Prevalence and Risk Factors of Silent Brain Infarcts in the Population-Based Rotterdam Scan Study

Sarah E. Vermeer, MD; Peter J. Koudstaal, MD, PhD; Matthijs Oudkerk, MD, PhD; Albert Hofman, MD, PhD; Monique M.B. Breteler, MD, PhD

**Background and Purpose**—Silent brain infarcts are commonly seen on magnetic resonance imaging (MRI) both in patients with a first stroke and in healthy elderly persons. These infarcts seem associated with an increased risk of stroke. It is unclear whether risk factors for silent infarcts differ from those for symptomatic stroke. We investigated the prevalence of, and cardiovascular risk factors for, silent brain infarcts.

**Methods**—The Rotterdam Scan Study is a population-based cohort study among 1077 participants 60 to 90 years of age. Participants underwent cerebral MRI. We assessed cardiovascular risk factors by interview and physical examination. Associations between risk factors and presence of infarcts were analyzed by logistic regression and adjusted for age, sex, and relevant confounders.

**Results**—For 259 participants (24%) 1 or more infarcts on MRI were seen; 217 persons had only silent and 42 had symptomatic infarcts. The prevalence odds ratio (OR) of both silent and symptomatic infarcts increased with age by 8% per year (95% CI, 1.06 to 1.10 and 1.04 to 1.13, respectively). Silent infarcts were more frequent in women (age-adjusted OR, 1.4; 95% CI, 1.0 to 1.8). Hypertension was associated with silent infarcts (age- and sex-adjusted OR, 2.4; 95% CI, 1.7 to 3.3), but diabetes mellitus and smoking were not.

**Conclusions**—Silent brain infarcts are 5 times as prevalent as symptomatic brain infarcts in the general population. Their prevalence increases with age and seems higher in women. Hypertension is associated with silent infarcts, but other cardiovascular risk factors are not. *(Stroke. 2002;33:21-25.)*

**Key Words:** cerebral infarction ■ magnetic resonance imaging ■ population ■ prevalence ■ risk factors

**Participants and Methods**

The Rotterdam Scan Study is designed to study causes and consequences of brain changes in the elderly. The participants originated from 2 large ongoing prospective population-based cohort studies, the Zoetermeer Study and the Rotterdam Study. The baseline data collection for the Zoetermeer Study took place from 1975 to 1978, and that for the Rotterdam Study occurred in 1990 to 1993. Both studies included independently and institutionalized living persons. The rationale for both studies has been described elsewhere.4,5

In 1995 to 1996, we randomly selected participants 60 to 90 years of age from both studies in strata of age (5 years) and sex. People with MRI contraindications were not eligible for our study and were excluded. A total of 1077 nondemented elderly individuals participated in our study (overall response 63%). The main reasons for not participating in the Rotterdam Scan Study were old age, too much trouble, not wanting to participate in brain research, and claustrophobia. The study design has been described in detail.6 Each participant gave informed consent. The medical ethics committee of the Erasmus Medical Centre Rotterdam approved the study.

**Cerebral Infarcts**

All participants underwent MRI of the brain. We made axial T1-, T2-, and proton-density-weighted scans on 1.5-T MRI scanners (MR Gyroscan, Philips, and MR VISION, Siemens). The slice thickness was 5 or 6 mm with an interslice gap of 20%. Laser hard copies were printed with a reduction factor of 2.7.

We defined infarcts as focal hyperintensities on T2-weighted images 3 mm in size or larger. Proton-density scans were used to distinguish infarcts from dilated perivascular spaces. Lesions in the white matter also had to have corresponding prominent hypointen-
sites on T1-weighted images for us to distinguish them from cerebral white matter lesions. Lesions were defined as possible infarcts if this distinction between infarcts and white matter lesions could not be made. We did not consider possible infarcts as infarcts in our analyses; participants with only possible infarcts (n = 73) were included in the reference group. A single trained physician who was blinded to history of stroke and transient ischemic attack (TIA) scored infarcts, including their localization and size. Intrarater study for detecting infarcts showed good agreement (κ = 0.80).

We obtained a history of stroke and TIA by self-report, and by checking medical records in all 1077 participants, independently on their MRI outcome. Stroke was defined as an episode of typical focal neurological deficits with acute onset and lasting for >24 hours. TIA was similarly defined, but with symptoms lasting <24 hours. An experienced neurologist with knowledge of the participants’ medical history subsequently reviewed the scans and categorized the infarcts on MRI as silent or symptomatic. We defined silent brain infarcts as evidence on MRI of 1 or more infarcts, without a history of a (corresponding) stroke or TIA. If prior stroke or TIA did correspond with a lesion, the latter was defined as a symptomatic infarct. Participants with both symptomatic and silent infarcts were included in the symptomatic infarct group. Intrarater reliability for the classification of infarcts as silent or symptomatic was excellent (κ = 1.0).

Cardiovascular Risk Factors

We obtained the cardiovascular risk factors by interview and physical examination in 1995 to 1996. Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. We used the average of these 2 measurements. We calculated pulse pressure by subtracting diastolic blood pressure from systolic blood pressure. Participants had hypertension if the systolic blood pressure was ≥160 mm Hg, if the diastolic blood pressure was ≥95 mm Hg, or if they reported the use of blood pressure-lowering medication. We considered diabetes mellitus to be present if a person was taking oral antidiabetics or insulin. A physician assessed participants’ medical history subsequently reviewed the scans and categorized the infarcts on MRI as silent or symptomatic. We defined silent brain infarcts as evidence on MRI of 1 or more infarcts, without a history of a (corresponding) stroke or TIA. If prior stroke or TIA did correspond with a lesion, the latter was defined as a symptomatic infarct. Participants with both symptomatic and silent infarcts were included in the symptomatic infarct group. Intrarater reliability for the classification of infarcts as silent or symptomatic was excellent (κ = 1.0).

Data Analysis

The prevalence of silent and symptomatic infarcts on MRI was calculated in 5-year age strata. We analyzed the associations between potential risk factors and presence of infarcts by multiple logistic regression. These analyses were done separately for silent and symptomatic brain infarcts. No distinction was made between participants with 1 or more infarcts on their scan. Adjustments were made for age and sex, and additionally for other relevant confounders.

Results

A total of 259 of 1077 participants (24%) had 1 or more infarcts on MRI. Of these, 217 (20%) had only silent infarcts, 26 (2.4%) symptomatic infarcts, and 16 (1.5%) had both. The majority of the participants with silent brain infarcts had lacunar infarcts in the basal ganglia, whereas one-third of those with symptomatic infarcts had cortical infarcts (Figure 1). Eight of the 42 participants with a symptomatic infarct reported no history of stroke or TIA themselves, but their medical records did. In 16 of these 42 participants, symptoms of a TIA corresponded to the infarct on MRI. Fourteen participants with a history of TIA were MRI negative and 17 had silent (noncorresponding) infarcts on their MRIs. Participants with infarcts were older and were more likely to have hypertension compared with persons without infarcts (Table 1).

| TABLE 1. Characteristics of Participants With and Without Infarcts Visible on MRI |
|-----------------------------------|----------|---------|------------------|---------|
| Age, y                           | 71±7     | 76±7    | 76±7             |
| Women                            | 50       | 58      | 45               |
| Systolic blood pressure, mm Hg   | 145±21   | 155±22  | 153±25           |
| Diastolic blood pressure, mm Hg  | 78±11    | 80±13   | 78±13            |
| Pulse pressure, mm Hg            | 67±17    | 75±17   | 75±18            |
| Hypertension                     | 46       | 71      | 79               |
| Diabetes mellitus                | 6        | 8       | 21               |
| Smoking                          | 34       | 40      | 24               |
| No smoking (0 pack-years)        | 34       | 40      | 24               |
| >0 and <20 pack-years            | 29       | 31      | 21               |
| ≥20 pack-years                   | 37       | 29      | 55               |
| Alcohol consumers (≥1 U/d)       | 40       | 38      | 50               |

Values are unadjusted means±SD or percentages.
they were analyzed continuously. To allow comparison of the strength of the associations, they are all expressed as adjusted odds ratio per SD increase in blood pressure measure. Systolic and diastolic blood pressure and pulse pressure were all associated with presence of silent brain infarcts. For symptomatic infarcts, no significant associations were found between systolic or diastolic blood pressure levels and presence of infarcts. Analysis in strata of antihypertensive treatment showed that in participants without treatment the proportion of participants with silent infarcts increased with increasing blood pressure (data not shown). The strength of the association of pulse pressure with symptomatic infarcts was very similar to that for silent infarcts, albeit not statistically significant. Pulse pressure was no longer related to silent brain infarcts after adjustment for systolic blood pressure (odds ratio, 0.95 per SD increase; 95% CI, 0.71 to 1.27). The strong colinearity between these blood pressure measures limits the interpretability of this finding. However, the effect of systolic blood pressure seems larger than that of pulse pressure (Table 3), which suggests that the latter may be mainly driven by the effect of systolic blood pressure.

All analyses were also performed with exclusion of participants with possible infarcts on MRI. This did not alter the strength of any of the associations described above.

**Discussion**

We found in our population-based study a prevalence of silent brain infarcts that gradually increased with age from 8% in the 60- to 64-year-old participants to 35% in the oldest (85 to 90 years of age). Silent infarcts were 5 times as frequent as symptomatic infarcts. The prevalence of silent infarcts was higher in women than in men. Hypertension was an additional independent risk factor for the presence of silent

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**TABLE 2. Association Between Cardiovascular Risk Factors and Subtypes of Infarcts (Odds Ratios [ORs] and 95% CIs)**

<table>
<thead>
<tr>
<th></th>
<th>Silent Infarcts</th>
<th>Symptomatic Infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude* OR (95% CI)</td>
<td>Adjusted† OR (95% CI)</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.08 (1.06–1.10)</td>
<td>1.08 (1.05–1.10)</td>
</tr>
<tr>
<td>Women</td>
<td>1.4 (1.0–1.8)</td>
<td>1.3 (0.9–1.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.4 (1.7–3.3)</td>
<td>2.3 (1.6–3.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.0 (0.5–1.9)</td>
<td>0.7 (0.4–1.5)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No smoking</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>&gt;0 and &lt;20 pack-years</td>
<td>1.1 (0.7–1.7)</td>
<td>1.2 (0.8–1.8)</td>
</tr>
<tr>
<td>≥20 pack-years</td>
<td>0.9 (0.6–1.4)</td>
<td>1.0 (0.6–1.5)</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex.
†Additionally adjusted for hypertension, diabetes mellitus, and smoking.

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**Figure 2.** Prevalence (%) of silent and symptomatic infarcts visible on MRI per 5-year age category.

**Figure 3.** Association between categories of systolic blood pressure, diastolic blood pressure, and pulse pressure and presence of silent brain infarcts (odds ratios and 95% CIs, adjusted for age, sex, diabetes mellitus, and smoking).
Infarcts. Other cardiovascular risk factors were only related to symptomatic infarcts.

Some potential methodological limitations of our study need to be discussed first. The response rate in our study was high, but not 100%. Hence, there is a possibility of selection bias. The participating persons were significantly younger than nonresponders.6 Because we found the prevalence of silent brain infarcts to be higher with increasing age, the prevalence may be even higher in the highest age category. Nonparticipation because of cognitive or functional deficits may also have introduced bias, probably leading to an underestimation of the prevalence of brain infarctions. There was no difference in response rate between men and women. Therefore, it is unlikely that the difference in silent brain infaracts between sexes is due to selection bias.

Furthermore, we may have misclassified brain infarcts in 2 different ways. First, we might have incorrectly identified them on the MRI scan. Despite our good intrarater agreement, it is possible that we systematically over- or underrated infarcts. Second, we may have misclassified infarcts as being silent or symptomatic. We tried to minimize error by obtaining participants’ history of stroke and TIA not only by self-report, but also by checking medical records. Both the reader of the MRI scans and the experienced neurologist who classified the silent and symptomatic infarcts were blinded to all other data. Therefore, any misclassification will have resulted in an underestimation of the strength of the associations. The strengths of our study are the large number of participating elderly and its population-based design.

Two other population-based studies, the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study, have found overall prevalences of silent brain infarcts of 11%3 and 28%,8 respectively. A Japanese community study, among participants who wished to receive health screening at their own expense, reported also a prevalence of 11%.9 However, in both the ARIC Study and the Japanese study the mean age of participants was much lower than in our study. The participants of the Cardiovascular Health Study had the same mean age, but had more women participating,10 compared with the Rotterdam Scan Study. Comparisons between all 4 studies are further hampered in that the MRI scanning protocol was not uniform; there were important differences in slice thickness, interlase gap, and type of scanner. Studies additionally differ in that none but ours verified the self-reported history of stroke and TIA by checking medical records. Besides, none of the other 3 studies checked whether prior stroke-like symptoms corresponded to the infarcts, as we did. When we take the age and sex differences into account, the prevalences of silent infarcts in the 3 studies mentioned above accord, however, largely with ours. Our prevalence also fits with what a Japanese autopsy study found, although those authors report slightly lower age-specific prevalences, but that might be due to the thick slices they used.11

Consistent with the study of silent lacunar infarcts in the Cardiovascular Health Study,2 but not with those authors’ results regarding overall silent infarcts,8 we observed a 30% to 40% higher prevalence among women. This is in contrast to common observations regarding symptomatic stroke that is reportedly more frequent in men. Although the sex difference was no longer statistically significant when we adjusted for other risk factors, our data are compatible with a higher prevalence of silent infarcts in women than in men. Such a sex difference may be due to differences in reporting and interpreting symptoms of stroke or TIA by both patients and physicians, similar to what has been observed for acute myocardial infarction.12,13 Recent studies reported about this sex difference in the treatment of cerebrovascular disease.14,15 Furthermore, women of this age more often live without a partner. Especially for transient neurological symptoms, one may hypothesize that those women will not report their symptoms at all. This might explain why the reverse is seen for symptomatic stroke, namely a higher prevalence in men,16 although we could not duplicate this finding, which probably results from the small number of stroke survivors in our study. This higher prevalence of silent brain infarcts in women was not found in the younger cohorts of the Japanese study9 or in the ARIC Study.3

Hypertension was the only additional risk factor associated with silent brain infarcts in our study. The strong association with hypertension suggests that hypertensive small-vessel disease plays a crucial role in the pathogenesis of silent brain infarcts. This finding accords with all other studies on silent and symptomatic infarcts. The absence of a significant association between symptomatic infarcts and systolic and diastolic blood pressure may result from the small numbers of participants with symptomatic infarcts or reflect that blood pressure often drops after a symptomatic infarct. Furthermore, the antihypertensive treatment in these participants with prior symptomatic stroke may also have contributed to the lack of association. Analysis in strata of antihypertensive treatment showed stronger associations between blood pressure level and presence of infarcts in persons without treatment, albeit probably because of small numbers, not significantly.

We could not find an association between any other cardiovascular risk factor and silent brain infarcts. Diabetes mellitus—which is known to exacerbate small-vessel disease next to hypertension—was associated only with symptomatic infarcts in our study. We considered that we might have underestimated the prevalence of diabetes mellitus in our population, particularly in subjects without symptomatic infarcts. For persons with symptomatic infarcts, assessment of diabetic status may have been more correct, because these people are more likely to receive more medical attention. We did not have data on blood glucose level at time of the MRI examination. However, half of our cohort had been screened

### Table 3: Association Between Systolic Blood Pressure, Diastolic Blood Pressure, and Pulse Pressure and Subtypes of Infarcts (Odds Ratios [ORs] Per SD Increase and 95% CIs)

<table>
<thead>
<tr>
<th></th>
<th>Silent Infarcts (Adjusted* OR (95% CI))</th>
<th>Symptomatic Infarcts (Adjusted* OR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>1.45 (1.23–1.71)</td>
<td>1.30 (0.94–1.79)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.27 (1.08–1.49)</td>
<td>1.08 (0.78–1.50)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>1.34 (1.13–1.58)</td>
<td>1.31 (0.96–1.79)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, diabetes mellitus, and smoking.
for diabetes mellitus just a few years before as part of the Rotterdam Study with an oral glucose load, and associations were similar in this part of the cohort. Although we cannot exclude that some differential misclassification may have occurred, we do not think that that can fully explain the discrepant findings for symptomatic and silent infarcts. The lack of association was consistent with the ARIC Study\(^3\) and the lacunar infarct study of the Cardiovascular Health Study,\(^2\) although not with the Japanese study.\(^9\) For smoking we likewise found a relation with symptomatic infarcts and not with silent infarcts. We think that a different distribution of infarct types may be the reason why. Smoking is known to enhance atherosclerosis leading to large-vessel disease, and we found a much larger proportion of cortical infarcts among the symptomatic infarcts. The majority of silent infarcts were lacunar, in which small-vessel disease is thought to play a more important role. The finding of Uehara et al\(^17\) that risk factors for silent infarcts in the white matter differed from those for basal ganglia infarcts also supports this. An association between smoking and silent infarcts was supported only by the ARIC Study.\(^3\) Unfortunately, the numbers in our study were too small to do risk factor analyses of the different subtypes of infarcts.

In conclusion, silent brain infarcts are common among the elderly. Silent brain infarcts are associated with hypertension, but not with other indicators of small- and large-vessel disease that are related to symptomatic infarcts. The prognosis of silent brain infarcts remains unclear. The study of Kobayashi et al\(^9\) showed that they increased risk of stroke onset 10-fold. However, as mentioned above, this study was not population-based. Prospective population studies will have to show the prognostic relevance of silent brain infarcts.

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