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,[4] a modification of the causative classification system (CCS) of acute ischemic stroke,[5] 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.[4]

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, antiplatelet 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 clinic 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 χ^2 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.[6] 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.[7] Significance tests were 2-sided with the probability of type I error at 0.05. Descriptive statistics and graph design were done using SPSS Version 21 and trend analysis was 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

Table.   Baseline Characteristics of Patients Presenting With Stroke/Transient Ischemic Attack in 3 Eras

	2002–2005 (n=968)	2005–2009 (n=1314)	2009–2012 (n=1164)	*P* Value
Continuous variables mean (SD)				
Age, y	66 (14)	64 (16)	65 (14)	0.41
Systolic blood pressure	146 (22)	141 (21)	141 (21)	<0.001
Diastolic blood pressure	80 (13)	82 (13)	81 (13)	0.005
Total cholesterol, mmol/L	5.1 (1.1)	5.0 (1.2)	4.7 (1.2)	<0.001
Triglycerides, mmol/L	2.0 (1.6)	1.8 (1.1)	1.7 (1.1)	<0.001
HDL cholesterol, mmol/L	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	0.020
LDL cholesterol, mmol/L	3 (1)	3 (1)	3 (1)	<0.001
Glucose, mmol/L	6 (2)	6 (2)	6 (4)	0.009
Categorical variables, n (%)				
Men	476 (49)	652 (50)	565 (49)	0.998
Body mass index >25	537 (63)	812 (65)	730 (67)	0.188
Never smoked	355 (37)	501 (38)	462 (40)	0.220
Active smoking	195 (20)	248 (19)	239 (21)	0.220
Quit smoking	418 (43)	565 (43)	463 (40)	0.220
Antiplatelet agents	446 (46)	596 (45)	537 (46)	0.937
Anticoagulants	84 (9)	88 (7)	86 (7)	0.252
Hypertension medications	630 (65)	810 (62)	697 (60)	0.050
Lipid medications	373 (39)	595 (45)	520 (45)	<0.001
Diabetes mellitus medications	127 (13)	177 (14)	166 (14)	0.411
Myocardial infarction	140 (15)	163 (12)	115 (10)	0.045
Atrial fibrillation	77 (8)	106 (8)	124 (11)	0.149
Patent foramen ovale	80 (8)	190 (15)	219 (19)	<0.001
Stroke subtypes, n (%)				
Large artery disease	441 (46)	400 (30)	291 (25)	<0.001
Cardioembolic	221 (23)	461 (35)	616 (53)	<0.001
Small vessel disease	110 (11)	150 (11)	94 (8)	<0.001
Other determined cause	89 (9)	86 (7)	46 (4)	<0.001
Undetermined	107 (11)	217 (17)	116 (10)	<0.001
Investigations,* n (%)				
Computed tomography	619 (64)	900 (69)	827 (71)	<0.001
MRI	349 (36)	547 (42)	424 (36)	<0.001
Holter	122 (13)	148 (11)	537 (46)	<0.001
Echocardiogram	316 (33)	454 (35)	732 (63)	<0.001

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

*All patients had carotid duplex ultrasound.

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[8] and a higher risk of severe disability compared with other stroke subtypes.[9,10] 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[11] and the risk of recurrent events is high early after the initial event[12]; 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
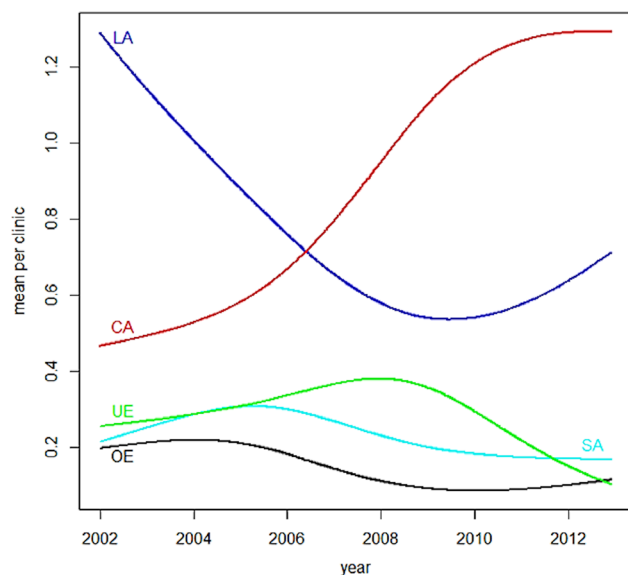
Figure 1. Secular trends in ischemic stroke subtypes 2002 to 2012. Cardioembolic (CA) strokes increased significantly (*P*=0.04), whereas all other stroke subtypes declined. LA indicates large artery; OE, other explained etiology; SA, small artery; and UE, unexplained.

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.[13] More recent studies show an higher prevalence of cardioembolic stroke, which represented 49% of strokes in Sweden and 56% of inpatients in Japan.[14]

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[15] and the Greater Cincinnati/Northern Kentucky region,[16] 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.

Large artery atherosclerosis was expected to decrease given that hypertension and hyperlipidemia are better controlled with the implementation of the Canadian Hypertension Education Program[17,18] and an increase in statin prescription.[19] We showed in 2000 to 2007 that baseline stroke risk factors of patients with minor or moderate stroke/TIA were better controlled over time.[20] 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.[21–23]

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.[24,25] 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,[4] 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.

Spectrum bias (the possibility that because some of the patients referred to the clinic were seen by other neurologists, we may have been seeing a different spectrum of patients) is a potential limitation in our study. However, this is unlikely, because patients were scheduled in the urgent TIA clinic on the basis of the first available appointment, usually on the next weekday. We were able to capture a representative sample of patients experiencing a minor or moderate stroke/TIA, but our conclusion cannot be generalized to all patients, particularly those with major disabling or fatal stroke. Moreover, it is likely that we missed information from patients with minor or moderate stroke/TIA who did not seek medical attention. However, in Ontario, patients who are not seen in a secondary stroke prevention center are more likely to have AF, myocardial infarction, congestive heart failure, diabetes mellitus, dementia, and a history of stroke, as compared with patients who are seen in this clinical setting and are more likely to have history of hyperlipidemia.[26] As a result, the incidence of cardioembolic stroke/TIA might be higher in our population.

Additional significant limitations of our study are the retrospective nature of our data and missing information such as race, socioeconomic status, physical activity, and diet.

Under-anticoagulation of patients with cardioembolic sources of stroke is an important problem, particularly in the elderly.[27] Among patients in the Canadian Stroke Registry presenting with stroke, and with known AF and no contraindication to anticoagulation, only 40% were receiving warfarin, 30% were on antiplatelet therapy, and 29% were on no antithrombotic therapy.[28] This situation may improve with the availability of new oral anticoagulants. However, investigation for cardioembolic sources may need to be more intensive. A Canadian multicenter study[29] found that in patients with cryptogenic stroke and a negative Holter recording at baseline, a repeat
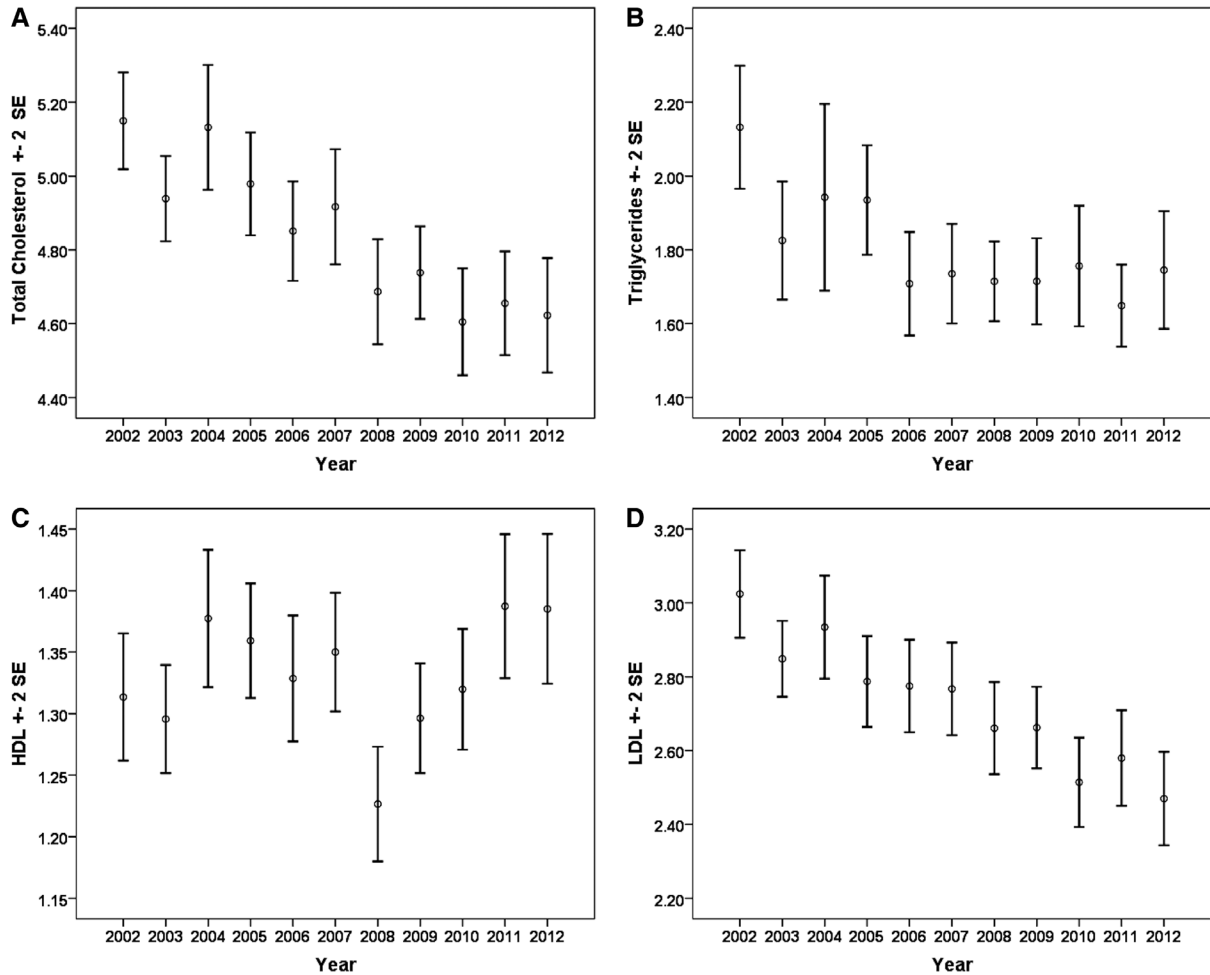
Figure 2. Trends in plasma lipid profile 2002 to 2012. (**A**) Total cholesterol; (**B**) triglycerides; (**C**) high-density lipoprotein (HDL) cholesterol; (**D**) low-density lipoprotein (LDL) cholesterol. Triglycerides, LDL cholesterol, and total cholesterol declined and HDL cholesterol increased significantly ($P<0.0001$; ANOVA).

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

Figure 3. Trends in blood pressure and heart rate 2002 to 2012. Blood pressure declined significantly.

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.

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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.

Disclosures

None.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18–e209.
2. Uchino K, Risser JM, Smith MA, Moyé LA, Morgenstern LB. Ischemic stroke subtypes among Mexican Americans and non-Hispanic whites: the BASIC Project. *Neurology*. 2004;63:574–576.
3. Hackam DG, Spence JD. Combining multiple approaches for the secondary prevention of vascular events after stroke: a quantitative modeling study. *Stroke*. 2007;38:1881–1885.
4. Bogiatzi C, Wannarong T, McLeod AI, Heisel M, Hackam D, Spence JD. SPARKLE (Subtypes of Ischaemic Stroke Classification System), incorporating measurement of carotid plaque burden: a new validated tool for the classification of ischemic stroke subtypes. *Neuroepidemiology*. 2014;42:243–251.
5. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. 2005;58:688–697.
6. MacCullagh P, Nelder JA. *Generalized Linear Models*. 2nd ed. London: Chapman and Hall/CRC; 1989.
7. Davison A.C., Hinkley D.V. *Bootstrap Methods and Their Applications*. New York, NY: Cambridge University Press; 1997.
8. Jones SB, Sen S, Lakshminarayan K, Rosamond WD. Poststroke outcomes vary by pathogenic stroke subtype in the Atherosclerosis Risk in Communities Study. *Stroke*. 2013;44:2307–2310.
9. Sandercock P, Bamford J, Dennis M, Burn J, Slattery J, Jones L, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire community stroke project). *BMJ*. 1992;305:1460–1465.
10. Steger C, Pratter A, Martinek-Bregel M, Avanzini M, Valentin A, Slany J, et al. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. *Eur Heart J*. 2004;25:1734–1740.
11. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. *Ann Intern Med*. 2007;147:590–592.
12. Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabín J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. *Stroke*. 2007;38:3225–3229.
13. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
14. Nakajima M, Inatomi Y, Yonehara T, Hashimoto Y, Hirano T. Acquisition of oral intake in severely dysphagic patients with acute stroke: a single-center, observational study involving a database of 4972 consecutive stroke patients. *J Neurol Sci*. 2012;323:56–60.
15. Béjot Y, Daubail B, Jacquin A, Durier J, Osseby GV, Rouaud O, et al. Trends in the incidence of ischaemic stroke in young adults between 1985 and 2011: the Dijon Stroke Registry. *J Neurol Neurosurg Psychiatry*. 2014;85:509–513.
16. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012;79:1781–1787.
17. McAlister FA. The Canadian Hypertension Education Program–a unique Canadian initiative. *Can J Cardiol*. 2006;22:559–564.
18. McAlister FA, Wilkins K, Joffres M, Leenen FH, Fodor G, Gee M, et al. Changes in the rates of awareness, treatment and control of hypertension in Canada over the past two decades. *CMAJ*. 2011;183:1007–1013.
19. Dawe DE, Ariyarajah V, Khadem A. Is there a role for statins in atrial fibrillation? *Pacing Clin Electrophysiol*. 2009;32:1063–1072.
20. Spence JD, Coates V, Li H, Tamayo A, Muñoz C, Hackam DG, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. *Arch Neurol*. 2010;67:180–186.
21. Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea; preliminary report. *J Am Med Assoc*. 1953;152:1090–1093.
22. McNamara JJ, Molot MA, Stremple JF, Cutting RT. Coronary artery disease in combat casualties in Vietnam. *JAMA*. 1971;216:1185–1187.
23. Webber BJ, Seguin PG, Burnett DG, Clark LL, Otto JL. Prevalence of and risk factors for autopsy-determined atherosclerosis among US service members, 2001-2011. *JAMA*. 2012;308:2577–2583.
24. Feigin V, Carter K, Hackett M, Barber PA, McNaughton H, Dyall L, et al; Auckland Regional Community Stroke Study Group. Ethnic disparities in incidence of stroke subtypes: Auckland Regional Community Stroke Study, 2002-2003. *Lancet Neurol*. 2006;5:130–139.
25. Lavados PM, Sacks C, Prina L, Escobar A, Tossi C, Araya F, et al. Incidence, case-fatality rate, and prognosis of ischaemic stroke subtypes in a predominantly Hispanic-Mestizo population in Iquique, Chile (PISCIS project): a community-based incidence study. *Lancet Neurol*. 2007;6:140–148.
26. Webster F, Saposnik G, Kapral MK, Fang J, O'Callaghan C, Hachinski V. Organized outpatient care: stroke prevention clinic referrals are associated with reduced mortality after transient ischemic attack and ischemic stroke. *Stroke*. 2011;42:3176–3182.
27. Spence JD. Stroke: Atrial fibrillation, stroke prevention therapy and aging. *Nat Rev Cardiol*. 2009;6:448–450.
28. Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke*. 2009;40:235–240.
29. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al.; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370:2467–2477.

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Online supplemental material

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Table I. Comparison of Ischemic Stroke Subtypes between studies based on the Causative Classification of acute ischemic Stroke

	Country	Year	# of cases	LAA (%)	CAE (%)	SVD (%)	OE (%)	UE (%)
Ay et al	U.S.A.	2000-2006	61	30	46	0	10	15
Michael et al	Switzerland	2003-2008	1742	27	32	15	9	17
Palm et al	Germany	2006-2007	626	29	35	26	1	9
Bogiatzi et al	Canada	2002-2012	3445	33	38	10	6	13

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

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
LA	176(51)	158(46)	107 (39)	125 (37)	103 (33)	90 (28)	82 (24)	82 (22)	69 (30)	66 (26)	74 (28)	1132 (33)
CA	73 (21)	70 (20)	78 (28)	84 (25)	98 (31)	127 (39)	154 (46)	184 (50)	146 (53)	139 (54)	147 (56)	1300 (38)
SV	29 (8)	44 (13)	37 (14)	46 (14)	42 (13)	29 (9)	32 (10)	36 (10)	24 (9)	16 (6)	18 (7)	353 (10)
OE	29 (8)	34 (10)	26 (10)	30 (9)	19 (6)	20 (6)	17(5)	13 (4)	10 (4)	11 (4)	12 (5)	221 (6)
UE	41 (12)	39 (11)	27 (10)	53 (16)	51 (16)	60 (18)	52 (15)	52 (14)	28 (10)	26 (10)	10(4)	439 (13)
Total	348	345	275	338	313	326	337	367	277	258	261	3445

Table III. Distribution of ischemic stroke subtypes in men by year. Percentages are shown in parentheses [n(%)]
CA= cardioembolic; LA = large artery; SA = small vessel, UE= undetermined; OE= other evident cause

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
LA	98 (57)	100(55)	59 (48)	80 (47)	66 (42)	52 (32)	56 (34)	53 (31)	43 (30)	37 (29)	46 (38)	690 (41)
CA	36 (21)	38 (21)	31 (25)	35 (21)	42 (27)	60 (37)	59 (36)	73 (42)	73 (51)	68 (53)	60 (50)	575 (34)
SV	14 (8)	17 (9)	17 (14)	24 (14)	21 (14)	13 (8)	13 (8)	22 (13)	13 (9)	9 (7)	7 (6)	170 (10)
OE	12 (7)	12 (7)	9 (7)	6 (4)	9 (6)	6 (4)	11 (7)	1 (1)	3 (2)	5 (4)	6 (5%)	80 (5)
UE	12 (7)	14 (8)	7 (6)	26 (15)	19 (12)	30 (19)	24 (15)	24 (14)	11 (8)	9 (7)	1 (1)	177 (11)
Total	172	181	123	171	157	161	163	173	143	128	120	1692

Table IV. Distribution of ischemic stroke subtypes in women by year. Percentages are shown in parentheses [n(%)]
CA= cardioembolic; LA = large artery; SA = small vessel, UE= undetermined; OE= other evident cause

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

Table V. Comparison of risk factors by year.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	p-value
Age	66±14	66±15	64±15	64±15	64±16	64±16	64±15	64.8±15	64±14	67±15	65±14	0.04
BMI	27±5	27±5	28±6	27±5	27±5	27±5	28±5	28±7	28±6	28±5	28±56	0.29
SBP	147±22	146±22	145±22	144±23	141±22	139±20	140±20	142±21	141±22	142±20	141±22	<0.01
DBP	79±13	80±14	81±12	83±14	83±12	80±12	81±12	81±13	82±13	80±13	80±13	<0.01
HR	70±12	70±14	71±12	71±13	71±13	71±12	71±12	71±11	70±11	70±12	70±13	0.98
TPA	1.9±1.8	1.6±1.5	1.3±1.4	1.5±1.5	1.2±1.3	1.1±1.4	1.1±1.2	1.2±1.4	1.2±1.3	1.1±1.2	1.2±1.4	<0.01
TChol	5.1±1.1	4.9±1	5.1±1.3	5±1.2	4.9±1.1	4.9±1.3	4.7±1.3	4.7±1.2	4.6±1.2	4.7±1.1	4.6±1.2	<0.01
Tg	2.1±1.4	1.8±1.4	1.9±1.9	1.9±1.3	1.7±1.2	1.7±1.1	1.7±1	1.7±1.1	1.8±1.3	1.6±0.9	1.7±1.3	<0.01
HDL	1.3±0.4	1.3±0.4	1.4±0.4	1.4±0.4	1.3±0.4	1.4±0.4	1.2±0.4	1.3±0.4	1.3±0.4	1.4±0.5	1.4±0.5	<0.01
LDL	3±1	2.8±0.9	2.9±1.1	2.8±1	2.8±1	2.8±1.1	2.7±1.1	2.7±1	2.5±1	2.6±1	2.5±1	<0.01
Hcy	13.2±17.2	10.3±5.5	9.7±5.3	11.1±11.7	11.3±4.9	11.6±11.8	10.8±8.8	10.4±4.5	11.9±5.9	11.6±4.7	12.2±5.3	<0.01
B12	323.8 ± 213.9	318.2 ± 198.4	332.3 ± 234	341.8 ± 226.8	321.3 ± 176.2	299.2 ± 198.5	326.9 ± 218.1	334.7 ± 216.8	313.7 ± 170.6	343.2 ± 230.8	360.3 ± 200.8	0.07
Glu	6±2	6±2	7±2	6±2	6±2	6±2	6±2	6±2	7±7	6±2	6±2	0.03

*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.

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

	LA	CA	SV	OE	UE	Total	p-value
Age	70.1±11	62.4±16.3	65.8±13.4	53.4±14.5	63.1±15.7	64.8±14.9	<0.01
BMI	27.3±5.7	27.5±6.1	28.7±5.9	27.7±6.1	27.4±5.1	27.5±5.8	0.003
SBP	146.2±22.1	135.9±18.6	159.2±24.5	138.2±18.4	140.7±18.6	142.4±21.7	<0.01
DBP	79.3±13.1	79.4±12	89.5±14.7	83.1±13	80.8±11.2	80.0±13	<0.01
HR	69.2±12.1	70.2±12.2	72.3±13.1	74±12.7	70.8±11.1	70.6±12.2	<0.01
TPA	2.4±1.6	0.7±1	1.1±1.1	0.5±0.8	0.7±0.8	1.3±1.4	<0.01
T.Chol	4.7±1.2	4.8±1.1	5±1.2	5.2±1.2	5±1.2	4.8±1.2	<0.01
Tg	1.9±1.3	1.7±1.1	2.1±1.6	1.9±1.4	1.8±1.2	1.8±1.3	<0.01
HDL	1.3±0.4	1.3±0.4	1.3±0.4	1.4±0.4	1.4±0.4	1.3±0.4	<0.01
LDL	2.7±1.1	2.7±1	2.8±1	3±1	2.8±1	2.7±1	<0.01
Hcy	12.4±12	11.2±8.5	10.9±4.7	9.1±4.1	10.1±4.3	11.3±9	<0.01
B12	327.5±213.7	327.4±200	337.3±213.5	313.1±167.9	331±239.1	328±209.4	0.77
Glucose	6.6±3.3	5.9±2.7	6.8±2.3	5.8±1.6	5.9±1.9	6.2±2.8	<0.01

*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.**

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
AF	23	22	15	19	23	20	25	37	21	27	21	253
Anticoag	2	4	2	5	9	4	6	13	5	5	4	59
Anticoag + INR≥2	2	4	2	4	8	3	5	12	4	4	3	51

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
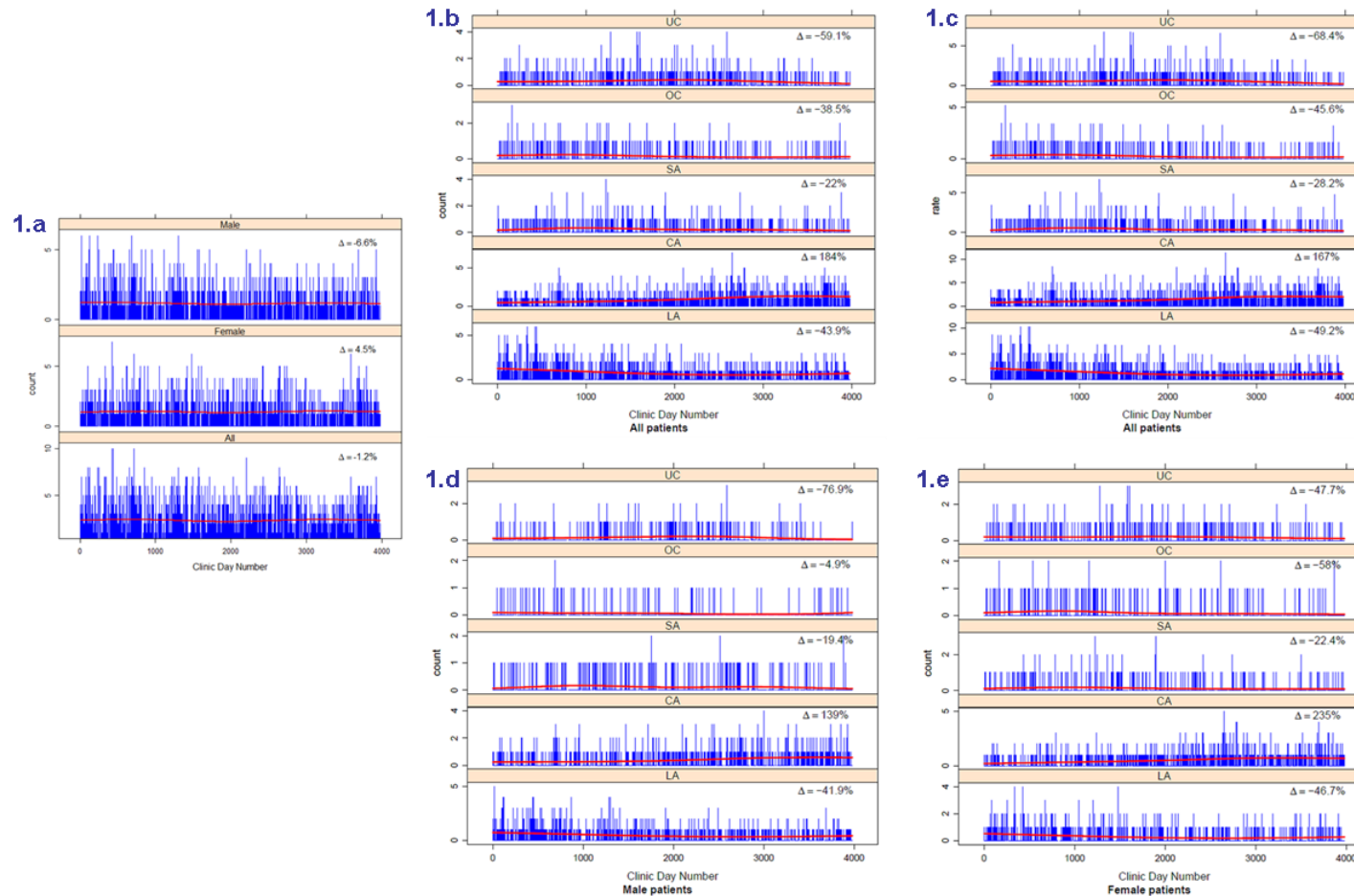

Lattice plots represent the count of patients present per each clinic day. In total, there were 4000 clinic days (Clinic Day Number), plotted on the x-axis of all graphs. The "Clinic Day Number" variable represents the response variable in the Poisson regression model [$y_t \sim Po(\mu_t)$].

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 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).
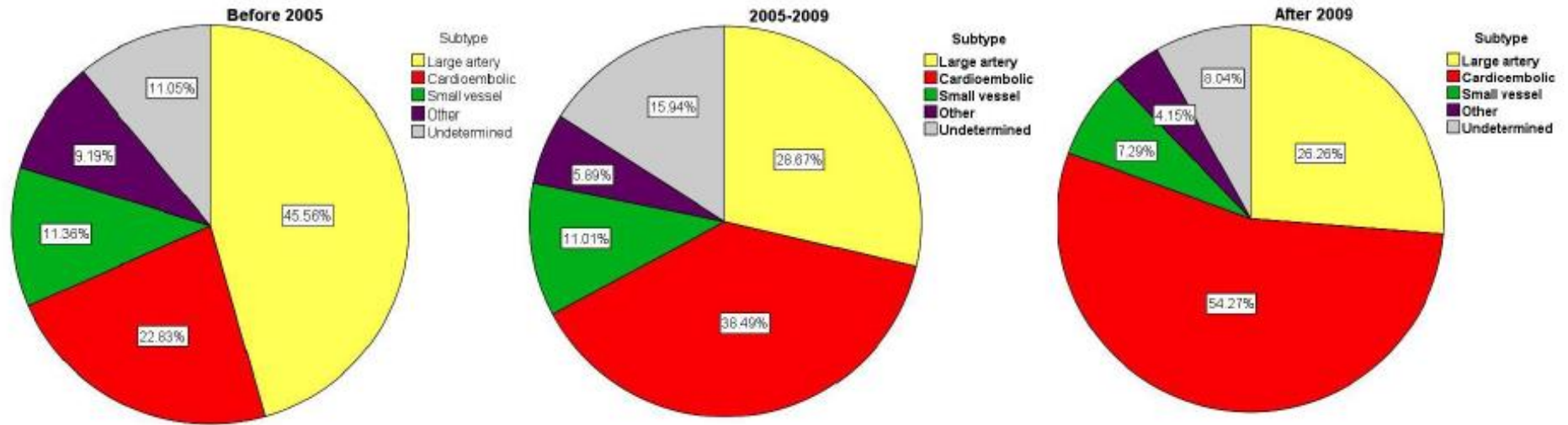
Figure II. Secular trends in ischemic stroke subtypes in men (Figure I.a) and in women (Figure I.b) after adjusting for population change.
CA= cardioembolic; LA = large artery; SA = small vessel, UE= undetermined; OE= other evident cause
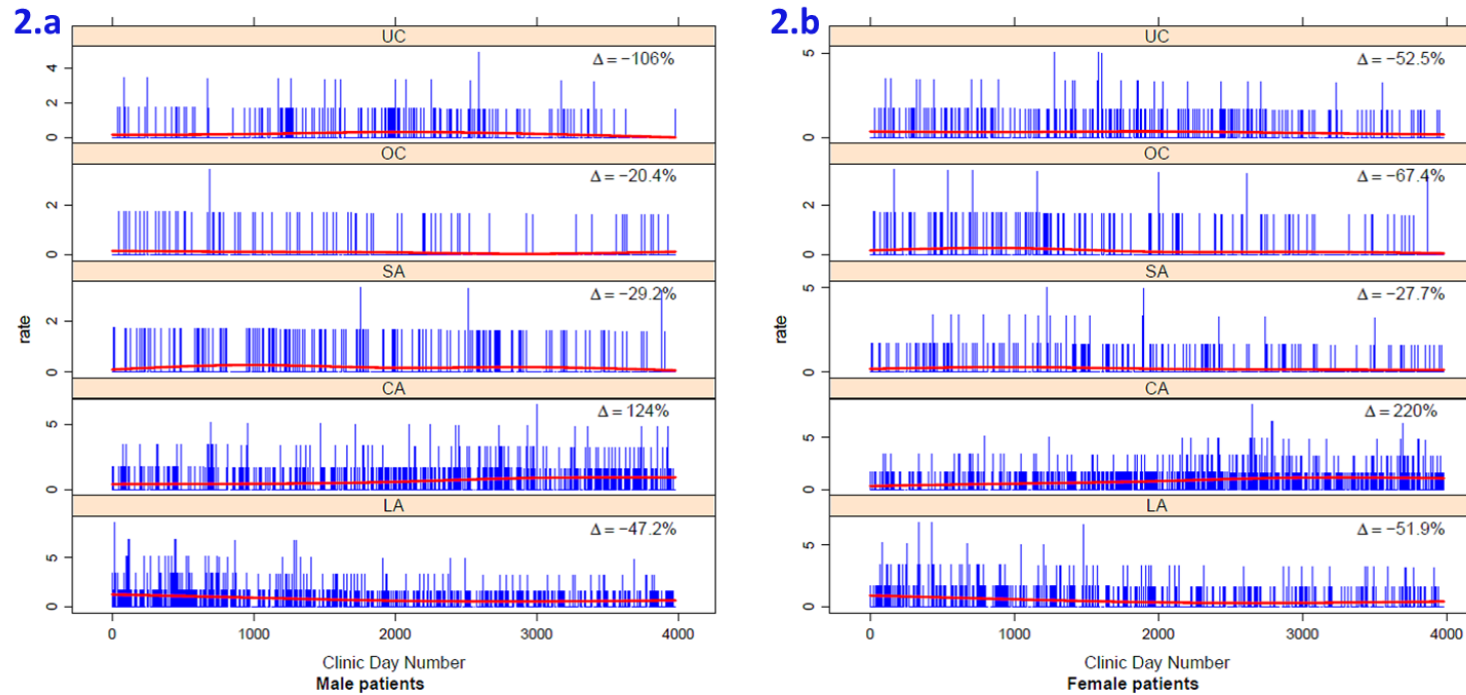
Secular trends in ischemic stroke subtypes show that in both men and women cardioembolic stroke/TIA increased significantly, while all other ischemic stroke subtypes have been significantly decreased after adjusting for population change (p<0.05 for trend).

Figure III. Changes in proportions of ischemic stroke subtypes in three eras: before 2005, 2005-2008, and since 2009.

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

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.

Figure IV. Secular trends of the average age of stroke/TIA patients in each ischemic stroke/TIA subtype.
CA= cardioembolic; LA = large artery; SA = small vessel, UE= undetermined; OE= other evident cause
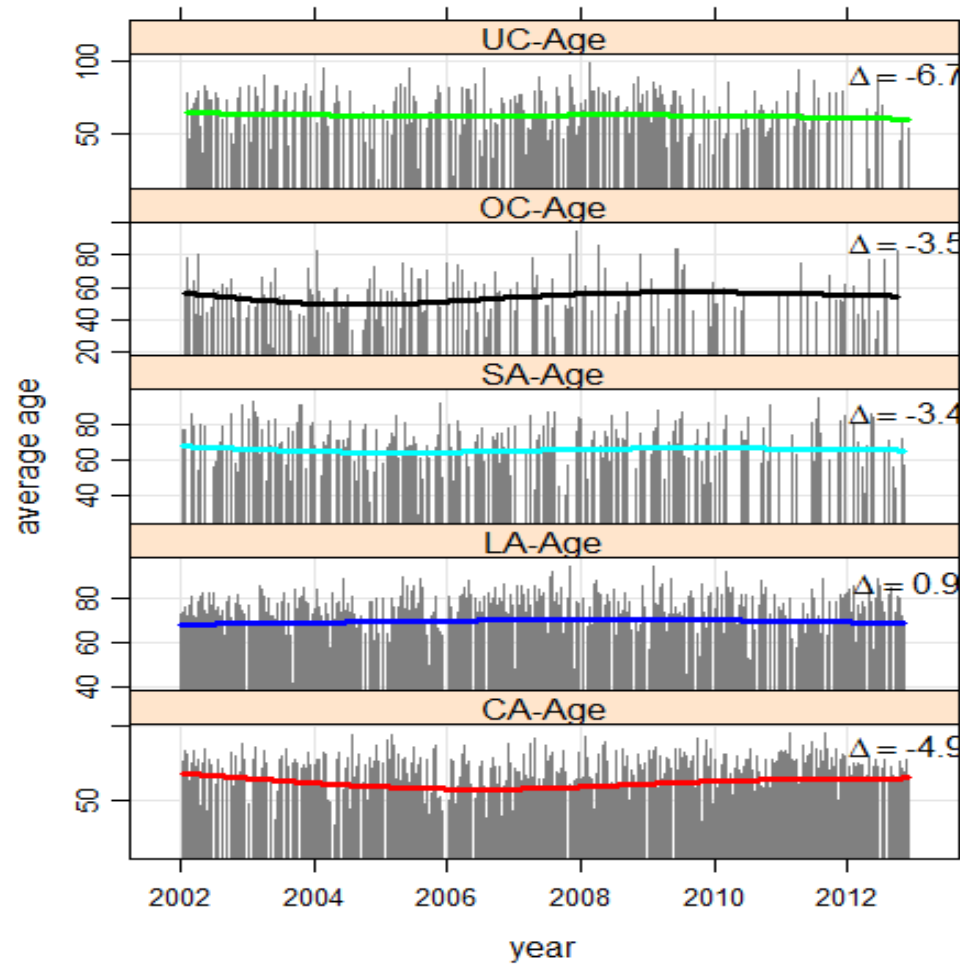
No change was seen in the average age of patients presenting with stroke/TIA on a given clinic day. Consequently, the significant increase in cardioembolic stroke/TIA and the decrease in all other ischemic stroke subtypes are not explained by a change in the age of the patients.

Abstract 6

허혈뇌졸중 아형과 뇌졸중 위험 인자의 장기 변동 추세

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

배경과 목적

뇌졸중의 빠른 진단과 치료는 환자의 임상 결과를 호전시키고, 원인에 대한 판단은 재발 위험도를 최대한 줄이는 적절한 치료 전략을 세우는데 매우 중요하다. 스타틴 사용의 증가와 같은 최근의 치료법 변화의 결과로 뇌졸중 아형이 변화하고 있다면 향후 변동 방향 예측은 역사적인 빈도 변화에 기반한 방법으로부터 수정되어야 할 것이다.

방법

우리는 2002년부터 2012년까지 응급 일과성허혈발작 클리닉에 방문한 일과성허혈발작 또는 경도 또는 중등도 뇌졸중을 가진 환자들에서 뇌졸중 위험인자 및 허혈뇌졸중 아형의 장기간 추세를 분석하였다.

결과

최근 저밀도지질단백질 콜레스테롤과 혈압의 유의한 감소가 보였고, 이는 대혈관질환 및 소혈관질환에 의한 뇌졸중의 감소와 연관되었다. 심인성 뇌졸중의 비는 2002년 26%에서 2012년 56%까지 증가하였다(*P*<0.05 for trend). 이러한 추세는 인구 변화를 보정한 후에도 지속적으로 유의하였다.

결론

지역사회에서 집중적인 약물 치료 효과로 동맥경화증의 위험인자와 대혈관동맥경화증과 소혈관질환에 의한 뇌졸중/일과성허혈발작이 유의하게 감소하고 있다. 결과적으로 심인성뇌졸중/일과성허혈발작이 유의하게 증가해왔다. 향후 더 집중적인 심장질환에 대한 평가와 항응고제 사용이 요구될 수 있다.
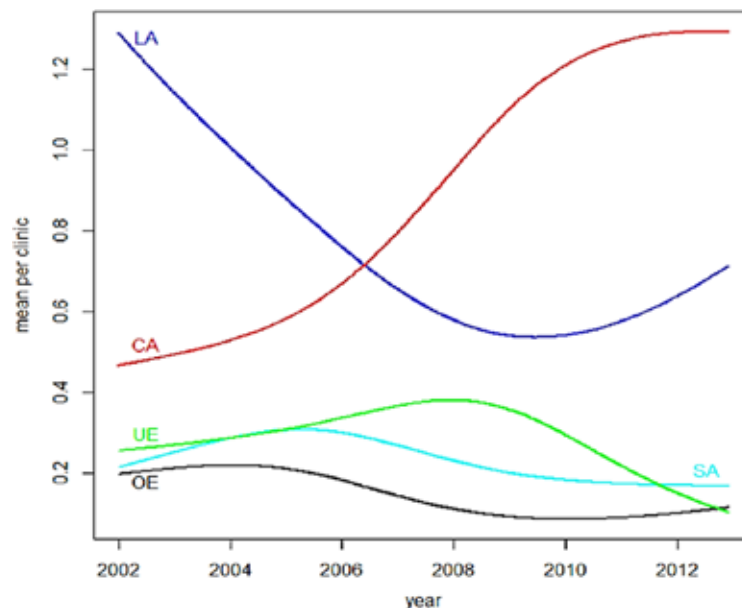
Figure 1. Secular trends in ischemic stroke subtypes 2002 to 2012. Cardioembolic (CA) strokes increased significantly (*P*=0.04), whereas all other stroke subtypes declined. LA indicates large artery; OE, other explained etiology; SA, small artery; and UE, unexplained.