Use of Antithrombotic Drugs and the Presence of Cerebral Microbleeds

The Rotterdam Scan Study

Meike W. Vernooij, MD; Mendel D. M. Haag, PharmD; Aad van der Lugt, MD, PhD; Albert Hofman, MD, PhD; Gabriel P. Krestin, MD, PhD; Bruno H. Stricker, MB, PhD; Monique M. B. Breteler, MD, PhD

**Background:** Cerebral microbleeds are hemosiderin deposits in the brain that are indicative of microangiopathy. Microbleeds in strictly lobar brain locations have been related to cerebral amyloid angiopathy, a bleeding-prone disease state.

**Objective:** To investigate the relation between antithrombotic drug use and the presence of cerebral microbleeds, especially those in strictly lobar locations.

**Design:** A population-based, cross-sectional analysis that used magnetic resonance imaging (MRI) to assess the presence and location of microbleeds. Complete information on outpatient use of platelet aggregation inhibitors and anticoagulant drugs before MRI was obtained from automated pharmacy records.

**Setting:** The Rotterdam Scan Study, a population-based imaging study in a general elderly community in the Netherlands.

**Participants:** A population-based sample of 1062 persons from a longitudinal cohort, 60 years and older, free of dementia, who underwent MRI examinations between August 15, 2005, and November 22, 2006.

**Main Outcome Measures:** Presence of cerebral microbleeds on MRI.

**Results:** Compared with nonusers of antithrombotic drugs, cerebral microbleeds were more prevalent among users of platelet aggregation inhibitors (adjusted odds ratio [OR], 1.71; 95% confidence interval [CI], 1.21-2.41). We did not find a significant association for anticoagulant drugs and microbleed presence (OR, 1.49; 95% CI, 0.82-2.71). Strictly lobar microbleeds were more prevalent among aspirin users (adjusted OR compared with nonusers, 2.70; 95% CI, 1.45-5.04) than among persons using carbasalate calcium (adjusted OR, 1.16; 95% CI, 0.66-2.02). This difference was even more pronounced when comparing persons who had used similar dosages of both drugs.

**Conclusions:** This cross-sectional study shows that use of platelet aggregation inhibitors is related to the presence of cerebral microbleeds. Furthermore, aspirin and carbasalate calcium use may differently relate to the presence of strictly lobar microbleeds.


Cerebral small-vessel disease is common in elderly persons, and well-studied markers on magnetic resonance imaging (MRI) include lacunar infarcts and white matter lesions. In the past decade, cerebral microbleeds have become acknowledged as new markers of small-vessel disease in the brain. These microbleeds, which consist of hemosiderin deposits in macrophages, can be visualized on T2*-weighted gradient-recalled echo (GRE) MRI as small areas of hypointensity. Generally, microbleeds are thought to occur on the basis of either cerebral amyloid angiopathy or arteriolosclerotic microangiopathy. There is accumulating evidence that microbleed location in the brain is reflective of their underlying origin. Microbleeds in deep or infratentorial locations are thought to be suggestive of hypertensive or arteriolosclerotic microangiopathy, whereas those occurring in strictly lobar brain sites are indicative of cerebral amyloid angiopathy. Cerebral...
amyloid angiopathy is characterized by accumulations of amyloid in the vessel wall that cause degeneration of smooth muscle cells, with the result that vessels are more susceptible to ruptures and hemorrhages. This finding suggests that especially strictly lobar microbleeds may be indicative of the presence of bleeding-prone brain vessels. In cerebral amyloid angiopathy, the use of platelet aggregation inhibitors and anticoagulants has been found to be related to increased occurrence of symptomatic hemorrhage. In a parallel manner, the development of asymptomatic lobar microbleeds in these persons perhaps also may be accelerated by use of these antithrombotic drugs. We hypothesized that microbleeds, especially those in strictly lobar locations, occur more often in persons using antithrombotic drugs. We therefore studied the association between the use of platelet aggregation inhibitors or anticoagulant drugs with the presence of microbleeds in different brain locations in a large elderly population.

**METHODS**

**STUDY PARTICIPANTS**

The study population was derived as described previously. In short, we randomly selected 1073 members of the first cohort expansion of the Rotterdam Study and in addition invited all Rotterdam Study participants who underwent brain imaging in the context of a previous round of the Rotterdam Scan Study (n=302) to participate in our study. Of these, a total of 1229 persons were classified in the frequency domain to 192 sections of 0.8 mm; acquisitions were performed between August 15, 2005, and November 22, 2006, of which 36 images had to be excluded because of artifacts, leaving a total of 1062 images to be analyzed.

**BRAIN MRI**

We performed a multisequence MRI protocol on a 1.5-T MRI machine (General Electric Healthcare, Milwaukee, Wisconsin) as described previously, including a T1-weighted, proton density-weighted, and fluid-attenuated inversion recovery sequence. For microbleed detection, we used a high-resolution 3-dimensional T2*-weighted GRE sequence, optimized to increase the conspicuity of cerebral microbleeds (repetition time, 45 milliseconds; echo time, 31 milliseconds; matrix size, 320 × 224; flip angle, 13°; field of view, 25 × 17 cm²; parallel imaging acceleration factor, 2; 96 sections encoded with a section thickness of 1.6 mm interpolated in the frequency domain to 192 sections of 0.8 mm; acquisition time, 5 minutes 55 seconds).

**RATING OF CEREBRAL MICROBLEEDS**

All 3-dimensional T2*-weighted GRE images were reviewed as described previously by 1 of 2 trained raters (one of whom, M.W.V., is a coauthor of this study), who recorded the presence, number, and location of cerebral microbleeds. Microbleeds were defined as focal areas of low-signal intensity on the 3-dimensional T2*-weighted GRE image, and they were categorized into 1 of 3 locations: lobar (cortical gray and lobar white matter), deep (deep gray matter [basal ganglia and thalamus] and white matter of the internal or external capsule and corpus callosum), and infratentorial (brainstem and cerebellum). All potential cerebral microbleeds were reviewed with an experienced neuroradiologist (A.v.d.L.). Intraobserver and interobserver reliabilities for microbleed detection were good.

**ANTITHROMBOTIC DRUG USE**

Study participants were registered at 1 or more of 7 community pharmacies that serve the study area. Of these pharmacies, complete records of all outpatient filled prescriptions in automated format were available as of January 1, 1991. Records included the product name, international nonproprietary name, Anatomical Therapeutic Chemical code, total number of delivered units (eg, tablets or capsules), prescribed daily number of units, and date of delivery and drug dosage.

We determined the use (categorized into yes or no) of antithrombotic drugs from January 1, 1991, onward. We classified antithrombotic drugs based on the Anatomical Therapeutic Chemical system according to pharmacologic subgroup into platelet aggregation inhibitors and anticoagulant drugs. Antiocoagulant drugs were further classified according to chemical subgroup (vitamin K antagonists and heparins).

Among platelet aggregation inhibitors, we distinguished aspirin and carbasalate calcium (also known as Ascal) preparations. The active ingredient of both aspirin and carbasalate calcium is salicylate, which is formed after hydrolysis in the intestines and liver. Carbasalate calcium is a complex of calcium acetylsalicylate and urea, which readily dissolves in water. Carbasalate calcium is generally thought to have pharmacokinetic properties and antiplatelet effects similar to those of aspirin. However, carbasalate calcium is shown to have a lower risk of mucosal damage and bleeding in the gastrointestinal tract than aspirin. Recent reports suggest that this difference is due to distinct systemic effects of carbasalate calcium compared with aspirin, rather than local effects at the level of the mucosal lining. We therefore hypothesized that aspirin and carbasalate calcium may differentially relate to microbleed presence. To take into account the fact that aspirin and carbasalate calcium can also be used as pain medication, we determined whether these drugs were used for inhibition of platelet aggregation on the basis of prescribed dose and regimen. A dose of 1 mg of carbasalate calcium is equivalent to 0.8 mg of aspirin. National guidelines dictate the use of aspirin and carbasalate calcium up to 80 and 100 mg, respectively, for the purpose of platelet aggregation inhibition. The dosage criterion was overruled only if the regimen clearly indicated the indication of use or if used as the loading dose at the start of therapy (3.4% of all prescriptions). Dosages of aspirin or carbasalate calcium of approximately 30 or 38 mg, respectively, are generally specifically advised in case of previous cerebrovascular events (“neuro dosages”), whereas dosages of approximately 80 to 100 mg, respectively, are considered “cardiac dosages.”

**CONFOUNDING BY INDICATION**

Associations between drug use and certain outcomes may be confounded by the indication for which the drugs are prescribed. Antithrombotic drugs are usually prescribed in persons at risk for or with a history of ischemic cardiovascular or cerebrovascular disease, which in turn can be related to the risk of cerebral microbleeds. We therefore assessed cardiovascular risk factors as potential confounders. Furthermore, we determined whether persons had a known history of cerebrovascular disease. Finally, we recorded the presence of infarcts and the volume of white matter lesions on MRI because these are known markers of ischemic cerebrovascular disease and therefore more likely to be influenced by confounding by indication.

**CARDIOVASCULAR RISK FACTORS**

For cardiovascular risk factors, we used information that was obtained by interview and laboratory and physical examination at the
**Table 1. Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%) of Patients (N=1062)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>69.6 (7.2)</td>
</tr>
<tr>
<td>Women</td>
<td>543 (51.1)</td>
</tr>
<tr>
<td>Cerebral microbleeds</td>
<td>250 (23.5)</td>
</tr>
<tr>
<td>Strictly lobar</td>
<td>146 (13.7)</td>
</tr>
<tr>
<td>Deep or infratentorial</td>
<td>104 (9.6)</td>
</tr>
<tr>
<td>Any use of antithrombotic drugs</td>
<td>363 (34.2)</td>
</tr>
<tr>
<td>Exclusive use of platelet aggregation inhibitors</td>
<td>245 (23.1)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>67 (6.3)</td>
</tr>
<tr>
<td>Carbasalate calcium</td>
<td>141 (13.3)</td>
</tr>
<tr>
<td>Exclusive use of anticoagulant drugs</td>
<td>61 (5.9)</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>51 (4.9)</td>
</tr>
<tr>
<td>Heparin</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>144.4 (18.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>80.2 (10.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>310 (29.7)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>445 (42.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>95 (8.9)</td>
</tr>
<tr>
<td>Total serum cholesterol, mean (SD), mg/dL</td>
<td>219.3 (37.2)</td>
</tr>
<tr>
<td>HDL-C, mean (SD), mg/dL</td>
<td>55.6 (14.9)</td>
</tr>
<tr>
<td>Known history of cerebrovascular disease</td>
<td>36 (3.4)</td>
</tr>
<tr>
<td>Infarcts on MRI</td>
<td>119 (11.2)</td>
</tr>
<tr>
<td>WML volume, median (IQR), mL</td>
<td>3.4 (2.0-7.3)</td>
</tr>
</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; MRI, magnetic resonance imaging; WML, white matter lesion.

SI conversion factors: To convert HLD-C and total cholesterol to millimoles per liter, multiply by 0.0259.

aData are presented as number (percentage) of patients unless otherwise indicated. Data are missing for smoking (n=17) and use of anticoagulant drugs (n=24).

bWith or without microbleeds in a lobar location.

preceding regular visit of study participants to the research center.1 We computed the Framingham risk score for each participant using age, sex, systolic and diastolic blood pressure, serum total cholesterol level, serum high-density lipoprotein cholesterol level, presence of diabetes mellitus, and smoking status.17

**HISTORY OF CEREBROVASCULAR DISEASE**

A known history of cerebrovascular disease was assessed as follows. On entry into the Rotterdam Study, history of stroke is assessed.18 Subsequently, participants are continuously monitored for incident stroke through automated linkage of the study database with files from general practitioners and hospital discharge information. All reported events are validated by an experienced neurologist.19

**INFARCTS AND WHITE MATTER LESIONS ON MRI**

Infarcts were rated on fluid-attenuated inversion recovery, proton density-weighted, and T1-weighted sequences by the 2 raters who had scored the cerebral microbleeds, as described previously.20 All infarcts were reviewed in a consensus meeting with an experienced neuroradiologist (A.v.d.L.). For white matter lesion volume quantification, we used a validated tissue classifier21 to automatically segment MRIs into gray matter, white matter, cerebrospinal fluid, and white matter lesions. White matter lesion volumes were calculated by summing all voxels of the white matter lesion class across the whole brain to yield volumes in milliliters.

**RESULTS**

Population characteristics are given in Table 1. The mean age of the population was 69.6 years (age range, 60.7-96.7 years) and 543 (51.1%) were women. There were 363 persons (34.2%) who had used any kind of antithrombotic drug in the years before MRI. Of these, 245 persons (23.1%) had exclusively used platelet aggregation inhibitors and anticoagulants before MRI and in addition studied all separate drug types (aspirin, carbasalate calcium, vitamin K antagonists, and heparins). Non-users of antithrombotic drugs served as reference, unless specified otherwise. All analyses were adjusted for age and sex. To adjust for cardiovascular risk without overfitting the model,21 we also adjusted all analyses for the Framingham risk scores.

For comparison, we also studied the association between antithrombotic drug use and the presence of brain infarcts and volume of white matter lesions (dichotomized at the 75th percentile). We performed all analyses again excluding persons with a known history of cerebrovascular disease.

Furthermore, we tested whether the mean daily dose that was prescribed for aspirin and carbasalate calcium differed. To control for differences in dosage of these drugs, and thus for possible differences in indication,16 we performed a direct comparison between users of aspirin or carbasalate calcium who had only been prescribed so-called cardiac dosages (>50 mg/d). All analyses were performed using a commercially available software program (SPSS, version 11.0.1 for Windows; SPSS Inc, Chicago, Illinois).

We categorized persons based on the location of their microbleeds as described previously.4 In short, we made a category of persons who had 1 or more microbleeds restricted to a lobar location (“strictly lobar”). Persons who had at least 1 microbleed in a deep or infratentorial brain location were assigned to the category “deep or infratentorial microbleeds.”

We analyzed the relation between exclusive use of platelet aggregation inhibitors and anticoagulants before MRI and the presence of microbleeds using multiple logistic regressions. We performed these analyses again for microbleeds in specific locations (strictly lobar and deep or infratentorial) and in addition studied all separate drug types (aspirin, carbasalate calcium, vitamin K antagonists, and heparins). Non-users of antithrombotic drugs served as reference, unless specified otherwise. All analyses were adjusted for age and sex.

**DATA ANALYSIS**

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Table 2. Use of Platelet Inhibitors or Anticoagulant Drugs and the Presence of Cerebral Microbleeds, Infarcts, and White Matter Lesions

<table>
<thead>
<tr>
<th>Antithrombotic Therapy</th>
<th>Any Microbleed (n=250)</th>
<th>Infarct (n=119)</th>
<th>High White Matter Lesion Volume (n=266)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1c</td>
<td>Model 2d</td>
<td>Model 1c</td>
</tr>
<tr>
<td>Any use of antithrombotic drugs (n=383)</td>
<td>1.55 (1.14-2.09)</td>
<td>1.56 (1.15-2.12)</td>
<td>2.55 (1.69-3.84)</td>
</tr>
<tr>
<td>Platelet aggregation inhibitors (n=245)</td>
<td>1.68 (1.20-2.35)</td>
<td>1.71 (1.21-2.41)</td>
<td>2.31 (1.46-3.67)</td>
</tr>
<tr>
<td>Anticoagulant drugs (n=61)</td>
<td>1.47 (0.81-2.67)</td>
<td>1.49 (0.82-2.71)</td>
<td>1.41 (0.59-3.36)</td>
</tr>
<tr>
<td>Both platelet aggregation inhibitors and anticoagulant drugs (n=57)</td>
<td>1.10 (0.59-2.08)</td>
<td>1.06 (0.56-2.03)</td>
<td>5.16 (2.72-9.81)</td>
</tr>
</tbody>
</table>

a Exclusive users of given drug categories. Persons with a history of use of more than 1 type of antithrombotic drug are investigated separately.

b Dichotomized at the 75th percentile.

c Model 1 was adjusted for age and sex.

d Model 2 was adjusted for age, sex, and Framingham risk score.

Table 3. Use of Antithrombotic Drugs and the Presence of Cerebral Microbleeds According to Location

<table>
<thead>
<tr>
<th>Antithrombotic Therapy</th>
<th>Strictly Lobar Microbleeds (n=146)</th>
<th>Deep or Infratentorial Bleeds (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1b</td>
<td>Model 2c</td>
</tr>
<tr>
<td>No use (n=699)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Any use of antithrombotic drugs (n=383)</td>
<td>1.43 (0.98-2.08)</td>
<td>1.42 (0.97-2.08)</td>
</tr>
<tr>
<td>Platelet aggregation inhibitors (n=245)</td>
<td>1.66 (1.10-2.50)</td>
<td>1.63 (1.08-2.48)</td>
</tr>
<tr>
<td>Aspirin (n=67)</td>
<td>2.67 (1.44-4.97)</td>
<td>2.70 (1.45-5.04)</td>
</tr>
<tr>
<td>Carbasalate calcium (n=141)</td>
<td>1.12 (0.65-1.93)</td>
<td>1.16 (0.66-2.02)</td>
</tr>
<tr>
<td>Anticoagulant drugs (n=61)</td>
<td>1.37 (0.66-2.87)</td>
<td>1.39 (0.67-2.71)</td>
</tr>
<tr>
<td>Vitamin K antagonists (n=51)</td>
<td>1.52 (0.68-3.42)</td>
<td>1.53 (0.68-3.45)</td>
</tr>
<tr>
<td>Both platelet aggregation inhibitors and anticoagulant drugs (n=57)</td>
<td>0.59 (0.22-1.58)</td>
<td>0.61 (0.23-1.62)</td>
</tr>
</tbody>
</table>

a Exclusive users of given drug categories. Users of more than 1 type of antithrombotic drug are investigated separately.

b Model 1 was adjusted for age and sex.

c Model 2 was adjusted for age, sex, and Framingham risk score.

d Only a few cases (n=5) were available for exclusive use of heparin, prohibiting separate investigation of this exposure group.

for cardiovascular risk did not change any of the associations (Table 2). Exclusion of persons with a known history of cerebrovascular disease (n=36) attenuated the associations between antithrombotic drug use and infarcts or white matter lesions but did not alter the relation with cerebral microbleeds (data not shown).

When analyzing according to microbleed location, antithrombotic drug use appeared similarly related to the presence of strictly lobar and deep or infratentorial microbleeds (Table 3). Remarkably, aspirin users more often had strictly lobar microbleeds (adjusted OR, 2.70; 95% CI, 1.45-5.04) than nonusers. This occurrence was not seen for users of carbasalate calcium (OR for the presence of strictly lobar microbleeds, 1.16; 95% CI, 0.66-2.02; Table 3). In contrast, both aspirin and carbasalate calcium were equally strongly related to the presence of deep or infratentorial microbleeds (Table 3). The pattern for infarcts and white matter lesion load was reversed: users of carbasalate calcium more often had infarcts (OR, 2.64; 95% CI, 1.52-4.95) or high white matter lesion load (OR, 1.80; 95% CI, 1.16-2.79) than nonusers, but this was not true for aspirin users (OR of aspirin users compared with nonusers for infarcts, 1.73; 95% CI, 0.78-3.83; and OR of aspirin users compared with nonusers for white matter lesions, 1.01; 95% CI, 0.52-1.95). Further investigation of anticoagulant drugs into exposure to vitamin K antagonists vs heparin was less informative because of the low numbers of heparin users, although use of vitamin K antagonists seemed related to deep or infratentorial microbleeds but not to strictly lobar microbleeds (Table 3). Among users of platelet aggregation inhibitors, the mean prescribed daily dose of aspirin was higher than the dose of carbasalate calcium (89.0 vs 72.2 mg [equivalent to 57.8 mg of aspirin]; P <.001). This finding was mainly attributable to carbasalate calcium being more often prescribed in low doses (neuro dosage) 14-16: 56% of persons using carbasalate calcium had been prescribed at any time a low-dose preparation (dose of <50 mg/d) vs none of the persons using aspirin. Restricting our analysis to users of high doses (cardiac dosage) 16 of either aspirin or carbasalate calcium, we found an even more marked difference between aspirin use and carbasalate calcium use and the presence of strictly lobar microbleeds (Table 3).
of strictly lobar microbleeds (Table 4), whereas mean prescribed daily dose no longer differed significantly (89.0 mg for aspirin vs 102.8 mg for carbasalate calcium [equivalent to 82.2 mg of aspirin]). This finding again indicated that aspirin users more often had strictly lobar microbleeds compared with users of carbasalate calcium. Again, this discrepancy was not present for microbleeds in deep or infratentorial locations or for infarcts and high white matter lesion load.

### Table 4. Use of Cardiac Dosage Aspirin or Carbasalate Calcium and Cerebral Microbleeds, Infarcts, and White Matter Lesions

<table>
<thead>
<tr>
<th>Use of carbasalate calcium in cardiac dosage (n=61)</th>
<th>Use of aspirin in cardiac dosage (n=66)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of carbasalate calcium in cardiac dosage (n=61)</td>
<td>Use of aspirin in cardiac dosage (n=66)</td>
<td>Any Microbleed Strictly Lobar Microbleeds Deep or Infarct Microbleeds Infarct High White Matter Lesion Volume</td>
</tr>
<tr>
<td>Model 1</td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>2.05 (0.94-4.49)</td>
<td>4.02 (1.34-12.04)</td>
<td>1.00 (0.36-2.76)</td>
</tr>
<tr>
<td>1.88 (0.84-4.18)</td>
<td>3.83 (1.25-11.70)</td>
<td>0.95 (0.34-2.68)</td>
</tr>
</tbody>
</table>

- **a** Dichotomized at the 75th percentile.
- **b** Model 1 was adjusted for age and sex.
- **c** Model 2 was adjusted for age, sex, and Framingham risk score.

We found that cerebral microbleeds were more prevalent in persons who had used or were using antithrombotic drugs. Furthermore, our data show a higher prevalence of strictly lobar microbleeds among aspirin users than among people using carbasalate calcium.

Before discussing the implications of our findings, we need to address some methodologic considerations. First, our study was not prospective, which limited our ability to draw conclusions regarding cause and effect. Presence of cerebral microbleeds on MRI does not provide information on when these bleeds actually occurred because hemosiderin deposits can remain visible in the brain for an undefined period. Therefore, it is possible that some of the microbleeds we assessed actually occurred before use of antithrombotic drugs. If this occurred, it may have influenced our results. Second is the issue of confounding by indication. Because cerebral microbleeds may be related to the presence of cardiovascular or cerebrovascular disease in general, antithrombotic drugs may be more often prescribed to persons with an increased risk of developing microbleeds, which would confound our results. We have tried to minimize confounding by indication by adjusting our analyses for cardiovascular risk and by excluding persons with a known history of cerebrovascular disease from our analyses.

We found that anticoagulant drug use was not significantly related to the presence of microbleeds, whereas platelet aggregation inhibitor use was. This result contrasts with those from meta-analyses that compare the relative risks of anticoagulant vs aspirin therapy in patients with atrial fibrillation, which have reported that oral anticoagulant therapy was associated with an increased risk of major (symptomatic) bleeding (hazard ratio of 1.7) compared with aspirin. Lack of statistical significance for anticoagulants in relation to microbleeds in our study may be attributable to the lower number of anticoagulant users in our population. Furthermore, if anticoagulant drugs indeed predispose persons to symptomatic intracranial bleeds, which usually have major clinical impact, these persons would have been less likely to be included in our population-based study. Alternatively, one could hypothesize that the different associations for anticoagulants and platelet aggregation inhibitors result from different hemostatic mechanisms. It may be that microbleed formation is more dependent on the sealing of small-vessel–wall defects by platelet aggregation than it is on clot stabilization.

We furthermore found a differential relation between use of aspirin or carbasalate calcium and the presence of strictly lobar microbleeds, which are thought to be indicative of cerebral amyloid angiopathy. This difference is not likely caused by confounding by indication because we did not observe such a difference for deep or infratentorial microbleeds or for infarcts and white matter lesions, all of which are known to be more strongly related to vascular risk than strictly lobar microbleeds. The difference was even more pronounced when comparing persons who had used only the cardiac dosage of these drugs, which indicates that prescribed doses or differences in indication did not play a role either. We cannot rule out the possibility that ours is a chance finding: replication of our observations is needed. However, in view of the increasing evidence that microbleeds in different locations reflect a different underlying vascular condition, the possibility that the observed difference is caused by an underlying biological mechanism merits consideration. One could speculate that aspirin and carbasalate calcium differentially affect microbleed development in cerebral amyloid angiopathy. Although aspirin and carbasalate calcium have the same active component, salicylate, the bioavailability of aspirin may differ from carbasalate calcium and both drugs may not have similar systemic effects. Alternatively, the mode of administration of aspirin and carbasalate calcium, for example, in effervescent tablets or enteric-coated tablets, may influence biological availability or effect. Unfortunately, our data set lacked power to investigate
whether the mode of administration may have played a role in our observations.

There is currently major interest in bleeding risks with the use of antithrombotic or thrombolytic treatment in persons who have microbleeds that are apparent on MRI.\(^{1-30}\) Because this may affect treatment in patients with cardiovascular or cerebrovascular disease. Our data show an association between use of platelet aggregation inhibitors and the presence of cerebral microbleeds. The cross-sectional design of our analyses prohibited an investigation of whether persons with cerebral microbleeds are at increased risk for symptomatic hemorrhage when using platelet aggregation inhibitors. Of note is that the beneficial effects of well-indicated antithrombotic drugs in persons at risk for myocardial infarction or ischemic cerebrovascular disease should not be disregarded because these have been shown to outweigh any risks of bleeding.\(^ {31-36}\) Nevertheless, it may be that in selected persons (eg, those with signs of cerebral amyloid angiopathy), this risk-benefit ratio may differ for certain drugs (eg, aspirin), thus influencing treatment decisions. The cross-sectional associations between antithrombotic drugs and microbleeds in the general population on which we report would therefore justify further longitudinal research into this association. Of particular clinical interest would be a study of whether the presence of microbleeds increases the risk of symptomatic intracerebral hemorrhage in persons using antithrombotic medication.

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Correspondence: Monique M. B. Breteler, MD, PhD, Department of Epidemiology, Erasmus MC University Medical Center, Dr. Molewaterplein 50, 3015 GE, Rotterdam, the Netherlands (m.breteler@erasmusmc.nl).

Author Contributions: Study concept and design: Vernooij, Haag, Van der Lugt, Hofman, Krestit, and Breteler. Acquisition of data: Vernooij, Haag, and Stricker. Analysis and interpretation of data: Vernooij, Haag, Stricker, and Breteler. Drafting of the manuscript: Vernooij, Haag, Stricker, and Breteler. Critical revision of the manuscript for important intellectual content: Vernooij, Haag, Van der Lugt, Hofman, Krestit, Stricker, and Breteler. Statistical analysis: Vernooij and Breteler. Obtained funding: Hofman, Krestit, and Breteler. Administrative, technical, and material support: Vernooij and Haag. Study supervision: Van der Lugt, Hofman, Krestit, Stricker, and Breteler.

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REFERENCES


