCCB users, 173 incident cases of Parkinson’s disease were detected during 461,984 person-years of follow-up, compared with 5,538 cases during 17,343,641 person-years of follow-up among nonusers. After adjustment for age, sex, year, propensity score, and use of other antihypertensive drugs and statins, DiCCB use was associated with a reduced risk of Parkinson’s disease (rate ratio (RR) = 0.71, 95% confidence interval (CI): 0.60, 0.82). This association was not present in patients who had previously used DiCCBs (RR = 1.04, 95% CI: 0.87, 1.24). DiCCB users aged ≥65 years were at lower risk of Parkinson’s disease than DiCCB users aged <65 years (RR = 0.59, 95% CI: 0.40, 0.85). Among patients with Parkinson’s disease, DiCCB use was associated with reduced risk of death (adjusted RR = 0.66, 95% CI: 0.47, 0.91) but not dementia (adjusted RR = 0.97, 95% CI: 0.60, 1.56). In conclusion, DiCCB exposure was associated with a reduced risk of incident Parkinson’s disease, particularly in older patients, and with reduced mortality among patients with Parkinson’s disease.

antihypertensive agents; calcium channel blockers; neurology; Parkinson’s disease

Abbreviations: ATC, anatomic-therapeutic-chemical; CCB, calcium channel blocker; CI, confidence interval; DiCCB, dihydropyridine calcium channel blocker; ICD, International Classification of Diseases; RR, rate ratio; SD, standard deviation.

Parkinson’s disease is a neurodegenerative disorder that affects approximately 1% of the population over 60 years of age in industrialized countries (1). Degeneration and death of dopaminergic neurons leads to neurologic impairment, including tremor, rigidity, and bradykinesia (2). Patients also suffer from various nonmotor symptoms, and approximately 40% develop dementia (3). Current treatment strategies offer adequate symptom control in early stages of the disease but eventually fail or are associated with unacceptable side effects (2). Except for a recent study suggesting that the monoamine oxidase B inhibitor rasagiline may have disease-modifying effects (4), there are no drugs that prevent the disease or slow its progression.

The cellular pathogenesis of neurodegeneration in Parkinson’s disease involves protein accumulation, mitochondrial dysfunction, oxidative and nitrative stress, neurotransmitter excitotoxicity, and inflammation (2). Several of these mechanisms involve calcium flux and overload (5) and form the basis for why calcium regulation has been proposed to represent a possible therapeutic target (6). L-type calcium channels located on the plasma membrane of dopaminergic cells are responsible for the extra- to intracellular calcium flux that plays a part in generating autonomous pacemaking signals in substantia nigra neurons (6). These L-type channels may be inhibited by dihydropyridine calcium channel blockers (DiCCBs), drugs that are commonly used to treat hypertension. In animal models of Parkinson’s disease, treatment with DiCCBs has been found to reduce toxin-induced loss of substantia nigra dopaminergic cells and to protect against toxin-induced motor deficits (7–9).

Epidemiologic data support a potential effect of DiCCBs in humans: 2 case-control studies found that use of DiCCBs
was less likely to occur in patients with Parkinson’s disease than in controls (10, 11). Three smaller reports found no significant associations (12–14).

In a nationwide historical cohort study in Denmark, we investigated the association between DiCCB use and the risk of Parkinson’s disease.

MATERIALS AND METHODS

The study population was identified using the Danish Civil Registration System (15) and included all persons aged ≥45 years living in Denmark between January 1, 1998, and December 31, 2006. We linked information from nationwide registries on filled drug prescriptions, hospital contacts with a diagnosis of Parkinson’s disease, and covariates. The primary outcome measure was risk of incident Parkinson’s disease among new users of any DiCCB, compared with nonusers. Secondary analyses included specific DiCCBs and separate analyses by sex and age. We also studied the risks of dementia and death among patients with incident Parkinson’s disease. In further exploratory analyses, we assessed disease risk among users of non-DiCCBs.

The study was approved by the Danish Data Protection Agency. According to Danish law, ethics approval and patient consent is not required for registry-based studies.

Drug exposure

The Prescription Drug Registry (16) contains individual-level information on all prescriptions filled at Danish pharmacies. Each record contains the personal identification number, dispensing date, anatomic-therapeutic-chemical (ATC) code, number of packages, package size, and number of defined daily doses in the prescription. We included all DiCCBs (ATC code C08CA) in use in Denmark: amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nilvadipine, and nifedipine. Nimodipine was not included, because its sole indication in Denmark is prophylaxis against cerebral vasospasm after subarachnoidal hemorrhage. For exploratory analyses, the non-DiCCBs (ATC code C08D) verapamil and diltiazem were included.

Persons who had filled a prescription for a calcium channel blocker (CCB) within 2 years prior to cohort entry were excluded. This allowed selective inclusion of initiators of CCBs (new users), a design that reduces prevalent user bias (17) and allows estimation of exposure duration. Prevalent users—that is, patients who have received treatment for a longer period of time and therefore represent “survivors” of adverse drug events associated with the initial phase of treatment—may be less or more susceptible to the outcome under study.

Patients were defined as users if they had filled a minimum of 2 consecutive prescriptions for a CCB, and follow-up was started on the day the second prescription was filled. Throughout follow-up, patients were continuously monitored for their current drug exposure status. When patients were refilling prescriptions, a gap between prescriptions of up to 25% of the duration of the preceding prescription (in defined daily doses) was allowed in order to leave room for differences in drug intake habits. In case 2 prescriptions were overlapping, the overlap was disregarded and exposure time was counted from the dispensing day of the most recent prescription. Users who had exceeded the maximum allowed gap time between prescriptions were defined as past users and started contributing (unexposed) person-time to the past-user group from the day the maximum gap time after a prescription was exceeded. If they later again fulfilled criteria for use, past users were eligible for inclusion in the user group. Thus, each patient could contribute to several distinct use and past-use episodes which, when added, represented this patient’s person-time of use and past use, respectively. Nonusers were defined as persons who had never received a CCB prescription. Since persons who filled only 1 CCB prescription (not fulfilling criteria for current use) probably differed from nonusers, they were assigned to a distinct group (1-prescription users) and contributed person-time to this group also when unexposed. If they later fulfilled the criteria for use, they were eligible for inclusion in the user group. In subgroup analyses of specific CCBs, switching between different CCBs was permitted.

Parkinson’s disease

The National Patient Registry (18) contains information on hospitalizations and outpatient visits to hospital clinics and emergency departments, including International Classification of Diseases (ICD) diagnoses (the Tenth Revision of the ICD (ICD-10) was in use during the study period). Diagnoses are registered as 1 primary diagnosis and up to 20 secondary diagnoses. We identified incident cases of Parkinson’s disease, defined as any registration (primary or secondary diagnosis) in the National Patient Registry (ICD-10 code G20) and at least 1 prescription for an antiparkinson dopaminergic drug (ATC code N04B); disease onset was defined by the date of the first diagnosis or the first prescription, whichever came first. This case definition, requiring both diagnosis and prescription in order to be considered a case, was employed to increase specificity of the registered diagnosis and to identify the earliest possible date of disease onset. Persons diagnosed with Parkinson’s disease (code 342 from the Eighth Revision of the ICD (ICD-8) was used prior to 1994) or Parkinson’s-associated dementia (ICD-8: not applicable; ICD-10: code F02.3) prior to cohort entry were excluded.

Covariates and propensity score

Effect measures were adjusted for the following variables, with their status being continuously updated throughout follow-up: sex, age (in 5-year intervals), calendar year, and concomitant use of beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, amiloride, thiazides, non-DiCCBs, and statins. To adjust for baseline differences in the probability of receiving antihypertensive treatment, we estimated propensity scores as the probability of DiCCB treatment given variables thought to influence antihypertensive treatment prescribing: comorbid conditions, medications, hospitalizations, socioeconomic class, and degree of urbanization as defined at cohort entry (see Web Table 1, which is posted on the Journal’s Web site.
(http://aje.oxfordjournals.org/). The propensity score was estimated for each person in the cohort using logistic regression, and scores were stratified in quintiles.

**Statistical analyses**

Participants were followed from cohort entry to diagnosis of Parkinson’s disease, the end of follow-up (December 31, 2006), death, disappearance, or emigration, whichever occurred first. Applying a Poisson regression model (log-linear regression of the counts of Parkinson’s disease using the logarithm of follow-up time as the offset), we estimated the rate ratio for incident Parkinson’s disease in DiCCB users compared with nonusers. Covariates, as defined above, and the propensity scores were included in the model.

In analyses of dementia and death, we followed patients with incident Parkinson’s disease from the date of diagnosis to dementia or death. Patients with a history of any dementia (see ICD codes in Web Table 2) prior to the start of follow-up were excluded. Causes of death were derived from the National Cause of Death Registry (19). Rate ratios were adjusted for covariates (as defined above), socioeconomic class, degree of urbanization, and the Charlson comorbidity index (20, 21). The Charlson index was calculated on the basis of diagnoses registered until the start of follow-up; it did not include dementia and was defined by 3 levels of comorbidity: low (score 0), moderate (score 1–2), and severe (score ≥3).

**RESULTS**

**Cohort**

From a background population of 2,781,169 persons, we excluded 201,207 previous CCB users, 6,644 patients with Parkinson’s disease, and 37 patients with Parkinson’s-associated dementia diagnosed prior to cohort entry. Thus, the study cohort included 2,573,281 persons, among whom 202,836 had 1 or more episodes of treatment with a DiCCB. Table 1 shows the descriptive characteristics of cohort participants. During 18,277,474 person-years of follow-up (mean = 7.1 person-years (standard deviation (SD), 2.8)), a total of 5,968 incident cases of Parkinson’s disease were detected (57% males; mean age = 72 years (SD, 10)). The mean duration of DiCCB use was 2.3 years (SD, 2.1).

**Parkinson’s disease**

Table 2 presents rate ratios for Parkinson’s disease in users and past users of DiCCBs, as compared with nonusers. Use of DiCCBs was associated with a 29% reduced risk of Parkinson’s disease, after adjustment for age, sex, calendar year, propensity score, and use of other antihypertensive drugs and statins (RR = 0.71, 95% confidence interval (CI): 0.60, 0.82). Past use of DiCCBs was not significantly associated with reduced risk of Parkinson’s disease. Among 1-prescription users of DiCCBs (these persons did not fulfill criteria for use), the rate ratio was 0.92 (95% CI: 0.77, 1.10). In subgroup analyses by sex, use of DiCCBs was associated with similarly reduced risks of Parkinson’s disease in men and women (Table 2).

**Statistical analyses**

In sensitivity analyses (Web Table 4), we first tested the impact of variable exposure definitions. Results were materially unchanged when using a conservative definition of DiCCB use that did not allow gaps between prescriptions; when using a less stringent definition of DiCCB use, allowing a 50% gap in defined daily doses between prescriptions; and when extending the washout period, excluding all persons who had used DiCCBs within 4 years prior to cohort entry.

Accounting for time since discontinuation of DiCCB use in past users, the risk of Parkinson’s disease did not differ significantly by time since discontinuation (0–5.9 months, 6–11.9 months, or ≥12 months) (P = 0.66).

Using different strategies for the definition of cases, results were materially unchanged when restricted to cases with a primary diagnosis of Parkinson’s disease in the National Patient Registry; when defining Parkinson’s disease as any registration in the National Patient Registry, without requiring antiparkinson drug treatment; and when excluding patients...
with cerebrovascular disease, dementia, or secondary Parkinsonism. When moving back the index date of Parkinson’s disease diagnosis by 2 years, hypothetically accounting for the insidious onset of disease, there was no significant association between DiCCBs and Parkinson’s disease.

We also compared the risk of Parkinson’s disease in new users of DiCCBs with the risk in new users of other antihypertensive drugs; DiCCB users were at significantly lower risk of Parkinson’s disease. Among patients with incident Parkinson’s disease, DiCCB users were not at significantly reduced risk of death or dementia compared with users of other antihypertensive agents.

**DISCUSSION**

This large, nationwide historical cohort study found that use of DiCCBs was associated with a reduced risk of incident Parkinson’s disease, particularly in older patients. Beneficial associations were observed in both sexes and were similar for the two most commonly prescribed DiCCBs, amlodipine.
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Table 2. Risk of Incident Parkinson’s Disease Among Users of Dihydropyridine Calcium Channel Blockers, Overall and by Sex, Denmark, 1998–2006

<table>
<thead>
<tr>
<th>DCCB Use</th>
<th>Person-Years of Follow-up</th>
<th>No. With Incident Parkinson’s Disease</th>
<th>Age-Adjusted Incidence Rate per 100,000 Person-Years</th>
<th>Age-Adjusted RRa</th>
<th>95% CI</th>
<th>Adjusted RRb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>461,984</td>
<td>173</td>
<td>27</td>
<td>0.74</td>
<td>0.63, 0.86</td>
<td>0.71</td>
<td>0.60, 0.82</td>
</tr>
<tr>
<td>Past use</td>
<td>218,290</td>
<td>127</td>
<td>40</td>
<td>1.09</td>
<td>0.91, 1.30</td>
<td>1.04</td>
<td>0.87, 1.24</td>
</tr>
<tr>
<td>No use</td>
<td>17,343,641</td>
<td>5,538</td>
<td>37</td>
<td>1</td>
<td>Referent</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>223,005</td>
<td>102</td>
<td>54</td>
<td>0.77</td>
<td>0.63, 0.94</td>
<td>0.73</td>
<td>0.60, 0.89</td>
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<tr>
<td>Past use</td>
<td>95,182</td>
<td>66</td>
<td>76</td>
<td>1.09</td>
<td>0.85, 1.39</td>
<td>1.01</td>
<td>0.78, 1.30</td>
</tr>
<tr>
<td>No use</td>
<td>8,217,151</td>
<td>3,164</td>
<td>70</td>
<td>1</td>
<td>Referent</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>238,979</td>
<td>71</td>
<td>18</td>
<td>0.70</td>
<td>0.55, 0.89</td>
<td>0.67</td>
<td>0.53, 0.85</td>
</tr>
<tr>
<td>Past use</td>
<td>123,108</td>
<td>61</td>
<td>30</td>
<td>1.14</td>
<td>0.89, 1.48</td>
<td>1.08</td>
<td>0.83, 1.41</td>
</tr>
<tr>
<td>No use</td>
<td>9,126,490</td>
<td>2,374</td>
<td>26</td>
<td>1</td>
<td>Referent</td>
<td>1</td>
<td>Referent</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DCCB, dihydropyridine calcium channel blocker; RR, rate ratio.

a Adjusted for age (in 5-year intervals).

b Adjusted for age (in 5-year intervals), sex, year, propensity score, and use of beta blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, non-DCCBs, amiloride, and statins.

and felodipine. Among patients with incident Parkinson’s disease, we also found a significantly lower risk of death, but not of dementia, associated with DCCB use.

While the pathogenesis of Parkinson’s disease is complex (22), experimental studies suggest a key role for disturbances of calcium homeostasis (5, 6, 23). Research in humans further supports this proposal, demonstrating disease associations with polymorphic genes that code for products involved in calcium regulation (24–28). Dopaminergic cells in the substantia nigra possess pacemaking activity. In an animal study, Chan et al. (9) found that with increasing age, dopaminergic neurons relied more on L-type voltage-gated calcium channel 1.3 channels for their intrinsic pacemaking. This made them more vulnerable to toxin-induced injury, while neurons of younger animals used sodium-dependent, and thereby less susceptible, mechanisms for their activity. If voltage-gated calcium channel 1.3 channels in older animals were blocked by the DCCB isradipine, their neurons returned to using the less harmful mechanisms for their function. Isradipine also prevented toxin-induced motor deficits, indicating that these mechanisms translate to functional benefit. Furthermore, in vitro studies suggest that DCCBs inhibit neuronal apoptosis (29), which is considered the main mechanism of neural cell death in Parkinson’s disease (22).

Our study found that the inverse association between DCCB use and Parkinson’s disease was carried by older persons; this supports the hypothesis that an age-dependent calcium-mediated neural toxicity may also be present in humans (6). Our findings of an association of ongoing, but not past, DCCB use with reduced risk of Parkinson’s disease are consistent with previous research (10). Together with our findings of a rapid disappearance of effects upon discontinuation of DCCBs, this speculatively suggests that any clinical effects of DCCBs may be associated with symptomatic relief (preventing the development of clinical symptoms of early disease) rather than having a long-term impact on neurodegeneration. Since a protective association was also observed for non-DCCBs in exploratory analyses, possible effects of CCBs on Parkinson’s disease may not be limited to voltage-gated calcium channel 1.3 channels. Because hypertension is not a risk factor for Parkinson’s disease (30), blood pressure lowering is unlikely to explain the observed protective association for DCCBs. This is supported by our sensitivity analysis, which found a reduced risk of Parkinson’s disease when DCCB use was compared with use of other antihypertensive agents.

Our results are largely in concert with those of 2 previous case-control studies (10, 11). A primary-care-based United Kingdom study including 3,637 Parkinson’s disease cases found an inverse association between current long-term use of DCCBs and non-DCCBs and Parkinson’s disease (OR = 0.77, 95% CI: 0.63, 0.95) (10). The effect appeared somewhat stronger in women, persons older than 80 years, and DCCB users. A Danish case-control study that included 1,931 cases found an inverse association with ever use of DCCBs (excluding amlodipine, OR = 0.73, 95% CI: 0.54, 0.97) (11). The study found no significant association for amlodipine; the authors attributed this to the poorer brain penetration of the drug. Although a murine study showed poorer blood-brain barrier penetration for amlodipine as compared with other DCCBs, the brain concentrations attained were still significant (31). Therefore, an effect of amlodipine, as observed in our study, is biologically plausible. Furthermore, by design, a case-control study will have difficulties determining effects of on-treatment exposure. This may explain why the study failed to detect protective associations.
for non-DiCCBs (OR = 1.14, 95% CI: 0.93, 1.39), which contrasts with our findings. While using the same data sources as the previous Danish case-control study (11), our cohort study covered a longer period of time, was larger, and, importantly, was designed to assess the effects of on-treatment exposure employing a detailed analysis of drug use.

A study using 2 cohorts of US health professionals did not demonstrate any significant association between CCBs and Parkinson’s disease, but the investigators failed to categorize drug exposure status with detail, potentially misclassifying unexposed persons as exposed, which would have biased results towards the null (14). Furthermore, because of a limited number of exposed cases (n = 18), there was limited statistical power; a 27% decrease in risk of Parkinson’s disease associated with CCB use could not be excluded (14). Two other studies found no significant associations but suffered from small sample sizes (12, 13). To our knowledge, ours is the first study to address the risk of disease progression. Although dementia and mortality may be blunt measures in this regard, they are well-established complications of Parkinson’s disease (1). The protective association for death in our study was carried by noncardiovascular deaths and therefore cannot be explained by antihypertensive effects.

Strengths of our study include nationwide coverage, long-term follow-up, and the largest sample size thus far. Furthermore, in contrast to previous case-control studies, we investigated the hypothesis prospectively, applying a time-to-event analysis, and we used the new-user design, which reduces prevalent user bias (17). We also conducted several subgroup analyses including specific DiCCBs and different age groups and demonstrated the robustness of the results in a number of sensitivity analyses. The incidence of Parkinson’s disease in this study was consistent with previous reports (1). There has been no validation of Parkinson’s disease diagnoses in the Danish National Patient Registry, but misclassification is unlikely to vary with exposure to DiCCBs; it would therefore only bias results towards the null. In sensitivity analyses, results were consistent when the case definition was restricted to persons registered as having a primary diagnosis of Parkinson’s disease in the National Patient Registry, an approach that likely increases diagnostic specificity. Our sensitivity analysis moving the index date back in time by 2 years, which hypothetically compensates for the insidious onset of Parkinson’s disease, did not find a significant association between DiCCB use and Parkinson’s disease. This analysis should be interpreted with caution, however, as it will introduce nondifferential misclassification of DiCCB

![Figure 1](https://academic.oup.com/aje/article-abstract/175/7/627/154209/632-Pasternak-et-al)
exposure for cases where the time span between onset and diagnosis is not 2 years, thereby biasing results towards the null. Our case-finding strategy was based on hospital data, which fails to detect patients diagnosed exclusively by general practitioners. Misclassifying these patients as noncases would bias results towards the null. The unavailability of diagnostic data from primary care explains why some diagnoses (e.g., hypertension) were poorly represented in the propensity score; failure to account for patients’ propensity for drug use may represent a source of unmeasured confounding.

Patients with Parkinson’s disease suffer from autonomic dysfunction, including hypotensive tendencies (2). If autonomic dysfunction were already evident before diagnosis, it would confer a lower propensity for prescription of antihypertensive agents to patients subsequently diagnosed with Parkinson’s disease; this could lead to overestimation of the protective association. However, prediagnostic hypotension was not a feature of Parkinson’s disease in a large cohort study (30). A lower propensity for antihypertensive treatment could still exist, as some patients may experience orthostatic hypotension or imbalance before diagnosis (32, 33). However, if these factors were to increase the probability of antihypertensive treatment cessation, an elevated risk of Parkinson’s disease would have been observed in past users of DiCCBs; this was not the case. Additionally, if these factors were to have a strong influence, a lower propensity would have existed for any antihypertensive treatment and a clear difference between DiCCBs and other antihypertensive agents would not have been observed in our sensitivity analysis. This is consistent with previous research (10, 11).

It should be noted, however, that our finding of reduced mortality risk associated with DiCCB use among patients with established Parkinson’s disease may have been influenced by disease severity. That is, antihypertensive treatment cessation is more likely in patients with severe disease (with increased risk of mortality) than in patients with less severe disease. Therefore, it would erroneously appear as if DiCCB use protects against mortality.

We lacked data on smoking, which is associated with cardiovascular disease and therefore use of cardiovascular drugs but with a lower risk of Parkinson’s disease (34).

<table>
<thead>
<tr>
<th>Outcome and DiCCB Use</th>
<th>Person-Years of Follow-up</th>
<th>No. of Incident Cases</th>
<th>Adjusted Rate Ratioa</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>681</td>
<td>18</td>
<td>0.97</td>
<td>0.60, 1.56</td>
</tr>
<tr>
<td>Past use</td>
<td>661</td>
<td>22</td>
<td>1.29</td>
<td>0.83, 2.01</td>
</tr>
<tr>
<td>No use</td>
<td>19,470</td>
<td>558</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>681</td>
<td>38</td>
<td>0.66</td>
<td>0.47, 0.91</td>
</tr>
<tr>
<td>Past use</td>
<td>661</td>
<td>71</td>
<td>1.19</td>
<td>0.93, 1.53</td>
</tr>
<tr>
<td>No use</td>
<td>19,470</td>
<td>1,526</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>Cause of death (among users)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseaseb</td>
<td>681</td>
<td>16</td>
<td>0.88</td>
<td>0.53, 1.47</td>
</tr>
<tr>
<td>All other somatic causes</td>
<td>681</td>
<td>20</td>
<td>0.54</td>
<td>0.34, 0.84</td>
</tr>
<tr>
<td>Accident/murder/suicide</td>
<td>681</td>
<td>2</td>
<td>1.00</td>
<td>0.24, 4.28</td>
</tr>
</tbody>
</table>

Abbreviation: DiCCB, dihydropyridine calcium channel blocker.

a Adjusted for age (in 5-year intervals), sex, year, socioeconomic class, degree of urbanization, Charlson comorbidity index, and use of beta blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, non-DiCCBs, amiloride, and statins.

b Includes cerebrovascular disease.
Consequently, smoking may have confounded the studied association. However, our comparison with other antihypertensive agents showing a clear benefit in favor of DiCCBs argues against this possibility; this analysis may also have balanced out other unmeasured confounders.

In conclusion, we found a strong inverse association between ongoing DiCCB exposure and incident Parkinson’s disease, particularly among older patients. Among patients with Parkinson’s disease, DiCCB use was significantly associated with reduced mortality. With increasing life expectancy worldwide, it has been estimated that the prevalence of Parkinson’s disease will double between 2005 and 2030 (35). This emphasizes the need for effective, safe, cheap, and widely available drugs. DiCCBs represent a potential mechanism-based therapeutic approach for Parkinson’s disease that merits further investigation in randomized trials.

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