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

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Background and Purpose—The prevalence of silent brain infarcts in healthy elderly people is high, and these lesions are associated with an increased risk of stroke. The incidence of silent brain infarcts is unknown. We investigated the incidence and cardiovascular risk factors for silent brain infarcts.

Methods—The Rotterdam Scan Study is a prospective, population-based cohort study of 1077 participants 60 to 90 years of age. All participants underwent cranial MRI in 1995 to 1996, and 668 participants had a second MRI in 1999 to 2000 (response rate, 70%) with a mean interval of 3.4 years. We assessed cardiovascular risk factors by interview and physical examination at baseline. Associations between risk factors and incident silent infarcts were analyzed by multiple logistic regression.

Results—Ninety-three participants (14%) had ≥1 new infarcts on the second MRI; of these, 81 had only silent and 12 had symptomatic infarcts. The incidence of silent brain infarcts strongly increased with age and was 5 times higher than that of symptomatic stroke. A prevalent silent brain infarct strongly predicted a new silent infarct on the second MRI (age- and sex-adjusted odds ratio, 2.9; 95% confidence interval, 1.7 to 5.0). Age, blood pressure, diabetes mellitus, cholesterol and homocysteine levels, intima-media thickness, carotid plaques, and smoking were associated with new silent brain infarcts in participants without prevalent infarcts.

Conclusions—The incidence of silent brain infarcts on MRI in the general elderly population strongly increases with age. The cardiovascular risk factors for silent brain infarcts are similar to those for stroke. (Stroke. 2003;34:392-396.)

Key Words: cerebral infarction | incidence | magnetic resonance imagining | population | risk factors

Silent brain infarcts are frequently seen on MRIs in healthy elderly people. The prevalence of these asymptomatic lesions increases with age from ~5% at 60 years of age to 35% at 90 years of age.1-3 People with silent brain infarcts have an increased risk of stroke, independent of other stroke risk factors.4,5 In cross-sectional studies, the presence of silent brain infarcts is associated especially with older age and hypertension. No prospective longitudinal study has yet examined the incidence of and risk factors for silent brain infarcts. We investigated the incidence of silent brain infarcts and examined the cardiovascular risk factors for incident silent brain infarcts in the longitudinal population-based Rotterdam Scan Study in the Netherlands.

Methods

Participants

The Rotterdam Scan Study is a prospective follow-up study designed to study causes and consequences of brain changes on MRIs in elderly people.6 In 1995 to 1996, we randomly selected participants 60 to 90 years of age in strata of age (5 years) and sex from 2 large ongoing population-based studies.7,8 People with MRI contraindications or dementia at baseline were not eligible for our study and were excluded. A total of 1077 nondemented elderly people participated in our study (overall response, 63%). Each participant gave informed consent. The medical ethics committee of the Erasmus Medical Center approved the study.

Cerebral Infarcts

All participants underwent MRI of the brain at baseline in 1995 to 1996. We made axial T1-, T2-, and proton density–weighted scans on 1.5-T MRI scanners (for participants from Zoetermeer, MR Gyroscan, Philips; for participants from Rotterdam, MR VISION, Siemens, with comparable pulse sequences).6 For every participant, we made 60 slices (20 per acquisition) 5 or 6 mm thick with an interslice gap of 20%. In 1999 to 2000, all eligible participants were invited for a second MRI using MR VISION with the same MR sequences and protocol. Of the 1077 participants at baseline, 126 people were not eligible to participate in the second MRI examination (82 died, 19 had MRI contraindications, 19 were institutionalized, 3 moved abroad, and 3 could not be reached; Figure 1). In total, 668 of the 951 eligible persons underwent the second MRI in 1999 to 2000 with a mean interval of 3.4 years between the 2 MRI examinations (response rate, 70%). The reasons for refusal to undergo the second MRI examination were as follows: claustrophobia developed at the baseline MRI (n=98), too much trouble (n=90), no interest (n=77), and other reasons (n=18).

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The presence of infarcts was rated similarly at baseline and follow-up. We defined infarcts as focal hyperintensities on T2-weighted images that were ≥3 mm. Proton density scans were used to distinguish infarcts from dilated perivascular spaces. Lesions in the white matter also had to have corresponding prominent hypointensities on T1-weighted images to distinguish them from cerebral white matter lesions. A single trained physician (S.E.V.) who was blinded to history of stroke and transient ischemic attack (TIA) scored infarcts on both the baseline and second MRI, including location and size. Intra-rater study (n=110) 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 of their MRI outcome. Stroke was defined as an episode of typical focal neurological deficits with acute onset and lasting ≥24 hours. A trained physician (P.J.K.) who had knowledge of the participants’ medical histories 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 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 who had both symptomatic and silent infarcts were included in the symptomatic infarct group. Intra-rater reliability (n=50) for the classification of infarcts into silent or symptomatic was excellent (κ=1.0).

Cardiovascular Risk Factors
We obtained 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. Participants were asked to bring all prescribed drugs to the research center, and a physician checked the use. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications. We considered diabetes mellitus to be present if the random glucose level was ≥11.1 mmol/L or if a person was taking oral antidiabetics or insulin. The presence of atrial fibrillation was assessed by MEANS interpretation of a 12-lead ECG (ACTA ECG, ESAOTE). Serum total cholesterol and high-density lipoprotein were determined with an automated enzymatic procedure (Hitachi analyzer, Roche Diagnostics). Plasma total homocysteine levels were determined by fluorescence polarization immunoassay on an IMx analyzer (Abbott Laboratories). Participants underwent ultrasonography of both carotid arteries with a 7.5-MHz linear-array transducer and a Duplex scanner (ATL Ultra-Mark IV, Advanced Technology Laboratories). We examined the right and left carotid arteries for the presence of plaques in the common carotid artery, bifurcation, and internal carotid artery and calculated the total number of sites with plaques present. Intima-media thickness was measured by longitudinal 2-dimensional ultrasound of the common carotid artery. We calculated the mean common carotid intima-media thickness as the mean of 4 locations: the near and far walls of both the right and left common carotid arteries. A physician assessed participants’ smoking habits using a structured questionnaire and classified smoking status as current or not.

Statistical Analysis
The follow-up time between the date of the baseline MRI and the second MRI was calculated. We estimated the cumulative incidence of silent brain infarcts in 10-year age strata. We analyzed the associations between potential risk factors at baseline and incident silent brain infarcts by multiple logistic regression adjusted for age and sex. Separate analyses were done in participants with and without infarcts at baseline MRI. We excluded participants with symptomatic infarcts at baseline (n=22) and those with a history of stroke but without infarcts on the baseline MRI (n=10) for the risk factor analyses. No distinction was made between participants with 1 and those with more infarcts on their scan.

Results
The characteristics of all 1077 participants at baseline are listed in Table 1. Participants who underwent the second MRI did not differ in presence of infarcts on the baseline MRI from those who refused this second examination.

Overall, 93 of the 668 participants (14%) had ≥1 new infarcts on MRI, of whom 81 (12%) had only silent infaracts, 8 (1%) had only symptomatic infarcts, and 4 had (1%) both symptomatic and silent infarcts (Figure 1). Of these 93 participants, 63 (68%) had a single new infarct, and 30 (32%) had multiple new infarcts on MRI. The incidence of silent infaracts was higher for participants with multiple silent infaracts at baseline (29%; 12 of 42 participants) than for those with single infarcts on baseline MRI (22%; 18 of 81 participants). The cumulative incidence of silent brain infarcts over a mean period of 3.4 years increased from 8% in the 60 to 70 year olds at baseline to 22% in the oldest participants (Figure 2). No difference in incidence was observed between sexes. Most participants with incident silent brain infarcts had lacunar infaracts in the basal ganglia (Figure 3). The distribution of location of new silent infarcts was similar for
participants with or without silent infarcts on the baseline MRI.

A silent brain infarct at baseline strongly predicted a new silent infarct (age- and sex-adjusted odds ratio [OR], 2.9; 95% CI, 1.7 to 5.0). Additional adjustment for hypertension, diabetes mellitus, atrial fibrillation, homocysteine, intima-media thickness, carotid plaques, and smoking did not essentially change this estimate (fully adjusted OR, 2.6; 95% CI, 1.4 to 4.9). Further risk factor analyses were done in strata of presence of infarcts at the baseline MRI. In 46 (9%) of the 523 participants without prevalent infarcts, silent brain infarcts were seen on the second MRI (Figure 1). In these participants, the risk of silent brain infarcts increased with all vascular risk factors (Table 2). This was statistically significant for age, the presence of diabetes mellitus, and increasing intima-media thickness. Additional exclusion of participants using antihypertensive drugs or lipid-lowering drugs did not essentially change the risk estimates of the blood pressure or cholesterol measures (data not shown). Numbers were too small to allow risk factor analysis with the presence of atrial fibrillation. In participants with prevalent silent brain infarcts, of whom 30 had ≥1 new silent infarcts, no cardiovascular factor was associated with incident silent brain infarcts.

**Discussion**

We found that the incidence of silent brain infarcts in the general population strongly increases with age. A prevalent silent brain infarct strongly predicts a new silent infarct during follow-up. The risk factors for silent brain infarcts are similar to those reported for symptomatic stroke.

Several methodological issues should be addressed. First, there is a possibility of selection bias because we have incomplete follow-up. The participating persons were significantly younger and less often had vascular risk factors than the noneligible persons and those who refused the second scan. Therefore, the incidence of silent brain infarcts will be even higher in the general elderly population than what is reported here because we found an increase in incidence with increasing age. Furthermore, this might have led to an attenuation of the associations between risk factors and presence of silent brain infarcts.
incident silent brain infarcts. The true incidence of symptomatic infarcts will also be higher because people with a fatal or disabling stroke during follow-up could not undergo the second MRI. Second, we may have incorrectly identified brain infarcts or misclassified infarcts into silent or symptomatic. However, the intrarater agreement of both scoring infarcts and classifying silent or symptomatic infarcts was good. We tried to minimize misclassification of infarcts into silent or symptomatic by obtaining participants’ histories of stroke and TIA by self-report and by checking their medical records. If anything, any misclassification will have resulted in an underestimation of the strength of the associations. Although our study does not include people with MRI contraindications, we think our findings can be generalized to these people as well. Merits of our study are the large number of participating elderly from the general population and its prospective design.

We found a steep rise in the incidence of silent brain infarcts with increasing age. The incidence of silent infarcts was similar for men and women. No other population-based study has yet examined the incidence of silent infarcts. Compared with the incidence of symptomatic stroke in similar populations, the incidence of silent brain infarcts is \( \approx 5 \) times higher for all age groups.\(^{12,14}\)

A prevalent silent brain infarct nearly tripled the risk of a new silent infarct. This effect remained highly significant after adjustment for other stroke risk factors, suggesting that the presence of silent brain infarcts is a strong indicator of advanced vascular pathology. When we analyzed risk factors for first-ever silent brain infarcts separately, all cardiovascular risk factors showed an increased risk estimate for silent brain infarcts, although only age, diabetes mellitus, and intima-media thickness showed a significant association, probably because of small numbers. All risk estimates for silent brain infarcts were comparable to those for symptomatic stroke.\(^{15,16}\)

In the participants with prevalent silent brain infarcts, none of the risk factors was associated with an increased risk of subsequent silent infarcts. We earlier showed in a cross-sectional study that these participants already had a vascular risk profile at baseline.\(^3\) This is probably the reason that cardiovascular risk factors do not discriminate any further in these high-risk participants. Age and cardiovascular risk factors also do not seem to play a major role in predicting subsequent stroke in stroke patients.\(^{17,18}\) whereas infarct-related factors are of greater importance in recurrent stroke. Unfortunately, numbers were too small to analyze whether the risk of incident silent infarcts differed with varying location and with the size of the silent brain infarcts at baseline.

In conclusion, the incidence of silent brain infarcts on MRI is \( 5 \) times higher than that of symptomatic stroke in the general population and steeply increases with age. The presence of silent brain infarcts increases the risk of a new silent infarct 3-fold. Most cardiovascular risk factors known to increase the stroke risk—both indicators of small- and large-vascular disease—do also increase the risk of silent brain infarcts. This suggests that silent brain infarcts differ from symptomatic stroke only with respect to the lack of acute strokelike symptoms. Which infarct characteristics result in a symptomatic or silent infarct need further study.

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<tr>
<td>Age, per y</td>
<td>1.08 (1.04–1.13)</td>
<td>1.00 (0.94–1.06)</td>
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<tr>
<td>Women</td>
<td>1.0 (0.5–1.9)</td>
<td>1.4 (0.6–3.2)</td>
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<tr>
<td>Systolic blood pressure, per SD</td>
<td>1.29 (0.92–1.92)</td>
<td>0.66 (0.42–1.04)</td>
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<tr>
<td>Diastolic blood pressure, per SD</td>
<td>1.21 (0.87–1.69)</td>
<td>0.79 (0.52–1.20)</td>
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<tr>
<td>Hypertension</td>
<td>1.2 (0.6–2.4)</td>
<td>1.0 (0.3–3.6)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>2.9 (1.0–8.5)</td>
<td>1.9 (0.4–8.4)</td>
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<tr>
<td>Total cholesterol, per SD</td>
<td>1.08 (0.76–1.53)</td>
<td>1.07 (0.70–1.63)</td>
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<tr>
<td>High-density lipoprotein, per SD</td>
<td>0.81 (0.56–1.15)</td>
<td>1.03 (0.68–1.57)</td>
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<tr>
<td>Total homocysteine, per SD</td>
<td>1.31 (0.95–1.82)</td>
<td>0.86 (0.54–1.36)</td>
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<tr>
<td>Intima-media thickness, per SD</td>
<td>1.31 (1.01–1.71)</td>
<td>1.12 (0.66–1.90)</td>
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<tr>
<td>Plaques in carotid artery, per SD</td>
<td>1.20 (0.85–1.68)</td>
<td>1.10 (0.72–1.68)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.4 (0.6–3.3)</td>
<td>0.6 (0.2–2.2)</td>
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*OR with 95% confidence interval, adjusted for age and sex.
References


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