Common Carotid End-Diastolic Velocity and Intima-Media Thickness Jointly Predict Ischemic Stroke in Taiwan

Shao-Yuan Chuang, PhD; Chyi-Huey Bai, PhD; Jiunn-Rong Chen, MD; Wen-Ting Yeh, MSc; Hsin-Jen Chen, MSc; Hou-Chang Chiu, MD; Ruei-Shiang Shiu, MSc; Wen-Harn Pan, PhD

**Background and Purpose**—In Asian populations, few studies investigated the association between stroke and common carotid artery intima-media thickness (IMT). Our previous case-control studies showed that low end-diastolic velocity (EDV) in common carotid artery, a potential hemodynamic marker of intracranial resistance, was associated with ischemic stroke. Therefore, we investigated the relationship between both EDV and IMT and incident ischemic stroke in an Asian population.

**Methods**—Baseline data from 3175 adults (30 years or older) in the Cardiovascular Diseases Risk Factor Two-Township Study were linked to incidental ischemic stroke status derived from insurance claims and death certificate records. Hazard ratios for risk of ischemic stroke for high IMT and low EDV values measured in common carotid artery were calculated using Cox proportional hazard models.

**Results**—With 9.85 years (median) of follow-up, 184 persons had ischemic stroke develop. Compared with the first tertile of IMT, hazard ratios were 2.03 (95% confidence intervals, 1.27–3.25) for the second tertile and 3.87 (95% confidence intervals, 2.36–5.69) for the third tertile. Hazard ratios of EDV were 5.31 (95% confidence intervals, 3.52–7.99; first tertile) and 1.94 (95% confidence intervals, 1.21–3.09; second tertile) compared with the third tertile. The individuals with high IMT and low EDV had >2-fold ischemic stroke risk compared to those with low IMT and high EDV (2.10; 95% confidence intervals, 1.35–3.26) after adjusting for age, sex, and traditional cardiovascular risk.

**Conclusions**—Common carotid IMT and EDV jointly and independently predicted future ischemic stroke in this Taiwanese population. More prospective studies are required in various ethnic groups to understand the significance and implication of the current findings, particularly with respect to EDV. (Stroke. 2011;42:1338-1344.)

**Key Words:** end-diastolic velocity ■ intima-media thickness ■ ischemic stroke ■ prospective study

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**Stroke** is a major public health burden in both Asian and Western populations. Large-scale prospective studies in Europe and the United States have confirmed that the carotid intima-media thickness (IMT), an indicator of large-artery atherosclerosis, can independently predict all types of stroke, especially ischemic stroke (IS). Few Asian prospective studies investigate the relationship between carotid IMT and stroke. A prospective study in elderly Japanese men showed that maximum common carotid artery (CCA) IMT was an independent risk factor for future total stroke, but not IS. However, no such relationship between IMT and stroke has been established in Taiwan or other Chinese populations in which large-artery disease is less prevalent.

However, the relationship between carotid hemodynamic data and IS has not been well-studied. Our previous case-control study showed that end-diastolic velocity (EDV), peak systolic velocity (PSV), and resistive index (RI) measured in carotid artery were associated with IS. Among these, EDV, a potential marker of intracranial resistance, was most significant. Nevertheless, EDV was not studied before. There is some information on RI in the literature. RI, calculated as the ratio of the PSV–EDV difference to PSV, often is used to measure renal vessel resistance at the level of the interlobar arteries. The renal RI has been positively associated with age, systolic blood pressure, urinary albumin-to-creatinine ratio, and carotid wall thickness, and has been negatively associated with diastolic blood pressure. Subjects with an elevated RI had a high prevalence of microalbuminuria, left ventricular hypertrophy, and increased carotid IMT. Te desco et al suggested that renal RI can predict early...
cardiovascular damage and provide an accurate estimate of overall risk. Few studies have investigated the relationship between the RI of the internal carotid artery (ICA) and IS. Recently, Staub et al.\(^9\) showed that individuals with a high RI in ICA (≥0.66) had a higher risk of cardiovascular events from a study of 157 patients at high risk. As such, the association between these hemodynamic parameters and IS needs further prospective investigations.\(^9\)

We conducted a community-based prospective study in Taiwan in a population at low atherosclerotic risk to elucidate the associations between IS and IMT and between IS and hemodynamic parameters, including EDV of CCA, which can be simultaneously assessed by ultrasonography.

**Subjects and Methods**

The Cardiovascular Disease Risk Factors Two-Township study (CVDFACTS) is a community-based follow-up study focusing on risk factor evolution and cardiovascular disease development in Taiwan. From 1991 to 1993, all residents in the household registry >3 years old in 5 villages in Chu-Dung and another 5 villages in Pu-Tzu were invited to participate in the baseline examination. A total of 5146 residents aged 30 years and older participated in the cycle 3 examination (1994–1996) for the biochemical data. There were 3440 residents with carotid artery ultrasonographic measurements in cycle 4 examination (1997–1999). Of them, 140 residents were not covered by the national health insurance. Eleven subjects were without ultrasonographic measurements and 114 patients reported a history of stroke or had stroke develop before ultrasonographic measurements. Data from the 3175 eligible subjects were used for analyses. There is no difference between those included and those excluded in the distributions of age, sex, and cardiovascular risk factors. Further details about sampling and data collection have been described elsewhere.\(^13\) All participants gave informed consent at baseline and at follow-up.

**Study Protocol**

Examinations were performed in the study clinics set-up in the two townships. The weight, height, and waist circumference were measured in participants wearing light clothes.\(^16\) Blood pressure was measured 3 times after the subject had been seated for ≥5 minutes, and the mean of the last 2 readings was used for analysis. Hypertension\(^11\) was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or using antihypertension medication. All subjects were asked to fast overnight for ≥8 hours before blood specimen collection. After collection, blood specimens were stored at −70°C and fasting glucose and triglycerides were measured within 1 month. Diabetes mellitus\(^18\) was defined as fasting glucose ≥126 mg/dL, or using antidiabetic medication. Individuals attending the baseline and follow-up examinations also completed a questionnaire-based interview. The questionnaire contained items on demography, lifestyle, self-reported health conditions, and family history of disease.

**Quantitative Ultrasonography**

We used a color-coded and duplex Doppler ultrasonographic system (SONOs 1000; Hewlett-Packard) with a transducer frequency of 7.5 MHz and color Doppler frequency of 5.4 MHz. All ultrasonic readings were evaluated and appraised by 1 technician who had no previous information on patients’ profiles. A standardized protocol modified from Howard et al.\(^9\) was established for B-mode image analysis. All measurements of IMT were made at the smooth plaque-free portion on the far wall of the CCA in the longitudinal plane along a 1-cm length proximal to the carotid bulb. The IMT was defined as the distance between the intima-media interface and the adventitia-media junction. Plaque was defined as a localized wall thickening at least twice the thickness of adjacent IMT. After freezing the image, 1 measurement was made with electronic calipers, unfreezing the image on each occasion and relocating the position of the IMT, and another measurement was made. Magnification of the ultrasound image was used to improve the accuracy of placement of the calipers if necessary. In the case of an unusually continuous plaque along the whole 1-cm length, the IMT in the least affected portion was chosen. The averaged value from 2 repeated measurements was obtained for each side. IMT used in this study was the maximal thickness of 2 CCA measurements. The correlation coefficients between repeated measurements were 0.872 in right CCA and 0.871 in left CCA among 43 subjects. For Doppler spectral analysis, PSV and EDV were measured and calculated from 1 cardiac cycle in the cervical portion of CCA 2 to 4 cm proximal to the carotid bulb. The RI is defined as the [(PSV−EDV)/PSV]. The minimal EDV and PSV and the maximal RI in CCA, ICA, and external carotid artery were obtained. CCA data were used in this study among 3 parameters and only the results of EDV were presented in this manuscript, because the relation of EDV with IS was stronger than PSV and RI and 3 parameters were highly correlated.

**IS Ascertainment**

Two sources of information were used to determine the first-ever IS status and the time of onset, ie, death certificate data and insurance claim records of the National Health Insurance database.\(^20\) All of our studied subjects were covered by National Health Insurance. First, we identified subjects with International Classification of Diseases, 9th edition (ICD-9) codes between 430 and 438 (cerebrovascular disease) in medical claims or in death registry database. Second, the following information was extracted: (1) the date and the name of the hospitals that patients have visited; (2) the procedures patients underwent; (3) the kinds of medications and rehabilitation prescribed after the examination; and (4) all ICD codes checked by physicians at each visit. Third, a first-ever stroke was defined when any 1 of the following conditions was met (with ICD-9-codes 430 to 438): (1) hospitalization claim for 1 day under ICD-9 codes 430 to 438; (2) ≥3 consecutive outpatient visits to hospitals, followed by claims for various neurological imaging technology such as CT, MRI, transcranial or carotid Doppler sonography, and long-term stroke-related medications prescribed; or (3) additional consecutive outpatient visits, followed by claims for rehabilitation and long-term stroke-related prescriptions. For the latter 2 criteria, exclusion was made for those claims made by Chinese herbal doctors, dentists, or non-neurologists practicing in public health stations or private clinics. The date that the first stroke ICD code appeared was defined as the onset date for stroke event. Fourth, IS was defined by the ICD-9-CM codes 433, 434, or 436 with at least 3 instances of IS drug prescription. The sensitivity and specificity for these rules were 100% and 95%, respectively, in 508 hospital-based subjects from a previous study,\(^8\) when neurologists’ diagnoses recorded in the stroke registry were taken as the gold standard (Supplemental Figure, http://stroke.ahajournals.org).

**Statistical Methods**

We used survival analysis to evaluate the associations of IMT and of EDV with IS. Survival time was calculated from the date of ultrasound measurement to the onset of stroke, date of death, or the end of follow-up. The Kaplan-Meier method was used to estimate survival curves and the log-rank test to examine the equality among survival curves. The Cox proportional hazard model was used to estimate the hazard ratio and 95% CI. All statistics were calculated using SAS 9.1 software.

**Results**

**Incidence of Stroke**

The follow-up period was from 1997 to 2007. The median follow-up time was 9.85 years (mean, 9.23 years). During the follow-up period, 219 stroke events occurred. Among these,
184 were ischemic stroke. The incidence rate of all strokes was 9.18 per 1000 person-years in men (n = 119) and 6.12 per 1000 person-years in women (n = 100), respectively (P = 0.0032). The incidence rate of IS was 7.71 per 1000 person-years in men (n = 104) and 9.18 per 1000 person-years in women (n = 99), respectively (P = 0.0070).

**Association Between EDV, IMT, and IS**

Age, waist circumference, body mass index, triglycerides, total cholesterol, systolic/diastolic blood pressure, and glucose were positively associated with IMT (Table 1) and negatively associated with EDV (Table 2). The IS risk increased with every increment of IMT but decreased with increments of EDV. The IS incidence in the 9 groups of IMT–EDV is shown in Figure 1 and Supplemental Table.

Table 3 presents the associations between IMT, EDV, and IS in the age- and sex-adjusted models (model 1) and multivariate models (model 2). Model 1 and model 2 show that IMT alone, EDV alone, and combination of IMT and EDV were significantly associated with all stroke and ischemic stroke. Increment of IMT per SD and EDV per SD increased IS risk 18% and decreased IS risk 29%, respectively (model 2). Moreover, we combined the IMT and EDV to classify all subjects into 4 groups: low IMT and high EDV, high IMT and high EDV, low IMT and low EDV, and high IMT and low EDV. The survival curves of these 4 combinations were heterogeneous (P for log-rank test <0.0001; Figure 2). The multivariate adjusted hazard ratio of IS for high IMT–low EDV was 2.10 (95% confidence intervals, 1.35–3.26), for low IMT–low EDV it was 1.88 (1.15–3.09), and for high IMT–high EDV it was 1.24 (0.73–2.11) compared to the reference group (P for trend test = 0.0004; Table 3).

**Discussion**

This is the first prospective study in Chinese to our knowledge to investigate the relationship between measurements of EDV and IMT and incident IS. This study suggests that both IMT and EDV are significant predictors of IS, independent of traditional cardiovascular risk factors in this population at low risk for atherosclerosis. Furthermore, EDV and IMT additively predict risk for IS.

The independent and significant associations between IMT and stroke have been observed in middle-aged subjects of other populations, including those in the Netherlands, and middle-aged and elderly Americans. In Asian countries, studies on the effect of IMT and IS risk were scarce. The OSACA study investigating the relationship between atherosclerosis and stroke showed that the severity of carotid atherosclerosis is a useful indicator of the risk of IS in patients at high risk. In addition, among the elderly Japanese men, the higher CCA IMT group had significantly higher risk of total stroke compared with the lower CCA IMT group. Our community-based study found that the maximum CCA IMT was positively associated with IS, consistent with the findings in whites.
The degree of association between carotid IMT and IS may vary by IMT levels and plaque severity of the studied populations. Most previous prospective studies studying this phenomenon have focused on elderly subjects who often have high mean IMT values and are at high risk for atherosclerosis.\(^2,5,8\) The studies with high average IMT (average age range, 50.1–72.5 years; average IMT range, 0.74–1.05 mm) suggested that IMT was an independent risk factor for predicting future stroke,\(^2,4–6,8\) probably because of a wider distribution of IMT. The average carotid IMT in the current study was 0.55 mm in all subjects and 0.64 mm in elderly subjects aged 65 years or older, which are evidently lower than those of other studies.\(^2,5,6\) The association between IMT and IS in this population at low risk for atherosclerosis is slightly weaker than that in other studies\(^2,4,5\) (hazard ratio range, 1.27–1.38 per SD) and is likely attributable to a relatively small variation of IMT in our studied population.

With regard to the meaning of the low EDV in IS in a population at low risk for carotid atherosclerosis, we feel it may be considered as an index of intracranial resistance, the predictive power of which is better than that of the RI, the ratio of the gap between PSV and EDV to PSV. The lower the EDV, the higher of the RI, according to the formula. Few studies examined this subject carefully in the literature. One study revealed that RI in ICA can predict cardiovascular events.\(^14\) Our study showed that EDV per se, meaning the capacity to provide blood into intracranial circulation at diastolic phase, is a more sensi-
A predictive index to predict IS than RI and PSV (data not shown). This phenomenon was observed not only in CCA but also in ICA and external carotid artery, but the best predictor for IS was CCA EDV, possibly because of its better precision. We observed this phenomenon previously in a case-control study.\(^9\) The present article replicates the earlier finding in a prospective manner. The rationale behind this finding needs further investigation.

Several reasons may explain why EDV is a better indicator of stroke than IMT in a Chinese population. The Table 3. Hazard Ratio (95% CI) for All Stroke and Ischemic Stroke by Tertiles of Intima-Media Thickness, End-Diastolic Velocity, and Their Combination

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Stroke</th>
<th>Ischemic Stroke</th>
<th>All Stroke</th>
<th>Ischemic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>IMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.36 (0.88–2.10)</td>
<td>1.28 (0.79–2.05)</td>
<td>1.46 (0.80–2.39)</td>
<td>1.36 (0.80–2.32)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1.69 (1.13–2.54)</td>
<td>1.67 (1.08–2.60)</td>
<td>1.57 (0.98–2.53)</td>
<td>1.58 (0.95–2.63)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.0089</td>
<td>0.0140</td>
<td>0.0860</td>
<td>0.0787</td>
</tr>
<tr>
<td>Per SD (0.156 mm) increment</td>
<td>1.22 (1.10–1.36)</td>
<td>1.26 (1.13–1.40)</td>
<td>1.17 (1.03–1.33)</td>
<td>1.21 (1.07–1.37)</td>
</tr>
<tr>
<td>EDV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>2.56 (1.73–3.81)</td>
<td>2.52 (1.63–3.90)</td>
<td>2.11 (1.35–3.30)</td>
<td>2.20 (1.34–3.61)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.33 (0.86–2.05)</td>
<td>1.34 (0.83–2.15)</td>
<td>1.10 (0.68–1.77)</td>
<td>1.20 (0.71–2.03)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>0.0004</td>
</tr>
<tr>
<td>Per SD (5.7 cm/sec) increment</td>
<td>0.64 (0.55–0.76)</td>
<td>0.65 (0.54–0.77)</td>
<td>0.67 (0.57–0.83)</td>
<td>0.69 (0.56–0.84)</td>
</tr>
<tr>
<td>Combination of IMT and EDV*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low IMT–high EDV</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>High IMT–high EDV</td>
<td>1.34 (0.87–2.07)</td>
<td>1.39 (0.87–2.22)</td>
<td>1.18 (0.72–1.92)</td>
<td>1.24 (0.73–2.11)</td>
</tr>
<tr>
<td>Low IMT–low EDV</td>
<td>1.96 (1.29–2.97)</td>
<td>1.85 (1.16–2.94)</td>
<td>2.01 (1.29–3.14)</td>
<td>1.88 (1.15–3.09)</td>
</tr>
<tr>
<td>High IMT–low EDV</td>
<td>2.38 (1.67–3.37)</td>
<td>2.42 (1.65–3.54)</td>
<td>1.98 (1.32–2.98)</td>
<td>2.10 (1.35–3.26)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>0.0004</td>
</tr>
<tr>
<td>Per SD (0.156 mm) increment in IMT</td>
<td>1.17 (1.04–1.30)</td>
<td>1.20 (1.08–1.34)</td>
<td>1.13 (0.99–1.29)</td>
<td>1.18 (1.04–1.33)</td>
</tr>
<tr>
<td>Per SD (5.7 cm/sec) increment in EDV</td>
<td>0.66 (0.56–0.78)</td>
<td>0.67 (0.56–0.80)</td>
<td>0.70 (0.58–0.85)</td>
<td>0.71 (0.58–0.87)</td>
</tr>
</tbody>
</table>

The cut-points of tertiles: 0.48 and 0.60 mm for IMT, 15 and 20 cm/sec for EDV. CI indicates confidence interval; EDV, end-diastolic velocity; IMT, intima-media thickness. *The dichotomous cut-points: 0.60 mm for IMT and 15 cm/sec for EDV. Model 1: adjusted for age, sex, and age × sex. Model 2: adjusted for age, sex, age × sex, waist circumference (cm), body mass index (kg/m²), triglycerides (mg/dL), high-density lipoprotein cholesterol (mg/dL), total cholesterol (mg/dL), systolic blood pressure (mm Hg), fasting glucose (mg/dL), current smoking (yes vs no), and family history of stroke (yes vs no).

Figure 2. Cumulative hazard function of ischemic stroke events in various levels of intima-media thickness (IMT) and end-diastolic volume (EDV). There were no significant differences in groups with low IMT (<0.6 mm) plus low EDV (<15 cm/sec) and with high IMT (>0.6 mm) plus high EDV (>15 cm/sec) for stroke risk (P=0.3436; n=3175).
Taiwanese population had lower risk of atherosclerosis than the white population. In addition, the distribution of EDV was higher in variation (coefficient of variation = 0.321) than IMT (coefficient of variation = 0.286) to discriminate the stroke risk, especially in a Chinese population, which had extremely low prevalence of high IMT. However, EDV may be a marker of vascular resistance.²² Carotid EDV may reflect intracranial vascular disease. A case-control study had shown low CCA EDV was associated with high ischemic stroke risk.⁹

Two trials, including the North American Symptomatic Carotid Endarterectomy trial³³ and the Asymptomatic Carotid Artery Stenosis trial,⁴⁺ reported a higher EDV diagnostic threshold in ICA for those highly selected patients who underwent carotid endarterectomy. These patients had ICA disease, ie, critical stenosis or occlusion in ICA, and were at high risk for stroke in the near future. The higher EDV comes from the hemodynamic adaptation to high-grade stenosis in ICA. However, such patients are scanty in community studies, especially in Asian populations, including ours, in which a reduced EDV may potentially correspond to elevated intracranial resistance. Therefore, our findings on the low EDV and future risk of IS are particularly interesting in the context of low prevalence of asymptomatic carotid artery disease. Several studies have shown that there is a relatively higher prevalence of intracranial stenosis in Asians than in Caucasians.²⁵–²⁸ This phenomenon is coherent with our findings.

**Limitation**

This study has a few limitations. First, the biochemical profile and carotid artery assessment were measured 2.5 years apart. This limitation, however, should not affect the internal validity of this study. Second, this current study was performed in Asian subjects. Its findings should be tested by future studies in other ethnic groups. Third, the atheroembolic events are more often seen in North American and European whites (55%)³⁹ than in Taiwanese individuals (17%).⁴⁰ The difference between ethnicity and stroke subtypes should be considered in investigating the cause of IS and in applying the results of current study. Finally, PSV and EDV were measured only once. Although all ultrasonic readings were evaluated and appraised by 1 experienced technician, with good precision, we did not keep the reproducibility data. Nonetheless, we discovered the significant association between EDV and stroke.

**Conclusions**

In this population at low risk for atherosclerosis, the carotid IMT and EDV could jointly predict the risk of future IS events, and EDV value was more strongly associated with IS than IMT. For the first time to our knowledge, low EDV has been established as an independent risk factor of IS in a prospective Chinese study.

**Acknowledgments**

The authors express their gratitude to neurologists in Shin Kong WHS Memorial Hospital who helped review medical charts of stroke patients and provided consultation for the development of decision rules to identify new stroke cases from national health insurance data.

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**Disclosure**

None.

**References**

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## Supplemental Table

Range of IMT and EDV, numbers at risk, person-years, and events and incidence of ischemic stroke in nine groups

<table>
<thead>
<tr>
<th>IMT</th>
<th>EDV</th>
<th>N</th>
<th>PYs</th>
<th>IS events</th>
<th>Incidence†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.11-0.47</td>
<td>2.0-14.0</td>
<td>200</td>
<td>1873</td>
<td>14</td>
<td>7.47</td>
</tr>
<tr>
<td></td>
<td>15.0-19.0</td>
<td>313</td>
<td>3052</td>
<td>7</td>
<td>2.29</td>
</tr>
<tr>
<td></td>
<td>20.0-41.0</td>
<td>532</td>
<td>5133</td>
<td>6</td>
<td>1.17</td>
</tr>
<tr>
<td>0.48-0.59</td>
<td>2.0-14.0</td>
<td>293</td>
<td>2585</td>
<td>27</td>
<td>10.44</td>
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<tr>
<td></td>
<td>15.0-19.0</td>
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<td>2734</td>
<td>11</td>
<td>4.02</td>
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<tr>
<td></td>
<td>20.0-41.0</td>
<td>382</td>
<td>3628</td>
<td>12</td>
<td>3.03</td>
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<tr>
<td>0.60-1.34</td>
<td>2.0-14.0</td>
<td>480</td>
<td>3918</td>
<td>70</td>
<td>17.87</td>
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<tr>
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<td>15.0-19.0</td>
<td>370</td>
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<tr>
<td></td>
<td>20.0-41.0</td>
<td>314</td>
<td>2963</td>
<td>12</td>
<td>4.05</td>
</tr>
</tbody>
</table>

IMT = intima-media thickness; EDV = End-diastolic velocity; PYs = Person years; IS = Ischemic Stroke; †: per 1000 PY
A first-ever stroke was defined when any one of the following conditions was met (with ICD-9-code: 430-438): (1) hospitalization claim for one day under ICD-9 430-438, or (2) more than three consecutive outpatient visits to hospitals, followed by claims for various neurological imaging technology such as computed tomography, MRI, transcranial or carotid Doppler sonography and long-term stroke related medications prescribed, or (3) more than these consecutive outpatient visits, followed by claims for rehabilitation and long-term stroke related prescriptions. For the later two criteria, exclusion was made for those claims made by Chinese herbal doctors, dentists, or non-neurologists practicing in public health stations or private clinics. The date that the first stroke ICD code appeared was defined as the onset date for stroke event.

Supplemental Figure

<table>
<thead>
<tr>
<th>National Health Insurance dataset</th>
<th>National Death Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Identify potential Stroke patients</td>
<td>Identify subjects with ICD-9-codes between 430-438† in medical claims or in death registry.</td>
</tr>
<tr>
<td>2) A time sequenced electronic medical records were created using medical claim data and death for above subjects</td>
<td>The following information was extracted: (1) the date and the name of the hospitals that patients have visited, (2) the procedures patients went through, (3) the kinds of medications and rehabilitation prescribed after the examination, and (4) all ICD codes checked by physicians at each visit.</td>
</tr>
<tr>
<td>3) Define the first-ever stroke and the onset date</td>
<td>A first-ever stroke was defined when any one of the following conditions was met (with ICD-9-code: 430-438): (1) hospitalization claim for one day under ICD-9 430-438, or (2) more than three consecutive outpatient visits to hospitals, followed by claims for various neurological imaging technology such as computed tomography, MRI, transcranial or carotid Doppler sonography and long-term stroke related medications prescribed, or (3) more than these consecutive outpatient visits, followed by claims for rehabilitation and long-term stroke related prescriptions. For the later two criteria, exclusion was made for those claims made by Chinese herbal doctors, dentists, or non-neurologists practicing in public health stations or private clinics. The date that the first stroke ICD code appeared was defined as the onset date for stroke event.</td>
</tr>
<tr>
<td>4) Identify ischemic stroke</td>
<td>IS was defined by the ICD-9-CM codes 433, 434 or 436 with at least 3 times IS drug prescription.</td>
</tr>
</tbody>
</table>

†: codes for cerebrovascular disease from the International classification of Disease, 9th revision, Clinical Modification (ICD-9-CM): 430-438