Prevalence and Risk Factors of Acute Incidental Infarcts

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Background and Purpose—The study of silent stroke has been limited to imaging of chronic infarcts; acute incidental infarcts (AII) detected on brain magnetic resonance imaging have been less investigated. This study aims to describe prevalence and risk factors of AII in a community and a clinic-based population.

Methods—Subjects were drawn from 2 ongoing studies: Epidemiology of Dementia in Singapore study, which is a subsample from a population-based study, and a clinic-based case–control study. Subjects from both studies underwent similar clinical and neuropsychological assessments and brain magnetic resonance imaging. Prevalence of AII from these studies was determined. Subsequently, risk factors of AII were examined using multivariable logistic regression models.

Results—AII were seen in 7 of 623 (1.2%) subjects in Epidemiology of Dementia in Singapore (mean age, 70.9±6.8 years; 45% men) and in 12 of 389 (3.2%) subjects (mean age, 72.1±8.3 years; 46% men) in the clinic-based study. AII were present in 0.8% of subjects with no cognitive impairment, 1.9% of those with cognitive impairment not dementia, and 4.2% of subjects with dementia. Significant association of AII was found with cerebral microbleeds (≥5) in the Epidemiology of Dementia in Singapore (odds ratio, 6.76; 95% confidence interval, 1.28–35.65; P=0.02) and in the clinic-based cohort (odds ratio, 4.65; 95% confidence interval, 1.39–15.53; P=0.01). There was no association of AII with hypertension, diabetes mellitus, or hyperlipidemia.

Conclusions—AII are more likely to be present in those with cognitive impairment. Although a cause–effect relationship between the presence of AII and cognitive impairment is plausible, the association may be because of under-reporting of symptoms by individuals with cognitive impairment. The association between AII and cerebral microbleeds may indicate cerebral vasculopathy, independent of traditional vascular risk factors. (Stroke. 2015;46:2722-2727. DOI: 10.1161/STROKEAHA.115.009963.)

Key Words: cognition ■ infarct ■ ischemic ■ neuropsychological test ■ stroke

Stroke is a global epidemic that affects 15 million people annually, 5 million of whom are left with disability. Importantly, stroke doubles the risk of incident dementia in individuals aged >65 years. However, stroke is not synonymous with a cerebral infarct; stroke is diagnosed only when an infarct or hemorrhage presents with symptoms or signs attributable to the lesion. Hence, the introduction of the term silent stroke denotes an infarct with the absence of temporally correlated stroke-like symptoms. The prevalence of silent brain infarcts varies from 8% to 28%, increases with age, and is associated with increased risk of subsequent stroke, as well as cognitive impairment.

The study of silent stroke has been largely limited to imaging of chronic infarcts because of the small number of studies using diffusion-weighted imaging (DWI), which detects acute infarcts. Hence, few studies have reported on acute incidental infarcts (AII), with variable prevalence because of differences in study populations and methodologies. DWI hyperintense lesions were reported in 15% of patients with cerebral amyloid angiopathy. By contrast, 0.37% of individuals undergoing magnetic resonance imaging (MRI) for a wide range of conditions in a hospital setting were reported to have AII. Moreover, 0.92% (6/649) of subjects undergoing MRI scans for research studies in cognitive impairment had AII. By contrast, the community-based Prospective Urban Rural Epidemiological (PURE) Mind substudy recently reported no AII among 793 participants.

In view of these discrepancies, our aim is to describe the prevalence of AII and characteristics of subjects with AII,
as well as to examine associations of AII in 2 Singaporean studies.

Methods

Study Population
For this analysis, subjects were drawn from 2 ongoing studies: (1) the Epidemiology of Dementia in Singapore (EDIS) study, which is a subsample from a population-based study, with previously published methodology.11 (2) Clinic-based study uses a case–control design. Patients from 2 memory clinics with cognitive impairment on neuropsychological assessment are recruited as cases.12 Controls are individuals who are cognitively normal on objective neuropsychological assessment. For this study, 623 subjects were included from the EDIS study and 389 subjects from the clinic-based study.

Ethics approval was obtained from National Healthcare Group Domain-Specific Review Board, and both studies were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants, or their legally acceptable representatives, before recruitment.

Subjects in both studies underwent similar clinical and neuropsychological assessments and brain MRI. Medical history on previous diagnoses of hypertension, hyperlipidemia, diabetes mellitus, stroke, transient ischemic attack (TIA), and cardiovascular diseases was collated and confirmed by medical records.

Neuroimaging
MRI scans were performed on a 3T Siemens Magnetom Trio Tim scanner, using a 32-channel head coil. Standardized sequences included T2-weighted, fluid attenuated inversion recovery, DWI, apparent diffusion coefficient, susceptibility-weighted imaging, and magnetic resonance angiography.

AII were defined as hyperintense lesions on DWI imaging, without evidence of T2 shine-through, with/without hypointense signals on apparent diffusion coefficient. White matter lesions (WMLs) were graded using the Fazekas scale on fluid attenuated inversion recovery images.13 Significant periventricular lesions were defined as grade ≥2 (smooth halo or extending into deep white matter), whereas significant deep white matter lesions as grade ≥2 (beginning confluence or large confluent areas). The periventricular and deep white lesion scores were added to obtain a composite score, and significant total WMLs were defined as a composite score of ≥4. Chronic lacunes were defined as hyperintense lesions on T2, measuring 3 to 15 mm, that were of cerebrospinal fluid intensity on fluid attenuated inversion recovery and T2, with/without a fluid attenuated inversion recovery hyperintense ring. Cerebral microbleeds (CMBs) were graded on susceptibility-weighted imaging, in accordance with the Brain Observer MicroBleed Scale,14 and significant CMBs were defined as total microbleeds ≥5. Intracranial stenosis is defined as ≥50% decrease in luminal diameter of an intracranial vessel on magnetic resonance angiography.

Cognitive Assessment
Subjects in both studies underwent a neuropsychological test battery, which has been previously validated in Singapore,15 consisting of the following:

Memory domains
– Verbal memory: word list, story recall.
– Visual memory: picture recall, Wechsler Memory Scale—revised visual reproduction.

Nonmemory domains
– Executive function: frontal assessment battery, maze task.
– Attention: digit span, visual memory span, auditory detection.
– Language: Boston naming test, verbal fluency.
– Visuomotor speed: symbol digit modality test, digit cancellation.
– Visuoconstruction: Weschler Memory Scale—revised visual reproduction copy task, clock drawing and Weschler Adult Intelligence Scale—revised subtest of block design.

The cognitive battery was administered in subject’s habitual language. Education-adjusted cutoffs were used to determine failure in subtests constituting a specific domain (1.5 SD below established means on individual tests), whereas failure in at least half of the subtests in a cognitive domain was considered failure in that cognitive domain. All subjects were categorized as no cognitive impairment, cognitive impairment not dementia (CIND), and dementia—diagnosed at weekly consensus meetings attended by study clinicians and neuropsychologists. CIND was defined as impairment in at least 1 domain of the neuropsychological test battery.

Statistical Analysis
Demographic and clinical and imaging parameters of subjects with AII were collated, and proportion of subjects in each cognitive category with AII was calculated. For the purpose of calculating incidence of AII, it was assumed that a hyperintense DWI lesion would be detectable for 10 days.17

Univariate analysis was performed (χ² test for categorical and independent sample t test for continuous variables) to explore associations of AII in community- and in clinic-based studies. Associations between AII and the following variables were analyzed:

Demographics: age, sex, and education status (<6 versus ≥6 years).

Previous medical conditions: hypertension, diabetes mellitus, hyperlipidemia, heart disease, history of stroke or TIA, atrial fibrillation.

Radiological parameters: significant WML, significant CMB, presence of chronic lacunes, and intracranial stenosis.

Results
A total of 623 subjects were included from EDIS study and 389 from the clinic-based study (Figure). All subjects in EDIS underwent a single MRI scan, whereas 142 of the 374 subjects in the clinic-based study underwent 2 scans (baseline and at year 2). DWI were available for 562 of 623 (90.2%) subjects

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Associations with a value of P≤0.05 were then analyzed in a multivariate logistic regression model, using a backward stepwise selection strategy.

Values of P<0.05 were considered statistically significant. Parameter estimates and their 95% confidence intervals (CIs) are reported. Statistical analyses were performed using Statistical Package for Social Science, SPSS version 19 (SPSS Inc).

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from EDIS; 374 of 389 (96.1%) subjects underwent baseline scan and 100% of the 142 subjects underwent year 2 scan from the clinic-based study.

Subjects in the clinic-based cohort were older (mean difference, 1.4 years; 95% CI, 0.4–2.4) and more likely to have previous history of heart disease, atrial fibrillation, and stroke/TIA (P<0.01), whereas EDIS subjects were more likely to have hypertension (P<0.01).

AII were seen in 7 subjects (1.2%) in the EDIS. AII were noted in 12 subjects (3.2%) in the clinic-based cohort; of these, 7 AII were on baseline images, whereas 5 were on year 2 scans. None of the subjects with AII on year 2 scans had AII on baseline scans. All AIIIs were lacunar and subcortical; no cortical or large AIIIs were observed.

The characteristics of subjects with and without AII in both cohorts are shown in Table 1. Notably, 11 (57.8%) subjects with AII had a previous history of TIA/stroke, whereas 15 (78.9%) had chronic lacunar infarcts. In relation to cognition, AII were noted in 0.8% of no cognitive impairment subjects, 1.9% of CIND, and 4.2% of dementia (Table 2).

Univariate analysis showed statistically significant associations between the presence of significant CMB and AII in the both EDIS and clinic-based cohorts (Tables 3 and 4), which remained significant in multivariable analysis. In subjects with cognitive impairment, a similar significant association was noted between AII and significant CMB: EDIS: odds ratio of 6.17 (95% CI, 1.20–31.12; P=0.02) and clinic cohort: odds ratio of 6.08 (95% CI, 1.59–23.20; P=0.01). Of the 19 subjects with AII, 10 had lobar microbleeds (cortex or gray–white junction) and 7 deep microbleeds.

Table 1. Characteristics of Subjects With and Without AII, Comparing Community-Based (EDIS) and Clinic-Based Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>EDIS, n (%) or Mean (SD), As Applicable</th>
<th>Clinic-Based Study, n (%) or Mean (SD), As Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=7)</td>
<td>No All (n=555)</td>
</tr>
<tr>
<td>Age, y</td>
<td>77.3 (6.1)</td>
<td>70.8 (6.8)</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>3 (57.1)</td>
<td>247 (44.5)</td>
</tr>
<tr>
<td>Risk factors (vascular)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>6 (85.7)</td>
<td>460 (82.9)</td>
</tr>
<tr>
<td>HLD</td>
<td>4 (57.1)</td>
<td>393 (70.8)</td>
</tr>
<tr>
<td>DM</td>
<td>1 (14.3)</td>
<td>168 (30.3)</td>
</tr>
<tr>
<td>Heart disease (except AF)</td>
<td>1 (14.3)</td>
<td>24 (4.3)</td>
</tr>
<tr>
<td>AF</td>
<td>0 (0)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>TIA/stroke</td>
<td>2 (28.6)</td>
<td>47 (8.5)</td>
</tr>
</tbody>
</table>

| Radiological parameters              |           |              |      |           |              |        |
| Significant TWML                     | 4 (57.1) | 188 (34.1) | 0.19 | 7 (58.3) | 150 (41.8) | 0.19 |
| Significant PVWML                    | 4 (57.1) | 237 (42.7) | 0.32 | 8 (66.7) | 152 (42.3) | 0.11 |
| Significant DWML                     | 5 (71.4) | 242 (43.6) | 0.17 | 10 (83.3) | 210 (58.5) | 0.10 |
| Significant microbleeds              | 3 (42.9) | 27 (4.9) | <0.01 | 6 (50) | 48 (13.8) | <0.01 |
| Chronic lacunes                      | 5 (71.4) | 104 (18.7) | <0.01 | 10 (83.3) | 93 (25.7) | 0.07 |
| Intracranial stenosis                | 3 (42.9) | 93 (17.2) | 0.11 | 3 (25) | 63 (18.2) | 0.39 |

AF indicates atrial fibrillation; AII, acute incidental infarcts; DM, diabetes mellitus; DWML, deep white matter lesions; EDIS, Epidemiology of Dementia in Singapore; HLD, hyperlipidemia; HT, hypertension; PVWML, periventricular white matter lesions; TIA, transient ischemic attack; and TWML, total white matter lesions.

Table 2. Distribution of AII as Per Cognitive Status and Study

<table>
<thead>
<tr>
<th>Cognitive Category</th>
<th>EDIS</th>
<th>Clinic-Based Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Subjects</td>
<td>All, n (%)</td>
</tr>
<tr>
<td>NCI</td>
<td>168</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CIND</td>
<td>365</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>Dementia</td>
<td>29</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Total</td>
<td>562</td>
<td>7 (1.2)</td>
</tr>
</tbody>
</table>

All indicates acute incidental infarcts; CIND, cognitive impairment not dementia; EDIS, Epidemiology of Dementia in Singapore; and NCI, no cognitive impairment.

*Four vascular dementia and 2 Alzheimer disease with cerebrovascular disease.
cognitive impairment. By comparison, 387 had cognitive impairment (359 CIND and 28 dementia) without AII and of these subjects 24 (6%) had significant CMBs, 156 (41%) had significant WML, and 93 (24%) had chronic lacunes. Among subjects with cognitive impairment, no significant difference was noted between subjects with and without AII in terms of significant WML ($P=0.45$), whereas the presence of significant CMB ($P<0.01$) and chronic lacunes ($P<0.01$) was significantly higher in subjects with AII (Fisher exact test).

In the clinic-based cohort, prevalence of AII was 2.3% in no cognitive impairment, 2.6% in CIND, and 4.3% in dementia. Of the 12 subjects with AII, 10 had cognitive impairment; among these, 6 (50%) had significant CMBs, 7 (58%) had significant WML, and 10 (83%) had chronic lacunes. Only 2 had no cognitive impairment of whom none had significant CMBs, 1 (50%) had significant WML, and 1 (50%) had chronic lacunes. Further analysis was limited by small numbers. By comparison, 280 had cognitive impairment (147 CIND and 133 dementia) without AII; of these subjects, 45 (17%) had significant CMBs, 137 (50%) had significant WML, and 78 (28%) had chronic lacunes. Among subjects with cognitive impairment, no significant difference was noted between subjects with and without AII in terms of significant WML ($P=0.54$), whereas the presence of significant CMB ($P<0.01$) and chronic lacunes ($p=0.04$) was significantly increased in subjects with AII (Fisher exact test).

### Discussion

This is the first study to report AII in both community- and clinic-based populations. We show that AII are more likely to be present in subjects with cognitive impairment.

### Table 4. Significant Associations of Acute Incidental Infarcts in the Clinic-Based Studies

<table>
<thead>
<tr>
<th>Clinic-Based Study</th>
<th>Univariate analysis, OR (95% confidence intervals); $P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of stroke/TIA</td>
<td>7.06 (1.87–26.57); 0.004</td>
</tr>
<tr>
<td>Chronic lacunes</td>
<td>2.89 (0.91–9.19); 0.07</td>
</tr>
<tr>
<td>Significant microbleeds</td>
<td>6.25 (1.94–20.18); 0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate analysis, OR (95% confidence intervals); $P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of stroke/TIA</td>
</tr>
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<td>Significant microbleeds</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; and TIA, transient ischemic attack.

The PURE community-based substudy suggested that the prevalence of DWI-positive lesions is $<0.5\%$, whereas our results show a prevalence of 1.2% (95% CI, 0.3–2.2) in subjects drawn from the EDIS study. This may be explained by differences in population characteristics. The PURE substudy included subjects who were younger (58.4±8 versus 70.9±6.8 years) and excluded individuals with stroke and dementia. Also, the proportion of subjects with vascular risk factors in PURE was much lower (hypertension 18% versus 82.9% and diabetes mellitus 6.1% versus 30.1%). Thus, in older individuals, with a higher prevalence of vascular risk factors, a previous history of stroke or cognitive impairment, the prevalence of AII is likely to be higher.

A previous study has reported a prevalence of asymptomatic DWI lesions in 5.2% of patients drawn from a memory clinic (16 DWI hyperintense lesions in 13 patients; mean age, 73.3±8.3 years), with an estimated annual incidence of 2.3 new infants per person-year. Interestingly, no association was reported between the DWI lesions and age, sex, vascular risk factors, WMLs, or CMBs. An even higher prevalence (12 of 78; 15%) was reported in patients diagnosed with cerebral amyloid angiopathy (mean age, 78.2±8.9 years) undergoing MRI for various indications. Intriguingly, in the same study, no DWI lesions were noted among 55 older patients (88.4±8.1 years) with minimal cognitive impairment or Alzheimer disease, suggesting an association between vascular disease and DWI lesions. Assuming that a hyperintense DWI lesion is detectable for 10 days, the incidence of AII in our community-based cohort was 0.45 AII per person-year ($7/562$×$365/10$). The incidence of AII in the clinic-based population ranged from 0.68 (baseline) to 1.28 (year 2) per person-year, respectively. Given the short duration of DWI-positive lesions, baseline versus follow-up imaging in any given patient may provide informative data only if all lesions occur at high rates; however, follow-up imaging may be useful to understand the eventual fate of such lesions.

We observed an association among AII, chronic lacunes, and microbleeds, whereas no association was observed among hypertension, hyperlipidemia, or diabetes mellitus, which suggests an association with vascular disease, independent of traditional vascular risk factors. A recent report, based on data from the prospective population-based Rotterdam Scan Study, showed that CMBs may be predictors of chronic ischemic brain lesions and may represent an imaging marker of active vasculopathy. Our findings suggest that this association may hold true for AII as well although this requires confirmation. AII were significantly associated with the presence of chronic lacunes in EDIS, whereas a significant association between a history of stroke/TIA and AII was noted in the clinic-based cohort. Although seemingly discrepant, this may be explained by the fact that not all lacunar infarcts cavitate; thus, patients with a history of lacunar stroke may not have evidence of lacunes in subsequent imaging. Intriguingly, a recent study using serial MRI in 16 subjects indicated that clinically silent acute ischemic lesions may evolve into lesions with similar imaging characteristics as preexisting WMLs. Although we did not note significant association between AII and WMLs, the association between AII and history of cerebrovascular events or...
the presence of chronic lacunes may be evidence of an underlying active vasculopathy. The prevalence of AII was higher in individuals with cognitive impairment when compared with those with normal cognition. Although the trend was nonsignificant in the clinic-based cohort, this may be because of low numbers of subjects with AII. In the EDIS cohort, all subjects with AII were cognitively impaired. It is possible that the association between AII and impaired cognition may be causal. Infarcts, even those that are clinically silent have been shown to increase the risk of cognitive decline. Thus, accumulation of such infarcts over time, whether cavitating (chronic lacunes) or noncavitating (increasing WML volume), may cause decline in cognitive function. Over time, AII may either contribute to the WML volume or become evident as chronic lacunes. The association between cognitive impairment and AII may thus be mediated by the presence of other markers of vascular disease, specifically chronic lacunes and CMB. However, low numbers of AII in our cohorts limit statistical power. It is possible that the AIsIs detected in our study are silent strokes that were incidentally imaged in their acute phase, as indicated by an association with the presence of chronic lacunes. We have previously reported that a significant number of strokes may be silent because of lack of awareness of stroke-like symptoms in the elderly and those with cognitive impairment, which may lead to under-reporting of clinical symptoms. The association among AII, chronic lacunes, and CMBs suggests a common pathogenic mechanism, likely a vasculopathy.

Another possibility includes a common pathogenic mechanism(s), other than traditional vascular risk factors, that determine both AII and cognitive impairment. Certainly, the mechanism(s), other than traditional vascular risk factors, that affect estimation of the incidence of AII. In the EDIS cohort, this may be because of low numbers of subjects with AII. In the EDIS cohort, all subjects with AII were cognitively impaired. It is possible that the association between AII and impaired cognition may be causal. Infarcts, even those that are clinically silent have been shown to increase the risk of cognitive decline. Thus, accumulation of such infarcts over time, whether cavitating (chronic lacunes) or noncavitating (increasing WML volume), may cause decline in cognitive function. Over time, AII may either contribute to the WML volume or become evident as chronic lacunes. The association between cognitive impairment and AII may thus be mediated by the presence of other markers of vascular disease, specifically chronic lacunes and CMB. However, low numbers of AII in our cohorts limit statistical power. It is possible that the AIsIs detected in our study are silent strokes that were incidentally imaged in their acute phase, as indicated by an association with the presence of chronic lacunes. We have previously reported that a significant number of strokes may be silent because of lack of awareness of stroke-like symptoms in the elderly and those with cognitive impairment, which may lead to under-reporting of clinical symptoms. Although it is possible that the association between AII and dementia may be influenced by genetic factors or underlying amyloid angiopathy, these remain hypotheses and require confirmation in further studies.

Our study has some limitations. First, DWI images were not available for a minority of the subjects recruited, which may have led to an underestimation of AII. However, because 92.6% of all recruited subjects had DWI, this effect is likely to be minimal. Second, because this is an ongoing study, not all clinic-based subjects have yet undergone a year 2 repeat scan, affecting estimation of the incidence of AII. Third, the total number of subjects with AII remains small; thus, we were underpowered to examine associations. The strengths of our study include standardized 3T MRI procedures, for all subjects, as well as the utilization of a validated comprehensive neuropsychological test battery.

The implications of AII in terms of determining treatment measures are unknown. Should detection of AII trigger the addition/escalation of treatment for stroke prevention? It may be reasonable to treat individuals with AII in the same manner as those with stroke. Thus, secondary preventive measures, including antithrombotics, may be instituted for such individuals, as per guidelines. However, given the lack of evidence, in individuals who are already treated with recommended agents, clinical decisions on escalation of therapy may require further studies. Nevertheless, optimal management of known vascular risk factors must be considered and should be a research priority.

**Conclusions**

We report the prevalence of AII in community and clinic-based populations and show that individuals with dementia are more likely to have AII on brain imaging. Although a cause–effect relationship is plausible, the association may also be because of under-reporting of symptoms by individuals with cognitive impairment. The association among AII, CMB, and the presence of chronic lacunes may indicate cerebral vasculopathy, independent of the traditional vascular risk factors.

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**Disclosures**

None.

**References**


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