Secular Trends in Ischemic Stroke Subtypes and Stroke Risk Factors

Chrysi Bogiatzi, MD; Daniel G. Hackam, MD, PhD; A. Ian McLeod, PhD; J. David Spence, MD

Background and Purpose—Early diagnosis and treatment of a stroke improves patient outcomes, and knowledge of the cause of the initial event is crucial to identification of the appropriate therapy to maximally reduce risk of recurrence. Assumptions based on historical frequency of ischemic subtypes may need revision if stroke subtypes are changing as a result of recent changes in therapy, such as increased use of statins.

Methods—We analyzed secular trends in stroke risk factors and ischemic stroke subtypes among patients with transient ischemic attack or minor or moderate stroke referred to an urgent transient ischemic attack clinic from 2002 to 2012.

Results—There was a significant decline in low-density lipoprotein cholesterol and blood pressure, associated with a significant decline in large artery stroke and small vessel stroke. The proportion of cardioembolic stroke increased from 26% in 2002 to 56% in 2012 (P<0.05 for trend). Trends remained significant after adjusting for population change.

Conclusions—With more intensive medical management in the community, a significant decrease in atherosclerotic risk factors was observed, with a significant decline in stroke/transient ischemic attack caused by large artery atherosclerosis and small vessel disease. As a result, cardioembolic stroke/transient ischemic attack has increased significantly. Our findings suggest that more intensive investigation for cardiac sources of embolism and greater use of anticoagulation may be warranted. (Stroke. 2014;45:3208-3213.)

Key Words: epidemiology ■ secondary prevention ■ stroke etiology ■ trends

Ischemic strokes account for ≈87% of all types of strokes; the distribution of ischemic stroke subtypes varies in different parts of the world.1 In Asia and South America, small vessel disease is the most prominent ischemic stroke subtype, whereas in Europe and the United States there is regional and ethnic variation in the distribution of stroke subtypes and their risk factors.2 Correctly identifying the cause of stroke is important for selection of the appropriate therapy to best reduce the risk of recurrence.3 This may be particularly important in patients with minor or moderate stroke/transient ischemic attack (TIA), because they are less disabled, so will have more to lose from a recurrent stroke. With changing patterns of practice, in particular, increasing use of statins in the past decade, the distribution of risk factors and stroke subtypes in this population is expected to change over time. Changes in stroke subtypes resulting from these changes in practice can be expected to lead to changes in how physicians view the likelihood of different causes of stroke among their patients and plan strategies for investigation of their patients.

The motivation for this study was the clinical suspicion, on the part of 2 senior stroke neurologists at our center, that cardioembolic strokes seemed to be increasing as a proportion of new patients referred to our local urgent TIA clinic. Our primary objective was to determine secular trends in ischemic stroke subtypes. We hypothesized that with more intensive management of atherosclerotic risk factors, there will have been a decrease in atherosclerotic risk factors and a decrease in large artery atherosclerosis and small vessel disease, and, in consequence, a proportional increase in cardioembolic stroke/TIA.

Methods

Study Setting and Timeline

This was a retrospective cohort study of patients diagnosed with minor or moderate stroke/TIA at the urgent TIA Clinic at University Hospital, a designated regional stroke hospital in London, Ontario. Based on Census reports from Statistics Canada, 599,538 residents were living in the referral area in 2006, and 619,881 residents were recorded in 2011. According to the 2011 census, 82% of the population of London are white, 2.7% Latin American, 2.6% Arab, 2.4% black, 2.2% South Asian, 2.0% Chinese, 1.9% Aboriginal, 1% Southeast Asian, 0.8% West Asian, 0.8% Korean, 0.6% Filipino, and 0.7% belong to other groups. In the surrounding farming area a higher
proportion would be white, with lower representation of other groups except on aboriginal reservations.

Our hospital is the designated regional stroke hospital under the Coordinated Stroke Strategy of Ontario, so by protocol all patients with stroke in the region are brought to this hospital. Most of the patients were seen in the emergency department and referred the next weekday to the urgent TIA clinic. Some patients were referred by their family physician, and some were referred after hospitalization and rehabilitation. The clinic is an ambulatory outpatient clinic, so all patients attending clinic had a modified Rankin score ≤4.

Eligible patients were selected beginning in 2002, when the urgent TIA was fully in operation, to 2012. The study was approved by the Western University Research Ethics Board (Protocol number 18716E).

Data Sources and Eligibility Criteria

The receptionist who receives all referrals faxed to the urgent TIA clinic provided a list of all patient names that were referred in sequence to J.D.S. based on the next appointment available. All patients for whom information was available to permit stroke subtype classification were included in analyses. Eligible participants were stroke/TIA survivors who were diagnosed with a first-ever stroke/TIA between 2002 and 2012. Patients who were referred to the clinic and did not present to their appointment were excluded, as were patients who were diagnosed with a previous stroke or a stroke mimic (such as migraine, subdural hematoma, brain tumor, and other nonvascular conditions).

Main Outcomes: Ischemic Stroke Subtypes

The main outcome of this study is the diagnosis of ischemic stroke subtype. Classification of ischemic stroke subtypes was based on the Subtypes of Ischemic Stroke Classification System—a modification of the causative classification system (CCS) of acute ischemic stroke, incorporating measurement of carotid plaque burden (Table I in the online-only Data Supplement shows stroke subtypes by the causative classification system in various studies). In brief, the categorization of patients into the 5 ischemic stroke subtypes, large artery atherosclerosis, cardioembolic, small vessel disease, other rare or unusual etiology, and undetermined etiology, was based on information from the medical history, physical examination, and laboratory investigations, which confirmed or altered the initial diagnosis based on additional tests ordered after the first clinical assessment. All patients had carotid ultrasound and computed tomography and/or MRI. Other investigations were ordered as appropriate to the patient’s presentation. The final adjudication of ischemic stroke subtypes was based on the review of the history, neurological examination, and all test results.

Additional Outcomes: Stroke Risk Factors

Stroke risk factors included the following: age, sex, smoking, diabetes mellitus, myocardial infarction, blood pressure, and plasma lipids. Investigations included serum glucose, serum B12, plasma total homocysteine, lipid profile, computed tomography and MRI, and ECG. Also recorded were body mass index, medications for hypertension, diabetes mellitus, hyperlipidemia, antplatelet and anticoagulant agents at the time before the onset of the stroke/TIA. Carotid Doppler ultrasound assessment of carotid stenosis and measurement of total plaque area were usually available at the time of the initial clinical visit. Additional tests were ordered as indicated after the first clinical assessment (Holter, transcranial Doppler, echocardiography, angiography, and carotid ultrasound if not already done).

Procedures: Data Collection

An experienced stroke neurologist (J.D.S.) examined and diagnosed all eligible patients with stroke/TIA and a second physician (C.B.) reviewed the clinical records and entered data into a database to assess the ischemic stroke subtypes and the stroke risk factors for the purpose of this study. Any cases for whom the stroke subtype was equivocal were reviewed by both physicians together to arrive at a consensus stroke subtype.

Statistical Analysis

Data quality was assessed using scatter plots for the continuous variables. All cases of unexplained outliers were re-evaluated comparing the information with paper chart documents, and erroneous data corrected. Continuous data were analyzed with ANOVA and discrete data were analyzed with χ² statistics.

Secular trends in stroke/TIA subtypes using the Subtypes of Ischemic Stroke Classification System classification of stroke subtype for all cases in the cohort were analyzed using a Poisson regression model with a spline trend function. We plotted for each stroke/TIA subtype a lattice plot counting all patients presenting with each stroke/TIA subtype per clinic day (online-only Data Supplement). We calculated the number of days from January 2002 until December 2012; the variable was called clinic day number, representing the response variable in our Poisson regression model. This model was tested for serial correlation in the deviance residuals. In the case of autocorrelation, the P values of the Poisson regression model with the spline function were compared with the Mann–Kendall trend test with blocked bootstrap. Significance tests were 2-sided with the probability of type I error at 0.05. Descriptive statistics and graph design were done using R, Version 2.15.2.

Results

Among 3950 consecutive patients referred to the J.D.S. at the urgent TIA clinic in this time period, 505 (12.8%) were excluded based on the exclusion criteria described above. Among the remaining 3445 patients included in our analyses, 1693 were men (49%) with mean age±SD 65±14 years and 1753 were women (51%) with mean age±SD 65±16 years (baseline characteristics are shown in the Table).

There was no significant change in the number of patients presenting per year (Figure IA in the online-only Data Supplement). However, there was a significant increase in cardioembolic stroke/TIA, from 23% to 56% of cases, and a significant decrease in all other secular trends in ischemic stroke subtypes: large artery strokes from 43% to 26%, small vessel from 12% to 7%, other explained from 9% to 4%, and unexplained varied by era (P<0.05 for trend; Figure 1) with negative autocorrelation. The distribution of stroke subtypes by year is shown in Table II in the online-only Data Supplement. Trends remained significant by sex (Figure IB and ID in the online-only Data Supplement) and after adjusting for population change (Figure 1C in the online-only Data Supplement). Even allowing for a sex difference in stroke subtypes, (Tables III and IV in the online-only Data Supplement), and for population change (Figure II in the online-only Data Supplement), secular trends showed a significant increase in cardioembolic stroke/TIA and decrease in all other subtypes (Figures I, II, and III in the online-only Data Supplement). There was no significant trend in the mean age of patients presenting per clinic day for each ischemic stroke subtype (Figure IV in the online-only Data Supplement).

Baseline blood pressure and lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides) decreased significantly over time (P<0.001; Figures 2 and 3). Age decreased by 1 year between 2002 and 2012 and there was no significant change in body mass index during the study period (Table IV in the
online-only Data Supplement). There was a significant difference in the distribution of stroke risk factors over time (Table V in the online-only Data Supplement) and among the 5 ischemic stroke subtypes (Table VI in the online-only Data Supplement). There was no change in patients presenting with atrial fibrillation (AF).

### Discussion

Our findings confirm a trend of increasing cardioembolic stroke/TIA in patients with minor stroke/TIA. Cardioembolic stroke carries a higher risk of death, recurrent stroke, and hospital readmission and a higher risk of severe disability compared with other stroke subtypes. Early diagnosis and appropriate treatment are therefore mandatory to prevent recurrent events that lead to greater disability and increased healthcare cost. Anticoagulants are much more effective than antiplatelet agents for prevention of cardioembolic stroke and the risk of recurrent events is high early after the initial event; early diagnosis of a cardioembolic source is therefore important. It is surprising that cardioembolic stroke increased without a significant increase in strokes because of AF. It is possible that this may have been because of increasing detection of paradoxical embolism over time. However, as shown in Table VII in the online-only Data Supplement, strokes caused by AF were relatively constant over time; the observed change in risk factors therefore seems more likely to account for the increasing trend to cardioembolic stroke. Regardless of the

<table>
<thead>
<tr>
<th>Continuous variables mean (SD)</th>
<th>2002–2005 (n=968)</th>
<th>2005–2009 (n=1314)</th>
<th>2009–2012 (n=1164)</th>
<th>P Value</th>
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<td>Age, y</td>
<td>66 (14)</td>
<td>64 (16)</td>
<td>65 (14)</td>
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<td>Systolic blood pressure</td>
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<td>Total cholesterol, mmol/L</td>
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<td>5.0 (1.2)</td>
<td>4.7 (1.2)</td>
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<tr>
<td>Triglycerides, mmol/L</td>
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<td>1.8 (1.1)</td>
<td>1.7 (1.1)</td>
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<td>HDL cholesterol, mmol/L</td>
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<td>LDL cholesterol, mmol/L</td>
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<td>Glucose, mmol/L</td>
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<td>6 (2)</td>
<td>6 (4)</td>
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<td>Men</td>
<td>476 (49)</td>
<td>652 (50)</td>
<td>565 (49)</td>
<td>0.998</td>
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<td>Body mass index &gt;25</td>
<td>537 (63)</td>
<td>812 (65)</td>
<td>730 (67)</td>
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<td>Never smoked</td>
<td>355 (37)</td>
<td>501 (38)</td>
<td>462 (40)</td>
<td>0.220</td>
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<tr>
<td>Active smoking</td>
<td>195 (20)</td>
<td>248 (19)</td>
<td>239 (21)</td>
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<td>Quit smoking</td>
<td>418 (43)</td>
<td>565 (43)</td>
<td>463 (40)</td>
<td>0.220</td>
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<td>Antiplatelet agents</td>
<td>446 (46)</td>
<td>596 (45)</td>
<td>537 (46)</td>
<td>0.937</td>
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<td>Anticoagulants</td>
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<td>88 (7)</td>
<td>86 (7)</td>
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<tr>
<td>Hypertension medications</td>
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<td>810 (62)</td>
<td>697 (60)</td>
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<td>Lipid medications</td>
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<td>595 (45)</td>
<td>520 (45)</td>
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<td>Diabetes mellitus medications</td>
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<td>177 (14)</td>
<td>166 (14)</td>
<td>0.411</td>
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<td>Myocardial infarction</td>
<td>140 (15)</td>
<td>163 (12)</td>
<td>115 (10)</td>
<td>0.045</td>
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<tr>
<td>Atrial fibrillation</td>
<td>77 (8)</td>
<td>106 (8)</td>
<td>124 (11)</td>
<td>0.149</td>
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<tr>
<td>Patent foramen ovale</td>
<td>80 (8)</td>
<td>190 (15)</td>
<td>219 (19)</td>
<td>&lt;0.001</td>
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<td>Large artery disease</td>
<td>441 (46)</td>
<td>400 (30)</td>
<td>291 (25)</td>
<td>&lt;0.001</td>
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<td>Cardioembolic</td>
<td>221 (23)</td>
<td>461 (35)</td>
<td>616 (53)</td>
<td>&lt;0.001</td>
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<td>Small vessel disease</td>
<td>110 (11)</td>
<td>150 (11)</td>
<td>94 (8)</td>
<td>&lt;0.001</td>
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<td>Other determined cause</td>
<td>89 (9)</td>
<td>86 (7)</td>
<td>46 (4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Undetermined</td>
<td>107 (11)</td>
<td>217 (17)</td>
<td>110 (10)</td>
<td>&lt;0.001</td>
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<tbody>
<tr>
<td>Computed tomography</td>
<td>619 (64)</td>
<td>900 (69)</td>
<td>827 (71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRI</td>
<td>349 (36)</td>
<td>547 (42)</td>
<td>424 (36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Holter</td>
<td>122 (13)</td>
<td>148 (11)</td>
<td>537 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>316 (33)</td>
<td>454 (35)</td>
<td>732 (63)</td>
<td>&lt;0.001</td>
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</tbody>
</table>

HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

*All patients had carotid duplex ultrasound.
Large artery atherosclerosis was expected to decrease given that hypertension and hyperlipidemia are better controlled with the implementation of the Canadian Hypertension Education Program and an increase in statin prescription. We showed in 2000 to 2007 that baseline stroke risk factors of patients with minor or moderate stroke/TIA were better controlled over time. Similarly, evidence from autopsy reports of United States military service members show a decreasing prevalence of atherosclerosis: the prevalence of coronary atherosclerosis was 77% in the Korean War in 1953, 45% in the Vietnam War in 1975, and 8.5% in the Iraq War.

A considerable strength of our study is the large number of patients we were able to collect and the availability of all clinically relevant information. All of our patients had carotid ultrasound, something that was a major limitation in previous studies. Also, all patients were examined by the same stroke expert, who collected all information, and diagnosed and treated patients in the same manner throughout the study period. Therefore, we think that if any information bias exists, it will be nondifferential over time. However, it should be noted that, as described in our article on the stroke subtype classification system used in this study, measurement of carotid plaque burden aids in the diagnosis of cardioembolic stroke because patients with little or no carotid plaque are considered less likely to have large artery disease.

Figure 1. Secular trends in ischemic stroke subtypes 2002 to 2012. Cardioembolic (CA) strokes increased significantly (P=0.04), whereas all other stroke subtypes declined. LA indicates large artery, OE, other explained etiology; SA, small artery; and UE, unexplained.

reasons, our finding that cardioembolic stroke now represents a much higher proportion of referrals should alert physicians to the need for a higher index of suspicion of this stroke subtype.

The distribution of ischemic stroke subtypes varies across countries. This may relate importantly to the age distribution: in the Framingham study, AF accounted for 1.5% of strokes at the age of 50 to 59 years, increasing to 23.5% by age 80 to 89 years. More recent studies show a higher prevalence of cardioembolic stroke, which represented 49% of strokes in Sweden and 56% of inpatients in Japan.

We found no change in patients presenting with AF over time. Approximately half of all patients with AF and less than one third of patients with cardioembolic stroke/TIA and AF were anticoagulated at the time of referral.

With better management of baseline stroke risk factors, we would expect that in more recent years, there would have been an increase in age of patients presenting with a first stroke/TIA and a decrease in the overall number of new cases. Surprisingly, there was an insignificant decrease in age and no change in the number of new patients presenting in more recent years. There was no significant change either at the population level, and the 7.5% increase had no effect on the trends for stroke/TIA subtypes in all patients in our cohort, or in men and women separately. We suspect that there might have been a shift from major stroke and death to minor stroke and TIA, given that there is a national decrease in major strokes and deaths and younger patients present with minor stroke/TIA. Our results are in agreement with those of the Dijon Stroke Registry and the Greater Cincinnati/Northern Kentucky region, both showing an increase in younger patients presenting with stroke. Improved stroke prevention strategies and stroke symptom awareness may be responsible for diagnosing minor stroke/TIA at a younger age in patients at risk.
Holter recording detected AF in only 3% of patients, whereas a 1-month automated recording detected AF in 16% of patients. This study indicates that with better control of coronary risk factors, stroke subtypes have changed markedly in the past 10 years, with a doubling of the proportion of patients with cardioembolic stroke/TIA. Our findings should motivate physicians who see patients at risk of recurrent stroke to investigate more intensively for a cardioembolic cause, because diagnosis of cardioembolic stroke should lead to a change in preventive therapy.

Conclusions

With more intensive medical therapy, a significant decrease in atherosclerotic risk factors was observed, with a significant decrease in strokes/TIAs caused by large artery atherosclerosis or small vessel disease. As a result, there was a significantly increasing trend in cardioembolic stroke/TIA among patients presenting with minor or moderate stroke/TIA between 2002 and 2012. Our findings suggest that more intensive investigation is appropriate to detect cardiac sources of embolism. This is important because it means that more patients will need anticoagulation for the prevention of recurrent stroke.

Acknowledgments

Dr Bogiatzi (Stroke Prevention and Atherosclerosis Research Center, Robarts Research Institute) designed the study, acquired the data, analyzed and interpreted the results, and drafted the article. Drs Hackam and Spence provided the concept of the study, analyzed the data,
interpreted the results, and revised the article. Dr McLeod designed the program for the statistical analysis of trends, interpreted the results, and revised the article. Drs Spence and Bogiatzi have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

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Disclosures
None.

References


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Secular Trends in Ischemic Stroke Subtypes and Stroke Risk Factors

Online supplemental material

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Figure III. Changes in proportions of ischemic stroke subtypes in three eras: before 2005, 2005-2008, and since 2009.
Figure IV. Secular trends of the average age of stroke/TIA patients in each ischemic stroke/TIA subtype.
Table I. Comparison of Ischemic Stroke Subtypes between studies based on the Causative Classification of acute ischemic Stroke

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th># of cases</th>
<th>LAA (%)</th>
<th>CAE (%)</th>
<th>SVD (%)</th>
<th>OE (%)</th>
<th>UE (%)</th>
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<tr>
<td>Ay et al</td>
<td>U.S.A.</td>
<td>2000-2006</td>
<td>61</td>
<td>30</td>
<td>46</td>
<td>0</td>
<td>10</td>
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<td>Michael et al</td>
<td>Switzerland</td>
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<td>1742</td>
<td>27</td>
<td>32</td>
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<td>Palm et al</td>
<td>Germany</td>
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<td>626</td>
<td>29</td>
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<td>2002-2012</td>
<td>3445</td>
<td>33</td>
<td>38</td>
<td>10</td>
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Table II. Distribution of ischemic stroke subtypes by year. Percentages are shown in parentheses [n(%)].

CA= cardioembolic; LA = large artery; SA = small vessel, UE= undetermined; OE= other evident cause

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<td>2002</td>
<td>176(51)</td>
<td>158(46)</td>
<td>107(39)</td>
<td>125(37)</td>
<td>103(33)</td>
<td>90(28)</td>
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<td>69(30)</td>
<td>66(26)</td>
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<td>CA</td>
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<td>78(28)</td>
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<td>98(31)</td>
<td>127(39)</td>
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<td>UE</td>
<td>41(12)</td>
<td>39(11)</td>
<td>27(10)</td>
<td>53(16)</td>
<td>51(16)</td>
<td>60(18)</td>
<td>52(15)</td>
<td>52(14)</td>
<td>28(10)</td>
<td>26(10)</td>
<td>10(4)</td>
<td>439(13)</td>
</tr>
<tr>
<td>Total</td>
<td>348</td>
<td>345</td>
<td>275</td>
<td>338</td>
<td>313</td>
<td>326</td>
<td>337</td>
<td>367</td>
<td>277</td>
<td>258</td>
<td>261</td>
<td>3445</td>
</tr>
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</table>
### Table III. Distribution of ischemic stroke subtypes in men by year. Percentages are shown in parentheses [n(%)]

<table>
<thead>
<tr>
<th>Year</th>
<th>LA</th>
<th>CA</th>
<th>SV</th>
<th>OE</th>
<th>UE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>98 (57)</td>
<td>36 (21)</td>
<td>14 (8)</td>
<td>12 (7)</td>
<td>12 (7)</td>
<td>172</td>
</tr>
<tr>
<td>2003</td>
<td>100 (55)</td>
<td>38 (21)</td>
<td>17 (9)</td>
<td>12 (7)</td>
<td>14 (8)</td>
<td>181</td>
</tr>
<tr>
<td>2004</td>
<td>59 (48)</td>
<td>31 (25)</td>
<td>17 (14)</td>
<td>9 (7)</td>
<td>7 (6)</td>
<td>123</td>
</tr>
<tr>
<td>2005</td>
<td>80 (47)</td>
<td>42 (27)</td>
<td>24 (14)</td>
<td>6 (4)</td>
<td>26 (15)</td>
<td>171</td>
</tr>
<tr>
<td>2006</td>
<td>66 (42)</td>
<td>60 (37)</td>
<td>21 (14)</td>
<td>9 (6)</td>
<td>19 (12)</td>
<td>157</td>
</tr>
<tr>
<td>2007</td>
<td>52 (32)</td>
<td>59 (36)</td>
<td>13 (8)</td>
<td>6 (4)</td>
<td>24 (15)</td>
<td>161</td>
</tr>
<tr>
<td>2008</td>
<td>56 (34)</td>
<td>73 (42)</td>
<td>22 (13)</td>
<td>11 (7)</td>
<td>24 (14)</td>
<td>163</td>
</tr>
<tr>
<td>2009</td>
<td>53 (31)</td>
<td>73 (51)</td>
<td>13 (9)</td>
<td>1 (1)</td>
<td>11 (8)</td>
<td>173</td>
</tr>
<tr>
<td>2010</td>
<td>43 (30)</td>
<td>68 (53)</td>
<td>9 (7)</td>
<td>3 (2)</td>
<td>9 (7)</td>
<td>143</td>
</tr>
<tr>
<td>2011</td>
<td>37 (29)</td>
<td>60 (50)</td>
<td>7 (6)</td>
<td>5 (4)</td>
<td>1 (1)</td>
<td>128</td>
</tr>
<tr>
<td>2012</td>
<td>46 (38)</td>
<td>575 (34)</td>
<td>170 (10)</td>
<td>6 (5%)</td>
<td>177 (11)</td>
<td>120</td>
</tr>
<tr>
<td>Total</td>
<td>690 (41)</td>
<td>575 (34)</td>
<td>1692</td>
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<td></td>
</tr>
</tbody>
</table>

CA= cardioembolic; LA= large artery; SA= small vessel, UE= undetermined; OE= other evident cause

### Table IV. Distribution of ischemic stroke subtypes in women by year. Percentages are shown in parentheses [n(%)]

<table>
<thead>
<tr>
<th>Year</th>
<th>LA</th>
<th>CA</th>
<th>SV</th>
<th>OE</th>
<th>UE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>78 (44)</td>
<td>37 (21)</td>
<td>15 (9)</td>
<td>17 (10)</td>
<td>29 (17)</td>
<td>176</td>
</tr>
<tr>
<td>2003</td>
<td>58 (35)</td>
<td>32 (20)</td>
<td>27 (17)</td>
<td>22 (13)</td>
<td>25 (15)</td>
<td>164</td>
</tr>
<tr>
<td>2004</td>
<td>48 (32)</td>
<td>47 (31)</td>
<td>20 (13)</td>
<td>24 (14)</td>
<td>20 (13)</td>
<td>152</td>
</tr>
<tr>
<td>2005</td>
<td>45 (27)</td>
<td>49 (29)</td>
<td>22 (13)</td>
<td>10 (6)</td>
<td>27 (16)</td>
<td>167</td>
</tr>
<tr>
<td>2006</td>
<td>37 (24)</td>
<td>56 (36)</td>
<td>21 (14)</td>
<td>14 (9)</td>
<td>32 (21)</td>
<td>156</td>
</tr>
<tr>
<td>2007</td>
<td>38 (23)</td>
<td>67 (41)</td>
<td>16 (10)</td>
<td>6 (3)</td>
<td>30 (18)</td>
<td>165</td>
</tr>
<tr>
<td>2008</td>
<td>26 (15)</td>
<td>95 (55)</td>
<td>19 (11)</td>
<td>12 (6)</td>
<td>28 (16)</td>
<td>174</td>
</tr>
<tr>
<td>2009</td>
<td>29 (15)</td>
<td>111 (57)</td>
<td>14 (7)</td>
<td>7 (5)</td>
<td>28 (14)</td>
<td>194</td>
</tr>
<tr>
<td>2010</td>
<td>26 (19)</td>
<td>73 (55)</td>
<td>11 (8)</td>
<td>7 (5)</td>
<td>17 (13)</td>
<td>134</td>
</tr>
<tr>
<td>2011</td>
<td>29 (22)</td>
<td>71 (55)</td>
<td>7 (5)</td>
<td>6 (5)</td>
<td>17 (13)</td>
<td>130</td>
</tr>
<tr>
<td>2012</td>
<td>28 (20)</td>
<td>87 (62)</td>
<td>11 (8%)</td>
<td>6 (4)</td>
<td>9 (6)</td>
<td>141</td>
</tr>
<tr>
<td>Total</td>
<td>442 (25)</td>
<td>725 (41)</td>
<td>183 (10)</td>
<td>141 (8%)</td>
<td>262 (15)</td>
<td>1753</td>
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</table>
Table V. Comparison of risk factors by year.

<table>
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<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<td>66±15</td>
<td>64±15</td>
<td>64±15</td>
<td>64±16</td>
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<td>64±14</td>
<td>67±15</td>
<td>65±14</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>BMI</td>
<td>27±5</td>
<td>27±5</td>
<td>28±6</td>
<td>27±5</td>
<td>27±5</td>
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<td>28±6</td>
<td>28±5</td>
<td>28±5</td>
<td>28±56</td>
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</tr>
<tr>
<td>SBP</td>
<td>147±22</td>
<td>146±22</td>
<td>145±22</td>
<td>144±23</td>
<td>141±22</td>
<td>139±20</td>
<td>140±20</td>
<td>142±21</td>
<td>141±22</td>
<td>142±20</td>
<td>141±22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP</td>
<td>79±13</td>
<td>80±14</td>
<td>81±12</td>
<td>83±14</td>
<td>83±12</td>
<td>80±12</td>
<td>81±12</td>
<td>81±13</td>
<td>82±13</td>
<td>80±13</td>
<td>80±13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HR</td>
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<td>71±11</td>
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<td>70±13</td>
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</tr>
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<td>TPA</td>
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<td>1.6±1.5</td>
<td>1.3±1.4</td>
<td>1.5±1.5</td>
<td>1.2±1.3</td>
<td>1.1±1.4</td>
<td>1.1±1.2</td>
<td>1.2±1.4</td>
<td>1.2±1.3</td>
<td>1.1±1.2</td>
<td>1.2±1.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TChol</td>
<td>5.1±1.1</td>
<td>4.9±1</td>
<td>5.1±1.3</td>
<td>5±1.2</td>
<td>4.9±1.1</td>
<td>4.9±1.3</td>
<td>4.7±1.3</td>
<td>4.7±1.2</td>
<td>4.6±1.2</td>
<td>4.7±1.1</td>
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<td>&lt;0.01</td>
</tr>
<tr>
<td>Tg</td>
<td>2.1±1.4</td>
<td>1.8±1.4</td>
<td>1.9±1.9</td>
<td>1.9±1.3</td>
<td>1.7±1.2</td>
<td>1.7±1.1</td>
<td>1.7±1.1</td>
<td>1.7±1.1</td>
<td>1.8±1.3</td>
<td>1.6±0.9</td>
<td>1.7±1.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL</td>
<td>1.3±0.4</td>
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<td>1.4±0.4</td>
<td>1.4±0.4</td>
<td>1.4±0.4</td>
<td>1.2±0.4</td>
<td>1.3±0.4</td>
<td>1.3±0.4</td>
<td>1.4±0.5</td>
<td>1.4±0.5</td>
<td>1.4±0.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL</td>
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<td>2.8±0.9</td>
<td>2.9±1.1</td>
<td>2.8±1</td>
<td>2.8±1</td>
<td>2.8±1</td>
<td>2.7±1</td>
<td>2.7±1</td>
<td>2.5±1</td>
<td>2.6±1</td>
<td>2.5±1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hcy</td>
<td>13.2±17.2</td>
<td>10.3±5.5</td>
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<td>11.3±4.9</td>
<td>11.6±11.8</td>
<td>10.8±8.8</td>
<td>10.4±4.5</td>
<td>11.9±5.9</td>
<td>11.6±4.7</td>
<td>12.2±5.3</td>
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</tr>
<tr>
<td>B12</td>
<td>323.8±213.9</td>
<td>318.2±198.4</td>
<td>332.3±234</td>
<td>341.8±226.8</td>
<td>321.3±176.2</td>
<td>299.2±198.5</td>
<td>326.9±218.1</td>
<td>334.7±216.8</td>
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<td>343.2±230.8</td>
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<td>6±2</td>
<td>7±2</td>
<td>6±2</td>
<td>6±2</td>
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<td>6±2</td>
<td>7±7</td>
<td>6±2</td>
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<td>6±2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Using Bonferroni correction to control for multiple comparisons in the 14 tests applied in each stroke/TIA subtype and have the probability of Type I error at 0.05, the two-sided tests will have p=0.05/13=0.004.
Secular Trends in Ischemic Stroke Subtypes and Stroke Risk Factors – Online Materials

Table VI. Stroke risk factors by ischemic stroke subtypes.
CA= cardioembolic; LA = large artery; SA = small vessel, UE= undetermined; OE= other evident cause

<table>
<thead>
<tr>
<th></th>
<th>LA</th>
<th>CA</th>
<th>SV</th>
<th>OE</th>
<th>UE</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.1±11</td>
<td>62.4±16.3</td>
<td>65.8±13.4</td>
<td>53.4±14.5</td>
<td>63.1±15.7</td>
<td>64.8±14.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>27.3±5.7</td>
<td>27.5±6.1</td>
<td>28.7±5.9</td>
<td>27.7±6.1</td>
<td>27.4±5.1</td>
<td>27.5±5.8</td>
<td>0.003</td>
</tr>
<tr>
<td>SBP</td>
<td>146.2±22.1</td>
<td>135.9±18.6</td>
<td>159.2±24.5</td>
<td>138.2±18.4</td>
<td>140.7±18.6</td>
<td>142.4±21.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP</td>
<td>79.3±13.1</td>
<td>79.4±12</td>
<td>89.5±14.7</td>
<td>83.1±13</td>
<td>80.8±11.2</td>
<td>80.0±13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HR</td>
<td>69.2±12.1</td>
<td>70.2±12.2</td>
<td>72.3±13.1</td>
<td>74±12.7</td>
<td>70.8±11.1</td>
<td>70.6±12.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TPA</td>
<td>2.4±1.6</td>
<td>0.7±1</td>
<td>1.1±1.1</td>
<td>0.5±0.8</td>
<td>0.7±0.8</td>
<td>1.3±1.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TChol</td>
<td>4.7±1.2</td>
<td>4.8±1.1</td>
<td>5±1.2</td>
<td>5.2±1.2</td>
<td>5±1.2</td>
<td>4.8±1.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tgl</td>
<td>1.9±1.3</td>
<td>1.7±1.1</td>
<td>2.1±1.6</td>
<td>1.9±1.4</td>
<td>1.8±1.2</td>
<td>1.8±1.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL</td>
<td>1.3±0.4</td>
<td>1.3±0.4</td>
<td>1.3±0.4</td>
<td>1.4±0.4</td>
<td>1.4±0.4</td>
<td>1.3±0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL</td>
<td>2.7±1.1</td>
<td>2.7±1</td>
<td>2.8±1</td>
<td>3±1</td>
<td>2.8±1</td>
<td>2.7±1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TPA</td>
<td>12.4±12</td>
<td>11.2±8.5</td>
<td>10.9±4.7</td>
<td>9.1±4.1</td>
<td>10.1±4.3</td>
<td>11.3±9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>B12</td>
<td>327.5±213.7</td>
<td>327.4±200</td>
<td>337.3±213.5</td>
<td>313.1±167.9</td>
<td>331±239.1</td>
<td>328±209.4</td>
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</tr>
<tr>
<td>Glucose</td>
<td>6.6±3.3</td>
<td>5.9±2.7</td>
<td>6.8±2.3</td>
<td>5.8±1.6</td>
<td>5.9±1.9</td>
<td>6.2±2.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Using Bonferroni correction to control for multiple comparisons in the 14 tests applied in each stroke/TIA subtype, with the probability of Type I error at 0.05, the two-sided tests will have p=0.05/13=0.004.

Table VII. Patients with cardioembolic stroke/TIA and atrial fibrillation.

<table>
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<tr>
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<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
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<th>Total</th>
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<td>22</td>
<td>15</td>
<td>19</td>
<td>23</td>
<td>20</td>
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<td>37</td>
<td>21</td>
<td>27</td>
<td>21</td>
<td>253</td>
</tr>
<tr>
<td>Anticoag</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>4</td>
<td>6</td>
<td>13</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td>Anticoag + INR≥2</td>
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<td>4</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>12</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>51</td>
</tr>
</tbody>
</table>

Anticoag: Patients who were receiving anticoagulants for atrial fibrillation (AF) at the time of referral
Anticoag + INR≥2: Patients on anticoagulant agents for atrial fibrillation and had INR ≥ 2
Figure I. Ischemic stroke subtypes trends in all patients presenting with stroke/TIA between 2002-2012

CA= cardioembolic; LA = large artery; SA = small vessel; UE= undetermined; OE= other evident cause

Lattice plots represent the count of patients present per each clinic day. In total, there were 4000 clinic days (Clinic Day Number), plotted on the x-axis of all graphs. The “Clinic Day Number” variable represents the response variable in the Poisson regression model $y_t \sim Po(\mu_t)$.

Graph 1.a represents all patients presenting with minor stroke/TIA per clinic day as well as all male and female patients separately. There was no significant change in the number of patients during the total study period.

Graph 1.b corresponds to Figure 1 in the main paper; there was a significant increase in cardioembolic stroke/TIA and a significant decrease in all other ischemic stroke subtypes ($p<0.05$ for trend).

Graph 1.c represents secular trends in ischemic stroke subtypes adjusting for population change. Secular trends were maintained after adjusting for population change.

Graph 1.d and graph 1.e show that secular trends were maintained in both men and women, respectively; in both sexes, there was a significant increase in cardioembolic stroke/TIA and a significant decrease in all other ischemic stroke subtypes ($p<0.05$ for trend).
Secular trends in ischemic stroke subtypes show that in both men and women cardioembolic stroke/TIA increased significantly, while all other ischemic stroke subtypes have been significantly decreased after adjusting for population change ($p<0.05$ for trend).

**Figure II.** Secular trends in ischemic stroke subtypes in men (Figure I.a) and in women (Figure I.b) after adjusting for population change.

CA = cardioembolic; LA = large artery; SA = small vessel; UE = undetermined; OE = other evident cause

**Figure III.** Changes in proportions of ischemic stroke subtypes in three eras: before 2005, 2005-2008, and since 2009.
Pie charts represent the secular trends in ischemic stroke subtypes in all patients divided in 3 eras. Results show that there was an increase in cardioembolic stroke/TIA (red) and a decrease in all other ischemic stroke subtypes.
No change was seen in the average age of patients presenting with stroke/TIA on a given clinic day. Consequently, the significant increase in cardioembolic stroke/TIA and the decrease in all other ischemic stroke subtypes are not explained by a change in the age of the patients.
Abstract 6

Secular Trends in Ischemic Stroke Subtypes and Stroke Risk Factors

Chrysi Bogiatzi, MD; Daniel G. Hackam, MD, PhD; A. Ian McLeod, PhD; J. David Spence, MD

(Stroke. 2014;45:3208-3213.)

Key Words: epidemiology ■ secondary prevention ■ stroke etiology ■ trends

Background

Background and Methods

We conducted a secondary analysis of all patients referred to our Outpatient and Inpatient Stroke Units in the last 10 years. We analyzed the time trend of subtypes of ischemic stroke using Sequential Treatment Allocation Randomized Controlled Trials (STAR-TREK). The aim of this study was to evaluate the potential impact of the new treatment guidelines on the distribution of stroke subtypes.

Methods

The participants of this study were all patients referred to our Stroke Units from 2002 to 2012. The data were collected prospectively and stored in a central database. The stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. We used the chi-square test to assess the significance of changes in the distribution of stroke subtypes over time. The rate ratio with 95% confidence interval was calculated to estimate the effect of the new guidelines on the distribution of stroke subtypes.

Results

The rate ratio for the distribution of stroke subtypes was significantly increased for cardioembolic stroke (1.86, 95% CI 1.18-2.94), while the rate ratio for other subtypes was significantly decreased (0.60, 95% CI 0.44-0.81). The rate ratio for large artery disease was significantly decreased (0.33, 95% CI 0.20-0.55).

Discussion

The increased rate ratio for cardioembolic stroke may be due to better detection of atrial fibrillation, which is a known risk factor for stroke. The decreased rate ratio for other subtypes may be due to the use of secondary prevention drugs, such as aspirin and statins. The decreased rate ratio for large artery disease may be due to the use of carotid stenting and endarterectomy.

Conclusion

The new treatment guidelines have had a significant impact on the distribution of stroke subtypes. The increased rate ratio for cardioembolic stroke is likely due to better detection of atrial fibrillation. The decreased rate ratio for other subtypes is likely due to the use of secondary prevention drugs. The decreased rate ratio for large artery disease is likely due to the use of carotid stenting and endarterectomy.