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# Clopidogrel Use Is Associated With an Increased Prevalence of Cerebral Microbleeds in a Stroke-Free Population: The Rotterdam Study

Sirwan K.L. Darweesh, BSc; Maarten J.G. Leening, MD, MSc; Saloua Akoudad, MD, MSc; Daan W. Loth, MD, MSc; Albert Hofman, MD, PhD; M. Arfan Ikram, MD, PhD; Meike W. Vernooij, MD, PhD; Bruno H. Stricker, Mmed, PhD

***Background*—**Although clopidogrel reduces the incidence of atherothrombotic events, its use is associated with an increased risk of major bleeding. Cerebral microbleeds (CMBs) are indicative of subclinical microangiopathy in the brain and may prelude symptomatic intracerebral hemorrhage. We examined the association between use of clopidogrel and CMBs in persons without a history of stroke.

***Methods and Results*—**We performed a cross-sectional analysis using data from the Rotterdam Study, a prospective population-based cohort of persons aged 45 years and older. Among 4408 stroke-free individuals who underwent brain magnetic resonance imaging for the detection of CMBs, we identified 121 ever-users and 4287 never-users of clopidogrel before magnetic resonance imaging. We used multiple logistic regression to analyze the association between clopidogrel and CMBs with adjustment for age, sex, cardiovascular risk factors, and common cardiovascular medication. Users of clopidogrel had a higher prevalence of CMBs (odd ratio 1.55, 95% CI 1.01 to 2.37) than nonusers and more often had a high number (>4) of CMBs (odds ratio 3.19, 95% CI 1.52 to 6.72). Clopidogrel use was associated with a significantly higher prevalence of deep or infratentorial CMBs (odd ratio 1.90, 95% CI 1.05 to 3.45). Among clopidogrel users, we were unable to demonstrate differences in the prevalence of CMBs by indication of prescription, history of coronary heart disease, or common genetic variants in *CYP2C19*.

***Conclusions*—**In stroke-free individuals, clopidogrel use was associated with a higher prevalence and higher number of CMBs. Whether this association is causal requires confirmation in prospective studies, especially given the small number of participants taking clopidogrel and the possibility of residual confounding in this study. **(*J Am Heart Assoc.* 2013;2:e000359 doi: 10.1161/JAHA.113.000359)**

**Key Words:** cerebral microbleed • magnetic resonance imaging • platelet inhibitor • population studies



Clopidogrel is a commonly prescribed antiplatelet drug, especially during and after percutaneous coronary interventions (PCIs).[1,2] The addition of clopidogrel to aspirin monotherapy reduces the recurrence of atherothrombotic events.[3] Despite its considerable clinical benefit, clopidogrel use is also associated with an increased risk of major bleeding.[4] To date, there is still a gap in knowledge on subclinical bleeds under clopidogrel use.

*From the Departments of Epidemiology (S.K.L.D., M.J.G.L., S.A., D.W.L., A.H., M.A.I., M.W.V., B.H.S.), Cardiology (M.J.G.L.), Radiology (S.A., M.A.I., M.W.V.), and Neurology (S.A., M.A.I.), Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands; Inspectorate for Health Care (D.W.L., B.H.S.), The Hague, the Netherlands.*

**Correspondence to:** Bruno H. Stricker, Mmed, PhD, Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, P.O. Box 2040, 3000 CA, Rotterdam, the Netherlands. E-mail: b.stricker@erasmusmc.nl

Received July 11, 2013; accepted August 23, 2013.



Cerebral small-vessel disease is a common finding in elderly individuals[5], and cerebral microbleeds (CMBs) on magnetic resonance imaging (MRI) are a relatively newly recognized marker of the condition.[6] CMBs rarely disappear once they are present[7], and the presence of CMBs has been associated with prevalence and severity of spontaneous intracerebral hemorrhage.[8] In addition, the presence of CMBs may predict future occurrence or recurrence of intracerebral hemorrhage.[9,10]

We hypothesized that CMBs occur more often in persons using clopidogrel and studied the association among clopidogrel, *CYP2C19* genotype, and CMBs in a large population-based cohort study.

## Methods

### Study Population

This cross-sectional analysis of CMB occurrence was part of the Rotterdam Scan Study, an ongoing population-based cohort study investigating age-related brain changes on MRI

within the larger Rotterdam Study.[11,12] At the time of this study, a total of 5990 participants of the Rotterdam Study had at least once been invited to undergo a scan. Of these, 5449 participants were eligible, of whom 5007 participated and gave written consent (response rate 91.9%). After the exclusion of subjects with physical inabilities to complete an MRI examination, scans of 4930 subjects were obtained between 2005 and 2011, of which 34 images had to be excluded because of artifacts, leaving 4896 images to be analyzed.

Given the cross-sectional design of this study, it was impossible to assess whether a stroke or a CMB occurred first in the study participants in whom both were present on MRI. Both ischemic and hemorrhagic stroke are associated with an increased prevalence of CMBs.[13] Because an ischemic stroke can be an indication for use of clopidogrel,[14] the inclusion of persons with an ischemic stroke could lead to a spurious overestimate of the effect of the association between clopidogrel use and CMBs. Hemorrhagic stroke can be a contraindication for antithrombotic drug prescription,[15] so the inclusion of patients with such a condition could spuriously dilute the association between clopidogrel use and CMBs. Consequently, we excluded all persons with an MRI-defined hemorrhagic or ischemic stroke (n=488), leaving a study population of 4408 participants. The Rotterdam Study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. All participants provided written informed consent to participate in the study.

## Brain MRI and CMBs

All participants underwent a multisequence MRI protocol using a 1.5-T scanner (GE Healthcare), which included a custom-made accelerated 3-dimensional T2*-weighted gradient-recalled echo (3-dimensional T2* GRE) sequence with high spatial resolution and long echo time was used for CMB detection.[16] All scans were reviewed by experienced raters for the presence, number, and location of CMBs, which were defined as focal areas of very low signal intensity that were not accompanied by evident signal abnormality on other structural sequences.[6] All raters were blinded to the clinical data and genotype, and intraobserver and interobserver reliabilities for CMB rating were very good ($\kappa$=0.85 to 0.87).[17] As previously done by others,[18,19] CMB location was classified as lobar (cortical gray matter and subcortical or periventricular white matter), deep (deep gray matter: basal ganglia and thalamus, and the white matter of the corpus callosum, internal, external, and extreme capsule), or infratentorial (brainstem and cerebellum). CMBs in deep or infratentorial locations are believed to be suggestive of hypertensive or atherosclerotic microangiopathy,[20] whereas those occurring in strictly lobar brain sites are indicative of cerebral amyloid angiopathy.[21]

## Pharmacy Data

Nearly all participants of the Rotterdam Study are registered at 1 or more of the 7 community pharmacies that serve the study area.[12] As of January 1, 1991, complete records of all outpatient dispensed prescriptions of these pharmacies have been available in automated format, and concordance between pharmacy dispense records and patient interview data is strong.[22] Records include the product name, international nonproprietary name, Anatomical Therapeutic Chemical (ATC) code,[23] prescribed daily number of units, date of delivery, drug dosage, and the total number of delivered units,[24] the latter of which was used to determine cumulative exposure to clopidogrel. We used ATC codes B01AA, B01AB, B01AC, and B01AX for antithrombotic agent use (of which B01AC04 represents clopidogrel); C02, C03, C07, C08, and C09 for antihypertensive medication; and C10 for lipid-modifying medication.

## Covariables, Medical History and *CYP2C19*

At every regular visit of study participants to the Rotterdam Study research center, information on cardiovascular risk factors was obtained through interview, laboratory and physical examination.[25] A known history of myocardial infarction was assessed on entry of study participants into the Rotterdam Study and, subsequently, participants have been continuously monitored for incident myocardial infarction through automated linkage of the study database with files from general practitioners and hospital discharge information. For all cases, subsequent validation by research physicians and medical specialists was performed on the basis of clinical details from medical records as described earlier.[25]

As a prodrug, clopidogrel is activated by several hepatic enzymes, including cytochrome P450 subfamily 2C19 (CYP2C19); common variation in the *CYP2C19* gene alters enzyme activity and thereby platelet reactivity to clopidogrel.[26,27] As a result, individuals with at least 1 *CYP2C19*2* (681G>A, rs4244285) variant allele have a lower risk of bleeding,[28] whereas the *CYP2C19*17* (806C>T, rs12248560) variant is associated with a higher risk of major bleeding.[29] As previously described in detail,[12] the Illumina HumanHap 550k and 610-Quad arrays were used in the majority of participants of the Rotterdam Study to perform genotyping of autosomal SNPs. This included genotyping the rs12767583 and rs12243416 variants, which are, respectively, in complete linkage disequilibrium ($r^2$=1.0) with rs4244285 (*CYP2C19*2*) and rs12248560 (*CYP2C19*17*). Within clopidogrel users, we distinguished persons with at least 1 **2* allele (the **2* group), persons with at least 1 **17* allele (the **17* group), and wild-type homozygotes (defined by the absence of **2* and **17* variants). We hypothesized that CMB prevalence and number

would be lower in persons with a *CYP2C19*2* variant allele than in wild-type homozygotes and higher in persons with a *CYP2C19*17* variant allele.

## Data Analysis

We used multiple logistic regression analyses to calculate odds ratios (ORs) for the prevalence of CMBs in ever-users and never-users of clopidogrel before MRI, both overall and per brain location category ("strictly lobar" and "deep or infratentorial"). We also investigated the association of clopidogrel with the number of CMBs, both as a continuous (linear regression) and a categorical outcome measure (multinomial logistic regression). Based on the left-skewedness of the distribution of the number of CMBs in the general population,[30,31] we categorized the number of CMBs into 1, 2 to 4, and >4 and used CMB-free individuals as the reference category. In a separate analysis, we compared the prevalence of CMBs between individuals who only used salicylates, individuals who used both salicylates and clopidogrel, and individuals who used neither.

All analyses were performed twice using complete-case data: in the first model, adjustments were made for age and sex. For the second model, we adjusted additionally for traditional cardiovascular risk factors and cardiovascular medication: smoking (current, former, never), systolic and diastolic blood pressure, diabetes mellitus, total and high-density lipoprotein cholesterol, use of antihypertensive medication, use of lipid-modifying medication, and use of any antithrombotic agent other than clopidogrel. Also, we consecutively repeated model II analyses by adding duration of clopidogrel use as a categorical determinant (per 3 months of cumulative use, highest category >18 months) and separately adding the first prescription indication for clopidogrel as a categorical variable (PCI, other intervention, no intervention). Also, we added history of myocardial infarction into the model and studied the interaction term of myocardial infarction and use of clopidogrel in our study population. We repeated this analysis for a history of any coronary heart disease (myocardial infarction, PCI, or surgical coronary artery bypass graft surgery).

To assess the influence of *CYP2C19* in clopidogrel users, we compared CMB prevalence and number in the **2* group with wild-type homozygotes and the **17* group with wild-type homozygotes. We used a commercially available software program (IBM SPSS Statistics for Windows, Version 20.0).

## Results

Study population characteristics at the time of the scan are presented in Table 1. The mean age of the population was 63.6 years (age range 45.7 to 96.3 years), and 2136 (48.5%) were women. There were 121 persons (2.7%) who had used clopidogrel before MRI, 111 of whom had also used a salicylate. First prescription dose was available for 83 (68.6%) clopidogrel users; in all of these individuals, the same dose was prescribed (75 mg once daily). The association between clopidogrel use and the presence and location of CMBs is shown in Table 2. Users of clopidogrel had a higher prevalence of CMBs than nonusers of clopidogrel (adjusted OR for users compared with nonusers 1.55, 95% CI 1.01 to 2.37). Clopidogrel use was significantly associated with a higher prevalence of CMBs in deep or infratentorial locations (OR 1.90, 95% CI 1.05 to 3.45), but not with CMBs in strictly lobar locations (OR 1.34, 95% CI 0.81 to 2.21). Clopidogrel users had an average number of 1.6 CMBs, while non-users on average had 0.5 CMBs ($P$=0.01). The distribution of number of CMBs according to clopidogrel ever-use is shown in Figure. Clopidogrel use was significantly associated with presence of more than 4 CMBs (OR 3.19, 95% CI 1.52 to 6.72), but not with presence of 1 CMB (OR 1.35, 95% CI 0.79 to 2.31) and 2 to 4 CMBs (OR 1.14, 95% CI 0.55 to 2.36).

The multivariate model had reasonable discriminative ability for the presence of CMBs in any location (c-statistic 0.69, 95% CI 0.67 to 0.71), strictly lobar locations (c-statistic 0.67, 95% CI 0.65 to 0.70), and deep or infratentorial locations (95% CI 0.73 to 0.79). The overall calibration of the model was good for the presence of any CMB (Hosmer-Lemeshow goodness-of-fit statistic $\chi^2$=9.66, $P$=0.29), strictly lobar CMBs ($\chi^2$=11.84, $P$=0.16), and deep or infratentorial CMBs ($\chi^2$=5.71, $P$=0.68).

We found no evidence of effect modification between clopidogrel use and history of myocardial infarction ($P$=0.35). The OR for clopidogrel use was 1.63 (95% CI 0.93 to 2.88) in persons without a history of myocardial infarction and 1.03 (95% CI 0.49 to 2.15) in persons with a history of myocardial infarction. Similarly, we could not demonstrate effect modification between clopidogrel and a history of any coronary heart disease ($P$=0.44). In individuals without a history of coronary heart disease, those who used clopidogrel had an OR of 1.39 (95% CI 0.49 to 3.91); in individuals with a history of coronary heart disease, clopidogrel users had an OR of 0.76 (95% CI 0.43 to 1.35).

Within clopidogrel users, duration of use was not associated with a difference in prevalence ($P$=0.64) or number of CMBs ($P$=0.89). The indication for the first prescription of clopidogrel was retrieved in 104 clopidogrel users; in 87 of those a PCI was the indication. There was no significant difference in prevalence of CMBs between participants with a PCI as the first indication and participants with other indications ($P$=0.43).

Also, exclusion of ever-users of anticoagulants (n=435) did not affect the effect size of the association between

**Table 1.** Characteristics of the Study Population

| Characteristic | Study Population | Clopidogrel Ever Use | |
|---|---|---|---|
| | | Yes | No |
| No. of participants | 4408 | 121 | 4287 |
| Age, mean (SD), y | 63.6 (11.0) | 70.4 (11.2) | 63.4 (11.0) |
| Women, n (%) | 2136 (48.5) | 69 (57.0) | 2067 (48.2) |
| Participants with ≥1 cerebral microbleed, n (%) (%) | 783 (17.8) | 45 (37.2) | 738 (17.2) |
| 1 cerebral microbleed, n (%) | 509 (11.5) | 22 (18.2) | 487 (11.4) |
| 2 to 4 cerebral microbleeds, n (%) | 204 (4.6) | 10 (8.3) | 194 (4.5) |
| >4 cerebral microbleeds, n (%) | 70 (1.6) | 13 (10.7) | 57 (1.3) |
| Deep or infratentorial cerebral microbleeds, n (%) | 218 (5.7) | 19 (20.0) | 199 (5.3) |
| Strictly lobar cerebral microbleeds, n (%) | 565 (13.5) | 26 (25.5) | 539 (13.2) |
| Any ever use of antithrombotic drugs, n (%) | 1375 (31.2) | 114 (94.2) | 1261 (29.4) |
| Ever use of aspirin and/or carbasalate calcium, n (%) | 1142 (25.9) | 111 (91.7) | 1031 (24.0) |
| Ever use of anticoagulant drugs,* n (%) | 435 (9.9) | 32 (26.4) | 403 (9.4) |
| Ever use of other antithrombotic drug, n (%) | 11 (0.2) | 0 (0.0) | 11 (0.3) |
| Any current use of antihypertensive drugs, n (%) | 1319 (29.9) | 100 (82.6) | 1219 (28.4) |
| Any current use of lipid modifying drugs, n (%) | 714 (16.4) | 95 (78.5) | 619 (14.4) |
| Diabetes mellitus, n (%) | 276 (6.3) | 17 (14.0) | 259 (6.0) |
| Current smoker, n (%) | 879 (20.1) | 24 (19.8) | 855 (20.1) |
| Former smoker, n (%) | 2147 (49.0) | 79 (65.3) | 2068 (48.5) |
| Never smoker, n (%) | 1358 (31.0) | 18 (14.9) | 1340 (31.4) |
| Systolic blood pressure, mean (SD), mm Hg | 138 (21) | 142.3 (21.2) | 137.8 (20.9) |
| Diastolic blood pressure, mean (SD), mm Hg | 82 (11) | 78.2 (9.9) | 82.3 (10.8) |
| Total cholesterol, mean (SD), mmol/L | 5.6 (1.0) | 4.7 (1.1) | 5.6 (1.0) |
| HDL-cholesterol, mean (SD), mmol/L | 1.4 (0.4) | 1.2 (0.3) | 1.5 (0.4) |
| History of myocardial infarction, n (%) | 169 (3.9) | 53 (44.5) | 116 (2.7) |
| History of coronary heart disease, n (%)† | 258 (5.9) | 99 (83.2) | 159 (3.7) |
| Participants with ≥1 *CYP2C19*2* allele, n (%) | 1044 (28.4) | 29 (27.4) | 1015 (28.4) |
| Participants with ≥1 *CYP2C19*17* allele, n (%) | 1496 (40.6) | 43 (40.6) | 1453 (40.6) |
| Participants with both ≥1 *CYP2C19*2* and ≥1 **17* allele, n (%) | 265 (7.2) | 9 (8.5) | 256 (7.2) |

Data were missing for HDL (n=69) and total (n=67) cholesterol, systolic and diastolic blood pressure (both n=23), and smoking (n=24). *CYP2C19* status data were available for 3677 participants. HDL indicates high-density lipoprotein.

*This category comprises both ATC codes B01AA (oral anticoagulants) and B01AB (injectable anticoagulants).

†A history of any of the following: myocardial infarction, percutaneous coronary intervention, or surgical coronary artery bypass graft surgery.

clopidogrel use and prevalence of CMBs, although the association was no longer significant (OR 1.54, 95% CI 0.94 to 2.54). The prevalence of CMBs among ever- users of both clopidogrel and salicylates was 37.8% compared with 14.3% in never-users of clopidogrel and salicylates (OR 2.21, 95% CI 1.41 to 3.48) and 26.4% in ever-users of salicylates only (OR 1.42, 95% CI 0.90 to 2.23; of note, salicylate use as a covariate was removed from model II for this analysis).

A total of 97 (80.2%) clopidogrel ever-users could be placed in 1 of the 3 *CYP2C19* groups. The **2* group had no significantly different prevalence than wild-type homozygotes of CMBs in any location (OR 0.91, 95% CI 0.30 to 2.75), strictly lobar locations (OR 0.76, 95% CI 0.20 to 2.83), and deep or infratentorial locations (OR 1.25, 95% CI 0.26 to 6.03). The **17* group also had a similar prevalence as wild-type homozygotes of CMBs in any location (OR 0.81, 95% CI 0.31 to 2.08), strictly lobar locations (OR 0.64, 95% CI 0.21 to 2.00), and deep or infratentorial locations (OR 1.17, 95% CI 0.30 to 4.57). Neither **2* ($P$=0.12) nor **17* ($P$=0.32) status was associated with an altered number of CMBs in clopidogrel users, and **2* ($P$=0.35) and **17* ($P$=0.58) status was not related to duration of clopidogrel use.

**Table 2.** Clopidogrel and Cerebral Microbleeds

| Model | Total N | Any Location | | | Strictly Lobar | | | Deep or Infratentorial | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CMB Prevalence (%) | I OR (95% CI) | II OR (95% CI) | CMB Prevalence (%) | I OR (95% CI) | II OR (95% CI) | CMB Prevalence (%) | I OR (95% CI) | II OR (95% CI) |
| Clopidogrel nonusers (reference) | 4287 | 783 (18.3) | 1.00 | 1.00 | 539 (13.2) | 1.00 | 1.00 | 199 (5.3) | 1.00 | 1.00 |
| Clopidogrel users | 121 | 45 (37.2) | 2.07 (1.40 to 3.07) | 1.55 (1.01 to 2.37) | 26 (25.5) | 1.61 (1.01 to 2.58) | 1.34 (0.81 to 2.21) | 19 (20.0) | 3.13 (1.81 to 5.40) | 1.90 (1.05 to 3.45) |

CMB indicates cerebral microbleed; HDL, high-density lipoprotein; model I, adjusted only for age and sex; model II, additionally adjusted for smoking, systolic and diastolic blood pressure, diabetes mellitus, total and HDL cholesterol, antihypertensive medication, lipid-modifying medication, and antithrombotic agents other than clopidogrel; OR, adjusted odds ratio.




**Figure.** Number of cerebral microbleeds according to clopidogrel use. For every category of cerebral microbleed number, the reference is no cerebral microbleeds. *Significant difference between clopidogrel ever-users and never-users ($P<0.05$) after adjustment for age, sex, smoking, systolic and diastolic blood pressure, diabetes mellitus, total and HDL cholesterol, antihypertensive medication, lipid-modifying medication, and antithrombotic agents other than clopidogrel. HDL indicates high-density lipoprotein

## Discussion

In this population-based study on stroke-free persons, we demonstrate that ever-users of clopidogrel have a higher prevalence and more often a high number of CMBs compared with never-users. These findings add to earlier literature that showed that use of clopidogrel is an independent risk factor for major bleeding,[4] while CMBs might be a subclinical reflection of a bleeding-prone state and as such a predictor of hemorrhagic stroke.[32] To date, the only report that presented data on the association between clopidogrel use and CMB prevalence was restricted to stroke patients, and clopidogrel was associated with a nonsignificant increase in CMB prevalence of similar magnitude (OR 2.23, 95% CI 0.57 to 8.66).[33]

General strengths of our study included the availability of near-complete records on both clopidogrel use and a range of important covariates, as well as the use of a custom-made accelerated 3D T2* MRI sequence of the brain, which enabled us to detect CMBs with high sensitivity.[16] Some potential limitations of this observational study should also be discussed. First, despite a large source population, the number of clopidogrel users was relatively small. This limited

us in performing some sensitivity analyses. For instance, after excluding anticoagulant users, the association between clopidogrel use and CMBs was no longer significant. However, the exclusion did not affect the point estimate of the association between clopidogrel use and CMBs, which suggests that the nonsignificance was primarily caused by a further reduction in the number of clopidogrel users. Similarly, although the interaction term between myocardial infarction and clopidogrel use was nonsignificant, we may have lacked an adequate number of clopidogrel users to demonstrate effect modification, especially given the apparent disparity in ORs for clopidogrel between individuals with and individuals without myocardial infarction. The same holds for effect modification by any coronary heart disease.

Second, since all participants were prescribed the same dose of clopidogrel, no dose–effect relationship could be studied. Therefore, we assessed whether cumulative exposure to clopidogrel was associated with CMB presence and number, which was not the case. A possible explanation for this finding could be that clopidogrel causes CMBs shortly after initiation of its use, since the steady state of clopidogrel is typically reached within 1 week.[34] If so, one would still expect the number of CMBs to rise with increasing cumulative duration of use. The limited number of participants ever using clopidogrel in our study population did not allow us to adequately study the relationship between cumulative clopidogrel use and number of CMBs.

Third, the cross-sectional design of the study limits our ability to draw conclusions regarding causality. Since hemosiderin deposits remain visible in the brain for an undefined period of time, it is possible that some of the CMBs that we observed actually occurred before the initiation of clopidogrel use. In addition, during or after clopidogrel use, CMBs may still occur due to the underlying generalized atherothrombotic state for which individuals were prescribed clopidogrel. If this occurred, it may have led to spurious inference of the effect of clopidogrel use due to confounding by indication, taking into account that CMBs occur more frequently in persons at increased cardiovascular risk and that clopidogrel is almost exclusively prescribed in persons with a history of coronary or cerebrovascular disease.[13] Therefore, we adjusted for traditional cardiovascular risk factors and cardiovascular medication use. Moreover, we excluded participants with a history of stroke (since both ischemic and hemorrhagic strokes are associated with CMBs[13]). We still found an increased prevalence of CMBs in the clopidogrel group. However, given our inability to adequately perform all of the sensitivity analyses that could have more robustly supported a causal association between clopidogrel and CMBs, we cannot rule out the possibility of residual confounding.

Fourth, clopidogrel is often prescribed simultaneously with a salicylate,[1,35] of which we earlier demonstrated the association with the presence of CMBs.[36] The availability of near-complete pharmacy records of the study population enabled us to take the use of salicylates into account. We found that adjustment for use of salicylates and other antithrombotic agents did not alter the association between clopidogrel use and CMBs, while a comparison between salicylate users who did and did not use clopidogrel showed that users of the combination had a nonsignificantly higher CMB prevalence.

Last, although *CYP2C19* genotype does not provide us with more insight into the occurrence of atherothrombotic events in patients using clopidogrel, there is accumulating evidence of an effect of the *CYP2C19*2* and **17* variants on the association between clopidogrel and bleeding events.[28,29] Our sample size was probably too small to detect significant differences in prevalence of CMBs between *CYP2C19* genotype groups due to relatively small effect sizes.

In our population, clopidogrel use was associated with both strictly lobar and deep or infratentorial CMBs independent of age and sex. After we additionally adjusted for cardiovascular risk factors and cardiovascular medication, only the association with deep or infratentorial locations was still significant, suggesting that CMBs in clopidogrel users is related to aggravation of underlying hypertensive microangiopathy. This is in line with recent reports showing higher estimates for the association with deep or infrantentorial CMBs than strictly lobar CMBs of several antithrombotic agents.[33,37] In stroke medicine, the burning questions about CMBs concern their diagnostic significance and whether CMBs should guide the use of antithrombotic and thrombolytic drugs.[38,39] Our clinical follow-up period was too short to assess whether clopidogrel users with CMBs at baseline were at increased risk for symptomatic intracerebral hemorrhage. Therefore, our findings will not directly influence clinical practice. However, the association between clopidogrel use and CMBs in stroke-free persons emphasizes the necessity to study a possible cascade involving clopidogrel use, CMBs, and major bleeding events in prospective studies.

In conclusion, we have demonstrated that in persons without a history of stroke, use of clopidogrel is associated with an increased prevalence of CMBs. Whether this association is causal requires confirmation in prospective studies.

## Acknowledgments

The contribution of inhabitants, general practitioners, and pharmacists of the Ommoord district to the Rotterdam Study is gratefully acknowledged.

## Sources of Funding

The Rotterdam Study is supported by Erasmus Medical Center and Erasmus University Rotterdam; the Netherlands

Organisation for Scientific Research (NWO); the Netherlands Organisation for Health Research and Development (ZonMW); the Research Institute for Diseases in the Elderly (RIDE); the Netherlands Genomics Initiative (NGI); the Ministry of Education, Culture and Science; the Ministry of Health, Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. Support for the Rotterdam Scan Study was obtained from General Electric Health Care. This work was supported by a grant from the Netherlands Organisation for Health Research and Development (ZonMw) [grant 80-82500-98-10208 to Prof Stricker]. None of the funders had any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

## Disclosures

Mr Darweesh has received an Academy Assistantship grant from the Royal Netherlands Academy of Arts and Sciences (KNAW). Dr Ikram has received research support from the Dutch Heart Foundation, Netherlands Organisation for Health Research and Development (ZonMW), Internationale Stichting Alzheimer Onderzoek, and the Internationaal Parkinson Fonds and serves on the editorial board for *Neuroepidemiology*. Dr Vernooij was supported by a Fellowship grant of the Erasmus MC Vriendenfonds. Professor Stricker, professor Hofman, Dr Leening, Dr Akoudad and Dr Loth report no disclosures.

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Sirwan K.L. Darweesh, Maarten J.G. Leening, Saloua Akoudad, Daan W. Loth, Albert Hofman, M. Arfan Ikram, Meike W. Vernooij and Bruno H. Stricker

*J Am Heart Assoc.* 2013;2:e000359; originally published September 26, 2013;
doi: 10.1161/JAHA.113.000359
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980