Stroke Subtype Classification to Mechanism-Specific and Undetermined Categories by TOAST, A-S-C-O, and Causative Classification System

Direct Comparison in the North Dublin Population Stroke Study

Michael Marnane, MB, MRCPI; Caroline A. Duggan, MB, MRCPI; Orla C. Sheehan, MB, MRCPI; Aine Merwick, MB, MRCPI; Niamh Hannon, MB, MRCPI; Denis Curtin, MB; Dawn Harris, BSc; Emma B. Williams, PhD; Gillian Horgan, BSc; Lorraine Kyne, MD, MPH, FRCPI; Patricia M.E. McCormack, MD, FRCPI, DCH; Joseph Duggan, MD, FRCPI; Alan Moore, MD, FRCPI; Gloria Crispino-O’Connell, PhD; Peter J. Kelly, MD, MS, FRCPI

Background and Purpose—Reliable etiologic classification of ischemic stroke may enhance clinical trial design and identification of subtype-specific environmental and genetic risk factors. Although new classification systems (Causative Classification System [CCS] and ASCO [A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause]) have been developed to improve subtype assignment, few comparative data exist from large studies. We hypothesized that both CCS and ASCO would reduce the proportion of patients classified as cause undetermined compared with the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) scheme in a large population-based stroke study.

Methods—A single rater classified all first-ever ischemic strokes in the North Dublin Population Stroke Study, a population-based study of 294,529 North Dublin residents. Published algorithms for TOAST, CCS, and ASCO were applied.

Results—In 381 first-ever ischemic stroke patients, CCS assigned fewer patients as cause undetermined (26.2% versus 39.4%; P<0.000001), with increased assignment of cardio-aortic embolism (relative increase 6.9%; P=0.004), large artery atherosclerosis (relative increase 44.1%; P=0.00006), small artery occlusion (relative increase 27.3%; P=0.00006), and other causes (relative increase 91.7%; P=0.001) compared with TOAST. When ASCO grade 1 evidence was applied, fewer patients were classified as small artery disease (relative decrease 29.1%; P=0.007) and more as large artery/atherothrombotic (relative increase 17.6%; P=0.03). ASCO grade 1 did not reduce the proportion of cause undetermined cases compared with TOAST (42.3% versus 39.4%; P=0.2). Agreement between systems ranged from good (κ=0.61 for TOAST/ASCO grade 1 small artery category) to excellent (κ=0.95 for TOAST/CCS and ASCO grade 1/CCS cardio/aorto-embolism category). Application of ASCO grades 1 to 3 indicated evidence of large artery/atherosclerosis (73.3%), cardio-embolism (31.3%), small artery (64.7%), and other cause (12%) in TOAST-undetermined cases.

Conclusion—Both CCS and ASCO schemes showed good-to-excellent agreement with TOAST, but each had specific characteristics compared with TOAST for subtype assignment and data retention. The feasibility of a single combined classification system should be considered. (Stroke. 2010;41:1579-1586.)

Key Words: cerebral infarct ■ subtypes ■ causative classification system ■ TOAST ■ ASCO

Key outcomes such as disability, fatality, and recurrence after ischemic stroke differ according to subtype defined by stroke mechanism.1,2 Identification of the underlying cause of stroke is an important element of daily clinical practice, guiding treatment decisions and prognosis for individual patients. Accurate and reproducible assignment of the likely mechanism of ischemic stroke is also important in clinical trials investigating benefit in specific patient groups3 (eg, cardioembolic or atherosclerotic stroke) and in epidemiological studies investigating associations between environ-

Received December 8, 2009; final revision received April 12, 2010; accepted April 20, 2010.

From the Neurovascular Clinical Science Unit (M.M., C.A.D., O.C.S., A.M., N.H., D.C., D.H., E.B.W., G.H., L.K., J.D., P.J.K.), Mater University Hospital/University College Dublin, Ireland; Connolly Hospital (P.M.E.M.), Dublin, Ireland; Beaumont Hospital (A.M.), Dublin, Ireland; and Centre for Support and Training in Analysis and Research (G.C.-O.), University College Dublin, Ireland.

Correspondence to Dr Michael Marnane, Neurovascular Clinical Science Unit, Catherine McAuley Research Centre, Nelson Street, Mater University Hospital, Dublin 7, Ireland. E-mail mmarnane@gmail.com

© 2010 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.109.575373

1579
mental and genetic risk factors and specific stroke phenotypes.4,5

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system was initially developed to improve standardization of subtype assignment in a multicenter randomized clinical trial.5 It has since been used in settings such as epidemiological and genetic association studies for which it was not originally intended.5 Since development of the TOAST system, advances in diagnostic technology have resulted in an increasing proportion of stroke patients for which multiple potentially contributory mechanisms are identified.7 Under TOAST, such patients are classified as cause undetermined, along with those who have been investigated incompletely. This subgroup is often excluded from additional analysis, leading to suboptimal use of available information.

Newer stroke classification schemes such as the Causative Classification System (CCS) and A-S-C-O (A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause) Phenotypic System (ASCO) may improve our ability to identify the most likely cause where multiple potential mechanisms are found,4 accounting for the relative importance of each and the extent of the diagnostic evaluation.9 These schemes have considerable potential to refine subtype assignment and improve the efficiency of data use in clinical stroke studies. However, they have not been compared directly, and little information exists concerning their application in independent patient cohorts. Additional data are needed regarding the relative frequencies of subtype assignment under each scheme, differences in subtype assignment by CCS and ASCO compared with TOAST, and the characteristics of each in unselected population-based compared with hospital-investigated stroke cohorts.

We hypothesized that both CCS and ASCO would reduce the proportion of patients classified as cause undetermined and thus improve subtype assignment compared with TOAST when applied in a population-based stroke study. We aimed to address this hypothesis and to describe the frequencies of assigned subtypes in all (community plus hospital) and hospitalized ischemic stroke patients.

Methods

Study Population

We analyzed patients in the North Dublin Population Stroke Study, a population-based prospective cohort study conducted over 1 year of stroke and transient ischemic attack (TIA) among the 294,529 inhabitants of North Dublin city, defined by the Irish local government district electoral boundaries.10

Case Ascertainment

Multiple validated overlapping sources of hospital and community case ascertainment were used, according to recommended criteria for “ideal” studies of stroke incidence.11 Hot and cold pursuit methods were used.12 All 4 acute and the 9 nonacute hospitals in North Dublin city participated. Investigators undertook daily review of hospital admission records and consultation requests to relevant specialist services and daily visits to hospital wards and specialist units (intensive care, neurology, coronary care, cardiothoracic, and neurosurgery) to ascertain hospitalized and in-hospital events. All vascular and cerebral imaging data from participating institutions were reviewed twice weekly. Staff at specialist outpatient clinics (ophthalmology, geriatric, neurology, and vascular surgery) and physicians in nonacute hospitals were contacted regularly. More than 95% of North Dublin general practitioners and nursing homes participated directly and were contacted fortnightly to ascertain community-treated cases. A daily community-based minor stroke/TIA clinic was established to facilitate assessment of suspected cases from community health personnel, clinics, and emergency departments in the region. Review of pathology department records, death certificates, and coroner reports allowed identification of both community and hospital stroke fatalities.

All potential cases were reviewed for eligibility by medical file/imaging review by a study physician and verified by an experienced stroke physician. All patients with possible TIA, possible stroke for whom eligibility was unclear, or recurrent events were reviewed in person by an experienced stroke physician.

Each recruited case was assessed for the presence of specific vascular risk factors: hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, and peripheral and coronary arterial disease. Hypertension was recorded if patients were on antihypertensive therapy prestroke or had persistently elevated systolic blood pressure of ≥140 mm Hg or diastolic ≥90 mm Hg. Diabetes mellitus was recorded in patients with a prestroke diagnosis, 2 fasting venous plasma glucose measurements ≥7.0 mmol/L, or plasma glucose ≥11.1 mmol/L 2 hours after 75-g oral glucose load. Hyperlipidemia was defined as total cholesterol ≥5.0 mmol/L or low-density lipoprotein ≥3.5 mmol/L or if patients were on dietary or medical therapy prestroke. Coding of atrial fibrillation and carotid stenosis required diagnosis by ECG or extracranial vascular imaging, either before stroke or within 6 months of the qualifying event.

Ethics committee approval was obtained from all participating institutions and the Irish College of General Practitioners. All participants (or authorized surrogates) provided informed consent.

Eligibility Criteria for Subtype Analysis

The following prespecified inclusion criteria were applied: (1) ischemic stroke identified by an appropriate clinical syndrome (according to World Health Organization definition) in whom brain imaging or pathological examination was available to exclude primary intracerebral hemorrhage; (2) resident of North Dublin city during the 1-year study ascertainment period (December 1, 2005, through November 30, 2006); and (3) first-ever ischemic stroke in a lifetime.

Exclusion criteria were: (1) qualifying event of TIA, hemorrhagic stroke, or recurrent stroke; and (2) unavailability of brain imaging or pathology reports.

Subtype Classification

The TOAST system classifies ischemic stroke into 5 categories: cardio-embolism, large artery atherosclerosis, small artery occlusion, other determined etiologies, and stroke of undetermined etiology. The undetermined category is a heterogeneous group comprising cases with ≥2 causes identified, no cause found despite appropriate investigation, and incomplete evaluation.

The CCS scheme also assigns patients into 5 mechanism-based categories: cardio-aortic, large artery atherosclerosis, small artery occlusion, other determined etiologies, and stroke of undetermined etiology. The CCS system assigns the most likely subtype based on updated estimates of stroke risks associated with specific cardiac and vascular pathologies or clinical or imaging parameters known to be more commonly associated with particular stroke mechanisms.

The A-S-C-O (phenotypic) classification assigns a graded level of certainty (range 1 to 3) for the presence of each of 4 stroke mechanism categories: atherothrombosis (A), small vessel disease (S), cardio-embolism (C), and other causes (O). This combines etiologic information for individual patients in a single code, which can be grouped according to most likely mechanism (eg, high-risk [C1] cardioembolic source) or any occurrence of a shared phenotype (eg, all cases with evidence for atherosclerosis [A1+A2+A3]). ASCO also includes information on extent of diagnostic evaluation (eg, A0 denotes that no evidence of atherosclerosis was found despite appropriate investigation, whereas A9 signifies that appro-
priate investigations were not undertaken). Cases with ASCO grade 1 (ASCO1) evidence in a single domain were grouped for comparison with TOAST and CCS subtypes. Comparisons were repeated for ASCO1 and ASCO2 evidence. For these analyses, patients for whom a high risk source in a single domain was identified (ie, A1, S1, C1, or O1) were grouped together irrespective of whether a full diagnostic evaluation was completed or not. In clinical practice, not all patients undergo all etiologic investigations, especially when a known high-risk mechanism has already been identified (eg, severe ipsilateral carotid artery stenosis or metallic cardiac valve in the setting of subtherapeutic anticoagulation therapy). To assess possible effects of this method of grouping ASCO1 cases, we repeated the analysis in patients who underwent a diagnostic evaluation comprising all of brain imaging, ECG, ambulatory monitoring, echocardiography, extracranial vascular imaging, and other investigations as indicated.

A single trained stroke physician (M.M.) used published algorithms to perform data abstraction and subtype classification. Clinical, imaging, or pathological data relevant to subtype assignment were abstracted from the medical file at the time of recruitment (within 1 week of stroke onset) and again at 6 months after recruitment. Subtypes were assigned ≥6 months after a qualifying event to include the complete diagnostic evaluation in each case. For CCS, the web-based automated algorithm was used (http://ccs.martinos.org). In general, classification using the CCS computerized interface was completed more rapidly than ASCO or TOAST subtyping. In particular, automatic disabling and enabling of dependent elements in CCS focused the data abstraction process, and incorporation of pop-up definitions in the interface obviated the need for repeated reference to the original papers.

**Statistical Analysis**

The primary analysis comprised comparisons of nonindependent proportions to examine the success of different methods (CCS versus TOAST, ASCO versus TOAST, and CCS versus ASCO) for categorization of stroke subtype. The McNemar test was used to compare the probabilities of discordant categorization using each approach with Bonferroni correction for multiple comparisons. Agreement between systems was measured using the κ statistic, with values interpreted as moderate (0.41 to 0.6), good (0.61 to 0.8), or very good (0.81 to 1) agreement. The 95% CIs for the relative difference in paired proportions were calculated as described by Newcombe.

Independent proportions were computed using χ² or Fisher test as appropriate. Multiple-group comparisons of independent means were compared using one-way ANOVA. Analyses were performed in STATA (Version 9.0).

**Results**

**Clinical Characteristics**

A total of 568 patients with new stroke events were identified over the 1-year ascertainment period. Ischemic stroke was confirmed in 454 patients based on imaging (98.9%; 449 of 454) or pathological data (1.1%; 5 of 454). Of these, 83.9% (381 of 454) had first-ever ischemic stroke and were included for comparison of subtype classification systems. A total of 354 of 381 (92.9%) were admitted to hospital, whereas 27 of 381 (7.1%) were treated in the community. Demographic, risk factor, and investigation profiles of the cohort are presented in Table 1. Patients with cardio-embolism were older, more likely to have preexisting coronary disease, and least likely to smoke (P<0.01 for all; Supplemental Table I, available online at http://stroke.ahajournals.org). Those with large artery disease were more likely male and had highest smoking rates (P<0.01). Diabetes mellitus (but not hypertension) was more common in small artery disease by CCS (P=0.05) and ASCO (P=0.08).

**Comparison of TOAST and CCS in Population-Based Cohort**

A total of 39.4% (150 of 381) were classified as undetermined cause by TOAST (Table 2). This was because of identified competing mechanisms in 36.7% (55 of 150), no cause identified despite adequate evaluation in 35.3% (53 of 150), and incomplete evaluation in 28% (42 of 150). Compared with TOAST, the CCS scheme increased the assignment of patients to a defined subtype across all categories (P<0.01 for all comparisons; Bonferroni significance threshold 0.0125). This coincided with a 33.3% reduction of patients assigned to the cause undetermined category by CCS compared with TOAST (P<0.00001). Substantial relative increases in subtype assignment were observed across defined categories by CCS. This increase was most apparent for the other determined cause category (relative increase 91.7%; P=0.001), with increases in patients classified as large artery (relative increase 44.1%; P<0.0001), small artery (relative increase 27.3%; P<0.0001), and cardioembolic/cardioaortic (relative increase 6.9%; P=0.004) categories.

Agreement between TOAST and CCS ranged from good (for other determined and undetermined) to excellent (for cardio-embolism/cardio-aortic; Table 3).

**Comparison of TOAST and ASCO in Population-Based Cohort**

When cases with ASCO1 evidence for a defined mechanism were compared with TOAST, a reduction of patients assigned to the small artery group was observed (relative decrease
Table 2. Distribution of Stroke Subtypes by Classification System: Population-Based Cohort

<table>
<thead>
<tr>
<th>Subtype Category</th>
<th>Classification System</th>
<th>TOAST vs CCS</th>
<th>TOAST vs ASCO1</th>
<th>ASCO1 vs CCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Δ P</td>
<td>Δ P</td>
<td>Δ P</td>
</tr>
<tr>
<td>Cardioembolism/cardioaortic</td>
<td>TOAST 130/381</td>
<td>139/381</td>
<td>125/381</td>
<td>+6.9% 0.004</td>
</tr>
<tr>
<td></td>
<td>CCS 139/381</td>
<td>125/381</td>
<td>+11.4% 0.0006</td>
<td>−10.4% 2.8</td>
</tr>
<tr>
<td></td>
<td>ASCO1 125/381</td>
<td>+11.4% 0.0006</td>
<td>−10.4% 2.8</td>
<td>6.6 15.8</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>TOAST 130/381</td>
<td>139/381</td>
<td>125/381</td>
<td>+6.9% 0.004</td>
</tr>
<tr>
<td></td>
<td>CCS 139/381</td>
<td>125/381</td>
<td>+11.4% 0.0006</td>
<td>−10.4% 2.8</td>
</tr>
<tr>
<td></td>
<td>ASCO1 125/381</td>
<td>+11.4% 0.0006</td>
<td>−10.4% 2.8</td>
<td>6.6 15.8</td>
</tr>
<tr>
<td>Large artery/ atherothrombosis</td>
<td>TOAST 34/381</td>
<td>49/381</td>
<td>40/381</td>
<td>+44.1% 0.00006</td>
</tr>
<tr>
<td></td>
<td>CCS 49/381</td>
<td>40/381</td>
<td>+17.6% 0.03</td>
<td>+22.5% 0.06</td>
</tr>
<tr>
<td></td>
<td>ASCO1 40/381</td>
<td>+17.6% 0.03</td>
<td>+22.5% 0.06</td>
<td></td>
</tr>
<tr>
<td>Small artery occlusion/disease</td>
<td>TOAST 55/381</td>
<td>70/381</td>
<td>39/381</td>
<td>+27.3% 0.00006</td>
</tr>
<tr>
<td></td>
<td>CCS 70/381</td>
<td>39/381</td>
<td>−29.1% 0.007</td>
<td>+79.5% &lt;0.0000001</td>
</tr>
<tr>
<td></td>
<td>ASCO1 39/381</td>
<td>−29.1% 0.007</td>
<td>+79.5% &lt;0.0000001</td>
<td></td>
</tr>
<tr>
<td>Other determined causes</td>
<td>TOAST 12/381</td>
<td>23/381</td>
<td>16/381</td>
<td>+91.7% 0.001</td>
</tr>
<tr>
<td></td>
<td>CCS 23/381</td>
<td>16/381</td>
<td>+33.3% 0.13</td>
<td>+43.8% 0.13</td>
</tr>
<tr>
<td></td>
<td>ASCO1 16/381</td>
<td>+33.3% 0.13</td>
<td>+43.8% 0.13</td>
<td></td>
</tr>
<tr>
<td>Cause undetermined/no evidence for a single etiology</td>
<td>TOAST 150/381</td>
<td>100/381</td>
<td>161/381</td>
<td>−33.3% &lt;0.000001</td>
</tr>
<tr>
<td></td>
<td>CCS 100/381</td>
<td>161/381</td>
<td>+7.3% 0.2</td>
<td>−37.9% 0.0005</td>
</tr>
<tr>
<td></td>
<td>ASCO1 161/381</td>
<td>+7.3% 0.2</td>
<td>−37.9% 0.0005</td>
<td></td>
</tr>
</tbody>
</table>

Δ indicates relative change in subtype assignment between classification systems (95% CIs in parentheses).

92.1%; P=0.007; Table 2). A small increase in assignment to large artery/atherothrombotic was observed (relative increase 17.6%; P=0.03). However, this did not meet statistical significance after Bonferroni correction. ASCO1 did not change the assignment of patients to a defined subtype in other categories.

When comparing patients with ASCO1 or ASCO2 evidence with TOAST, a reduction in patients designated as cause undetermined was observed (relative decrease 18.7%; P<0.0001). This coincided with an increase in those assigned to small artery (relative increase 27.3%; P<0.0001). Smaller increases were observed in large artery/atherothrombotic (relative increase 20.6%; P=0.02) and other causes categories (relative increase 50%; P=0.03), but these did not meet Bonferroni-adjusted significance.

Agreement between TOAST and ASCO1 is presented in Table 3. Similar levels of agreement were observed when TOAST was compared with ASCO1 and ASCO2, with the exception of the small artery category, in which agreement increased substantially (from κ=0.61 to κ=0.86) by application of ASCO2 criteria.

Table 3. Agreement (κ) Between TOAST, CCS, and ASCO1 for Population and Hospital Cohorts

<table>
<thead>
<tr>
<th>Subtype Category</th>
<th>Cohort</th>
<th>TOAST vs CCS (κ)</th>
<th>TOAST vs ASCO1 (κ)</th>
<th>ASCO1 vs CCS (κ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolism</td>
<td>POP</td>
<td>0.95</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>CCS</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCO1</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>HOSP</td>
<td>0.94</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>CCS</td>
<td>0.94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCO1</td>
<td>0.94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery/</td>
<td>POP</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>atherothrombosis</td>
<td>CCS</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>ASCO1</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Small artery</td>
<td>POP</td>
<td>0.86</td>
<td>0.86</td>
<td>0.67</td>
</tr>
<tr>
<td>occlusion/disease</td>
<td>CCS</td>
<td>0.86</td>
<td>0.86</td>
<td>0.67</td>
</tr>
<tr>
<td>ASCO1</td>
<td>0.86</td>
<td>0.86</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Other determined</td>
<td>POP</td>
<td>0.67</td>
<td>0.67</td>
<td>0.76</td>
</tr>
<tr>
<td>causes</td>
<td>CCS</td>
<td>0.67</td>
<td>0.67</td>
<td>0.76</td>
</tr>
<tr>
<td>ASCO1</td>
<td>0.67</td>
<td>0.67</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Cause undetermined</td>
<td>POP</td>
<td>0.71</td>
<td>0.68</td>
<td>0.65</td>
</tr>
<tr>
<td>(TOAST, CCS)/no</td>
<td>CCS</td>
<td>0.71</td>
<td>0.68</td>
<td>0.65</td>
</tr>
<tr>
<td>grade 1 evidence</td>
<td>ASCO1</td>
<td>0.71</td>
<td>0.68</td>
<td>0.65</td>
</tr>
<tr>
<td>for a single</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>etiology (ASCO)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CCS and ASCO in Population-Based Cohort

Compared with ASCO1, CCS increased assignment of patients to small artery (relative increase 79.5%; P<0.000001) and cardio-embolism/cardio-aortic categories (relative increase 11.2%; P=0.004), with a trend toward increased large artery assignment (relative increase 22.5%; P=0.06), and a corresponding decrease in assignment to the undetermined category (relative decrease 37.9%; P=0.0005; Table 2). Agreement between CCS and ASCO1 ranged from good to excellent (Table 3).

Additional Information Provided by ASCO

We examined the additional data provided by application of ASCO in the entire cohort (n=381) and the subgroup designated as undetermined cause by TOAST (n=150).

Ninety-seven (out of a possible 625) unique codes resulted from application of the ASCO algorithm in the population cohort. These codes were grouped according to the presence or absence of disease to show the frequency of ASCO phenotypes (Table 4).

Cardiac investigations (echocardiography and ECG or ambulatory monitoring) were performed in 104 of 150 (69.3%) and vascular imaging (extracranial or intracranial) in 122 of 150 (81.3%) of TOAST-undetermined cases. A high-risk cardioembolic source (C1) was identified in 15.3% (23 of 150), whereas 31.3% (47 of 150) had evidence of any potential (C1/C2/C3) cardioembolic source. An ASCO-defined high-risk ipsilateral atherosclerotic source (A1) was identified in 16.7% (25 of 122), whereas 73.3% (110 of 122) had evidence of any large artery or aortic atherosclerosis (A1/A2/A3). For small artery disease, a high level (S1) of evidence was found in 15.3% (23 of 150) and some evidence (S1/S2/S3) in 64.7% (97 of 150). For the other causes category, a high level (O1) of evidence was found in 8% (12 of 150) and some evidence (O1/O2/O3) in 12% (18 of 150).

Comparison of Classification Schemes in Hospital-Admitted Subgroup

We repeated the comparisons of CCS and ASCO with TOAST in the hospital-admitted subgroup (n=354) because...
patients identified and treated in the community may have fewer investigations (Table 1).

The proportion of patients assigned by each classification scheme increased in the hospital subgroup compared with the population-based cohort for cardioembolic/cardioaortic, large artery, and other determined subtypes (Table 5). Slight reductions were observed in patients classified as small artery and undetermined in the hospital-admitted compared with the population cohort by TOAST, CCS, and ASCO systems. The absolute differences between specific subtype assignments in hospital and population cohorts were minimal (absolute difference range −1.6 to +0.8%).

We repeated our analysis in patients who underwent at least the combination of brain imaging, ECG or ambulatory monitoring, echocardiography, and extracranial vascular imaging (n=259). Again, CCS (but not ASCO1) reduced assignment to cause undetermined, with increased assignment to large and small artery groups (P<0.001 for all) and trends observed for other causes (P=0.06) and cardioembolic (P=0.125) groups compared with TOAST. Agreement between systems remained unchanged.

Assessment of Inter-Rater Reliability

Although not a primary aim of our study, we performed a secondary analysis to evaluate inter-rater reliability for CCS and ASCO1 assignment. Subtype assignments were retrospectively compared between a trained stroke physician (M.M.) and a nonstroke specialist (C.D.) based on original case record review in subgroups of ischemic stroke patients. Although the stroke physician was not blinded to assignments of the nonspecialist physician, all cases were classified based on the rater’s application of CCS and ASCO algorithms to abstracted data.

Thirty-eight CCS and 100 ASCO cases were classified by each rater. CCS inter-rater reliability was good to excellent for cardioaortic (κ=0.87), large artery atherosclerosis (κ=1.0), and other causes (κ=0.65), but only moderate for small artery occlusion (κ=0.48) and undetermined cause (κ=0.53). Similarly, ASCO1 inter-rater reliability was good to excellent for cardioembolic (κ=0.88), atherothrombosis (κ=0.79), and other causes (κ=0.66), but only moderate for small vessel disease (κ=0.48) and undetermined cause (κ=0.59).

Discussion

Our study describes the practical application of the CCS and ASCO subtyping systems compared with TOAST in a large population-ascertained cohort of ischemic stroke patients. Previous reports8,9,17 have described the derivation of both CCS and ASCO, but to our knowledge, neither has yet been applied in a large stroke study. Our findings support the validity of both classification systems but identify some points that may require additional refinement before there is wider use in epidemiological studies and clinical trials.

We found high levels of agreement between CCS and TOAST for classification of all stroke subtypes. Agreement was highest for cardioembolic/cardioaortic, small artery, and large artery atherosclerosis subtypes but remained good for other determined and undetermined cause categories. This is not unexpected because the CCS may be considered a refinement of TOAST based on updated evidence of the association of specific risk factors with ischemic stroke.

Table 4. Frequency of ASCO Phenotypes in Population-Based Cohort

<table>
<thead>
<tr>
<th>ASCO Phenotype</th>
<th>Disease Present (ASCO1, ASCO2, or ASCO3)</th>
<th>Disease Absent (ASCO0)</th>
<th>Insufficient Investigation (ASCO9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombosis (A) (%)</td>
<td>79 (301/381)</td>
<td>0 (0/381)</td>
<td>21 (80/381)</td>
</tr>
<tr>
<td>Small vessel disease (S) (%)</td>
<td>65.9 (251/381)</td>
<td>0 (0/381)</td>
<td>34.1 (130/381)</td>
</tr>
<tr>
<td>Cardioembolism (C) (%)</td>
<td>52.5 (200/381)</td>
<td>28.6 (109/381)</td>
<td>18.9 (72/381)</td>
</tr>
<tr>
<td>Other causes (O) (%)</td>
<td>9.7 (37/381)</td>
<td>71.7 (273/381)</td>
<td>18.6 (71/381)</td>
</tr>
</tbody>
</table>

Table 5. Distribution of Stroke Subtypes by Classification System: Hospital-Admitted Cohort

<table>
<thead>
<tr>
<th>Subtype Category</th>
<th>TOAST</th>
<th>CCS</th>
<th>ASCO1</th>
<th>TOAST vs CCS</th>
<th>TOAST vs ASCO1</th>
<th>ASCO1 vs CCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ</td>
<td>P</td>
<td></td>
<td>Δ</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism/cardioaortic</td>
<td>123/354</td>
<td>132/354</td>
<td>119/354</td>
<td>+7.3% 0.004</td>
<td>−3.3% 0.48</td>
<td>+10.9% 0.0002</td>
</tr>
<tr>
<td></td>
<td>(34.7%)</td>
<td>(37.3%)</td>
<td>(33.6%)</td>
<td>(2.6, 12)</td>
<td>(−10.1, 3.5)</td>
<td>(5.1, 16.7)</td>
</tr>
<tr>
<td>Large artery/atherothrombosis</td>
<td>32/354</td>
<td>47/354</td>
<td>38/354</td>
<td>+46.9% 0.00006</td>
<td>+18.8% 0.03</td>
<td>+23.7% 0.02</td>
</tr>
<tr>
<td></td>
<td>(9.0%)</td>
<td>(13.3%)</td>
<td>(10.7%)</td>
<td>(23.7, 70.1)</td>
<td>(3.9, 33.7)</td>
<td>(5.3, 42.1)</td>
</tr>
<tr>
<td>Small artery occlusion/ disease</td>
<td>47/354</td>
<td>62/354</td>
<td>37/354</td>
<td>+31.9% 0.00006</td>
<td>−21.3% 0.08</td>
<td>+67.6% &lt;0.00001</td>
</tr>
<tr>
<td></td>
<td>(13.3%)</td>
<td>(17.5%)</td>
<td>(10.5%)</td>
<td>(16.1, 47.7)</td>
<td>(−42.4, −0.2)</td>
<td>(42.1, 93.1)</td>
</tr>
<tr>
<td>Other determined causes</td>
<td>12/354</td>
<td>22/354</td>
<td>16/354</td>
<td>+83.3% 0.002</td>
<td>+33.3% 0.13</td>
<td>+37.5% 0.03</td>
</tr>
<tr>
<td></td>
<td>(3.4%)</td>
<td>(6.2%)</td>
<td>(4.5%)</td>
<td>(32.4, 134.2)</td>
<td>(0.8, 65.8)</td>
<td>(7.7, 67.3)</td>
</tr>
<tr>
<td>Cause undetermined/no ASCO1 evidence for</td>
<td>140/354</td>
<td>91/354</td>
<td>144/354</td>
<td>−35% &lt;0.00001</td>
<td>+2.9% 0.68</td>
<td>−36.8% &lt;0.00001</td>
</tr>
<tr>
<td>a single etiology</td>
<td>(39.6%)</td>
<td>(25.7%)</td>
<td>(40.7%)</td>
<td>(−44.1, −25.9)</td>
<td>(−7.4, 13.2)</td>
<td>(−46.3, −27.3)</td>
</tr>
</tbody>
</table>

Δ indicates relative change in subtype assignment between classification systems (95% CIs in parentheses).
However, the CCS substantially improved classification across all defined subtype groups compared with TOAST. No patient assigned to a TOAST category was assigned to a different category by CCS (Figure), indicating that disagreements between the systems related to greater assignment to each subtype by CCS. Marked improvements in classification were observed for other causes, large artery, and small artery subtypes (Table 2) and are further reflected by a one-third reduction in patients assigned to the undetermined group compared with TOAST. A similar pattern was observed when CCS and ASCO were compared. The CCS criteria that most frequently led to changes in TOAST and ASCO subtype assignments included: (1) presence of systemic embolism or complex aortic atheroma (cardioaortic); (2) TIA or stroke in the same vascular territory within 1 month before the qualifying event or presence of ipsilateral internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery (large artery atherosclerosis); (3) presence of stereotypic lacunar TIAs within 1 week or classic lacunar syndrome (small artery occlusion); and (4) specific disease process occurring in close temporal or spatial relationship to the onset of brain infarction, such as arterial dissection or cardiovascular interventions (other causes).

High levels of agreement were observed when ASCO1 (corresponding to high likelihood of causal association) classification was compared with TOAST, particularly for cardioembolic, large artery, and other causes categories. However, application of ASCO1 criteria did not change the proportion of patients assigned to these subtypes or to the cause undetermined group. Agreement with TOAST was lowest ($\kappa=0.61$) for classification of small vessel disease by
ASC01 criteria, associated with a substantial (29%) reduction in patients assigned to the small vessel disease category by ASC0. This probably relates to the more stringent requirements of ASC01 for small artery subtype classification. ASC01 criteria require demonstration of a small, deep infarct on imaging corresponding to symptoms and the presence of ≥1 additional feature, such as lacunar infarction in another territory, recent lacunar-type TIAs in the same territory, or imaging evidence of leucoariosis, microbleeds, or dilatation of perivascular spaces. In comparison, the TOAST small artery category requires a traditional clinical lacunar syndrome and either normal CT/MRI brain or a small brain stem or subcortical infarct in the relevant vascular territory. Similar to TOAST, ASC02 criteria permit assignment of small artery subtype if there is imaging evidence of a single deep branch artery stroke or an appropriate clinical syndrome. When we applied ASC01 and ASC02 criteria, agreement with TOAST increased substantially, and patients assigned to the small artery category increased by 27%. In addition to the less restrictive criteria outlined above, this increase is also partially attributable to the inclusion by ASC01 and ASC02 of other clinical syndromes suggestive of lacunar stroke, such as isolated dysarthria, hemichorea and hemiballism.9

Although the ASC0 system did not greatly increase the assignment to specific subtype categories, it provided additional information not available under the TOAST and CCS schemes. For example, although only 10.5% of patients met ASC01 criteria for large artery disease, an additional 68.5% (261 patients) had some evidence of atherosclerosis by ASC0 criteria (grades 1 to 3). Similar large increases were observed in cardioembolic and small artery categories. ASC0 also provided insights into patients coded as undetermined by TOAST, a group frequently excluded from analysis in clinical studies. For example, 15% to 17% of TOAST-undetermined patients had ASC01 evidence of a cardioembolic, large, or small artery subtype. An additional 31% to 73% had some evidence (ASC01 to ASC03) of these subtypes. It is possible that these characteristics of the ASC0 system may improve current methods for refinement of phenotype in stroke genetic studies or for patient selection for clinical trials of therapeutic agents targeting specific disease mechanisms. For example, it is possible that statin therapy may be of greater benefit to stroke and TIA patients with ASC01 to ASC03 evidence of atherosclerosis compared with other ASC0 phenotypes. Phenotypic classification systems such as ASC0 may also facilitate studying genetic/environmental risk markers in such groups. However, we emphasize that these hypotheses relating to the utility of ASC03 information in research and clinical practice settings remain to be proven.

Inter-rater reliability for both CCS and ASC01 was excellent or good for cardioaortic/cardioembolic, large artery atherosclerosis/atherothrombosis, and other determined cause categories, reflecting clarity in the definitions of causation used in both systems. For small artery disease, inter-rater reliability was only moderate, with resultant reduction in inter-rater reliability for the undetermined cause category. This finding could be explained by ambiguities in original case files or the effect of differing degrees of experience of the raters in adjudicating on lacunar stroke syndromes. We caution that these results require confirmation because this analysis was retrospective, and the sample size (particularly in the CCS analysis) was small. Kappa values are influenced by the number of observations which should be borne in mind when interpreting reliability analyses with low numbers.

Strengths of our study include the large sample size and population-based design, which adheres closely to recommended criteria for rigorous stroke epidemiological studies.11 A limitation is that not all investigations were performed in some patients. This is perhaps inevitable in observational studies of real-world practice and is reflected by rates of investigation similar to our study in other population and hospital studies.2,18 In some cases, investigations for stroke mechanism may cease when a high-risk source is found (eg, echocardiography may not be performed if ipsilateral high-grade carotid stenosis is detected). In others, investigating stroke mechanism may be considered of secondary importance (eg, in severe stroke when death is imminent). To allow comparison of ASC0 with TOAST and CCS subtypes, we grouped cases according to a reduction rule (ie, all patients with ASC0 evidence in a single domain were classified in that domain, including some patients who may not have had diagnostic investigations for other potential etiologies). This approach reflects clinical decisions often made in daily practice (eg, a patient with ischemic stroke and subtherapeutic anticoagulation for a metallic cardiac valve prosthesis may not have cerebrovascular imaging). However, it is possible that fewer patients may be designated as cause undetermined by this method. We addressed this issue by repeating our analysis on hospital-treated patients and on those for whom vascular imaging and cardiac studies were completed. Our findings remained unchanged, suggesting that the inclusion of patients without a full diagnostic evaluation was not a major contributor, and that they may be generalized to a broad range of study settings.

Our study clarifies several characteristics of both CCS and ASC0 systems. Both scales displayed high agreement with TOAST, with lowest agreement identified for ASC01 classification of small artery disease. The CCS improved assignment to specific stroke categories and reduced the proportion of patients classified as undetermined cause, suggesting an advantage when a high degree of specificity is required for subtype assignment. Other advantages of the CCS system include its derivation based on best-available evidence for association of stroke with identified risk markers and relative ease of application of the CCS algorithm via a computerized interface. The ASC0 system retained information with potential relevance to stroke etiology not captured by either TOAST or CCS schemes, which may have utility in some study settings. By setting more restrictive criteria, ASC0 may also increase the specificity of classification of small artery disease but with a reduction in sensitivity when grade 1 criteria are applied.

Given the specific strengths of both systems and the desirability of a single agreed subtyping scheme for clinical stroke research, a harmonized classification scheme that integrates the strengths of both systems should be considered. This might incorporate the evidence-based algorithm of CCS to improve the overall specificity of subtype assignment, with
additional levels of evidence (similar to ASCO2, ASCO3, and ASCO9 categories) to maximize retention of information where relevant in specific study settings. Consensus would be required on other points, such as categorization of aortic arch atherosclerosis. The feasibility of such an integrated system should be examined in future research.

Acknowledgments
We sincerely thank the patients, families, general practitioners, and hospital colleagues who participated.

Sources of Funding
M.M. is supported by awards from the Mater College of Postgraduate Education and Research, the Irish Heart Foundation, and an unrestricted educational grant from Pfizer Healthcare. O.C.S. is the recipient of Mater Foundation and Health Research Board of Ireland awards. P.J.K. is the recipient of awards from the Irish Heart Foundation and a Clinician Scientist Award from the Health Research Board of Ireland. L.K. is supported by a Health Research Foundation and a Clinician Scientist Award from the Health Research Board of Ireland. M.M. is supported by awards from the Mater College of Postgraduate Education and Research, the Irish Heart Foundation, and an unrestricted educational grant from Pfizer Healthcare. O.C.S. is the recipient of Mater Foundation and Health Research Board of Ireland awards.

Disclosures
None.

References
Stroke Subtype Classification to Mechanism-Specific and Undetermined Categories by TOAST, A-S-C-O, and Causative Classification System: Direct Comparison in the North Dublin Population Stroke Study

Michael Marnane, Caroline A. Duggan, Orla C. Sheehan, Aine Merwick, Niamh Hannon, Denis Curtin, Dawn Harris, Emma B. Williams, Gillian Horgan, Lorraine Kyne, Patricia M.E. McCormack, Joseph Duggan, Alan Moore, Gloria Crispino-O’Connell and Peter J. Kelly

Stroke. 2010;41:1579-1586; originally published online July 1, 2010;
doi: 10.1161/STROKEAHA.109.575373

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/8/1579

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/03/31/STROKEAHA.109.575373.DC1
我们根据卒中发生机制定义了卒中亚型，而缺血性卒中中的重要转归，如残疾、死亡及复发等均因亚型而异[1,2]。识别卒中的潜在病因是临床实践的重要组成部分，它将指导治疗方案的制定以及患者的预后。缺血性卒中的病因分型不仅可应用于临床试验中研究特定的患者群[3](如心源性脑栓塞或者动脉粥样硬化性卒中)的获益情况，也可应用于流行病学领域中研究环境和遗传危险因素与特殊卒中表型之间的关系[4,5]，因此其可重复性和准确性就显得尤为重要。

TOAST(Trial of ORG 10172 in Acute Stroke Treat-
分型体系起初是用来更好地解决多中心随机临床试验中亚型分类的标准化问题。而后来被应用于与流行病学和基因相关的研究，这是之前所未曾想到的。自从 TOAST 分型体系诞生以来，随着诊断技术的日新月异，对于有着多种潜在致病因子的卒中患者的检出率逐渐增加。自新卒中分型方法，如病因分型体系（CCS）和 ASCO 表型体系（A 代表动脉粥样硬化，S 代表小血管病变，C 代表心源性，O 代表其他病因），可帮助我们识别多种潜在致病因子中最有可能的病因，并了解它们之间的相对重要性以及诊断所需的评估手段。这些新方法对于完善亚型的分类和提高临床卒中研究中数据的使用效率有着相当大的潜力。尽管如此，尚无研究直接比较过这些方法的异同，也无资料显示它们在独立病例队列中的应用情况。因此，以下三个问题都值得深入研究：各分型体系中不同亚型出现的相对频率，CCS 和 ASCO 分型与 TOAST 分型之间的异同点以及各种分型方法在住院病例队列和以非选择性人口为基础的队列研究中的应用特点。

**方法**

**人口学研究**

我们分析了北都柏林市人群卒中研究中的所有患者。北都柏林市的范围按照爱尔兰当地政府的选举区划界，共纳入 294529 名居民进行前瞻性队列研究（1）。北都柏林市内 4 家急诊医院和 9 家非急诊医院参加了本项研究。我们假设 CCS 分型和 ASCO 分型应用于以人群为基础的卒中研究时可减少 TOAST 分型中不明病因者的比例。我们力求证明这一假说，并且将对所有卒中患者（社区加上医院）和所有住院的卒中患者中各亚型出现的频率加以描述。

**病例的筛选**

我们根据“理想”的卒中发病例的血管性危险因素都加以评估：高血压、糖尿病、高脂血症、吸烟和周围动脉疾病及冠状动脉疾病。若其在卒中发病前一直接受降压治疗或者收缩压持续大于 140 mm Hg 或舒张压持续大于 90 mm Hg，都可被记录为高血压。若其在卒中发病前已被诊断为糖尿病，2 次空腹血糖不低于 7.0 mmol/L 或者口服 75 g 葡萄糖负荷量 2 小时后血糖不低于 11.1 mmol/L，均被记录为糖尿病。若总胆固醇超过 5.0 mmol/L 或者低密度脂蛋白超过 3.5 mmol/L 或者患者发病前已在饮食控制或者接受药物治疗，就被记录为高脂血症。心房颤动和颈动脉狭窄可在卒中发病前或纳入标准化研究后 6 个月内，由 ECG 或者颅外血管影像来诊断。所有参加机构和爱尔兰开业医师协会都得到了伦理委员会的认可。所有参加人员（或经授权认可的代理人）均签署知情同意。

**入选标准**

以下为入选标准：(1) 经头颅影像学或病理学检查、已除外原发性颅内出血、符合世界卫生组织关于临床综合征定义的缺血性卒中；(2) 患者为北都柏林市居民，且在一年的病例筛选期内（从 2005 年 12 月 1 日到 2006 年 11 月 30 日）；(3) 人生中首次发病的缺血性脑卒中。排除标准如下：(1) TIA、出血性颅内卒中或者复发性脑卒中；(2) 无法取得头颅影像学资料或病理学报告。
亚型的分类

**TOAST** 分型将缺血性卒中分为五个类别：心源性脑栓塞、大动脉粥样硬化、小动脉闭塞、其他病因明确的卒中和病因不明的卒中。病因不明的卒中是一个多相群，它包含了两种以上病因共存的、完善检查后却无因可循的以及评估不完善的病例。

**CCS** 分型也将病例分为五种以机制为基础的类别：心主动脉源性脑栓塞、大动脉粥样硬化、小动脉闭塞、其他病因和不明病因。随着卒中风险评估手段的更新，我们认识到某些心脏、血管的病理过程或者临床变化、影像改变可能与特殊的卒中机制有着更多的关联。而**CCS** 体系正是对卒中风险不断更新认识才将患者归类于最有可能的亚型。

**ASCO** 表型分型对于四种卒中机制分类（A 代表动脉粥样硬化，S 代表小血管病变，C 代表心源性脑栓塞，O 代表其他病因）中的每一类别均按证据的可信程度分为 1 至 3 级。它在单一模式中为个体整合了病因学信息，从而可根据最有可能的发病机制（如高危的心源性栓塞 [C1]）或者共同的表型（如动脉粥样硬化证据的所有患者 [A1+A2+A3]）将其分门别类。**ASCO** 还包括了诊断性评估范围内的信息（如 A0 表示完善检查后仍无动脉粥样硬化的证据，而 A9 则提示检查尚不完善）。我们将在单病因范畴内仅有 ASCO 1 级证据的患者分组后与 TOAST 和 CCS 亚型进行比较。我们也分析了有 ASCO 1 级证据或为 ASCO 2 级证据的患者。在进行这些分析时，无论诊断性评估完善与否，单个病因范畴内的高危患者（如 A1, S1, C1 或者 O1）会被集中起来。在临床实践中，并不是所有的患者都会完成完整的病因学检查，尤其当我们已经发现一个已知的高危致病机制（例如病灶同侧的颈动脉严重狭窄者或者金属瓣膜术后接受抗凝治疗的患者）。为了评估不完善的诊断性评估对 ASCO 1 级证据的影响，我们重复分析了那些曾做过诊断性评估检查（如头颅影像、ECG、便携式监测、超声心动图、颅外段血管影像和其他检查）的患者。

一名接受过培训的卒中内科医师（M.M.）根据已出版的定义完成对资料的提炼整理以及对卒中亚型的归类分组 [6,8,9,13]。在入组和入组后 6 个月时将亚型分组相关的临床、影像以及化验资料从医疗文件中整理出来。每一病例完整的检查结果录人完成至少 6 个月后进行亚型的分类 [14]。我们应用以网络为基础的自动化算法完成 CCS 分型（http://ccs.martinos.org）。总而言之，由于 CCS 分型应用了计算机界面，其分类速度明显快于 ASCO 分型或 TOAST 分型。特别要提到的是，CCS 分型中相关因素的自动取消和应用注重于数据的提炼过程，而结合了定义弹出框的操作界面避免了寻找原文文献的重复操作。

统计分析

本研究的统计分析主要比较多非独立样本的构成比，其主要目的为了解不同卒中亚型分类方法的成功之处（CCS vs. TOAST，ASCO vs. TOAST 以及 CCS vs. ASCO）。组间比较采用 McNemar 试验，多重比较采用 Bonferroni 校正法。体系间一致性采用 κ 统计，其值可衡量一致性：中等（0.41-0.6），佳（0.61-0.8）以及极佳（0.81-1）[15]。配对样本间构成比的 95% 可信区间用 Newcombe 法 [16] 来描述。比较独立样本的构成比采用卡方检验或者 Fisher 精确检验。比较多个独立样本均数采用单因素方差分析。所有分析均采用 STATA 软件（版本为 9.0）。

结果

临床特征

在一年的病例确认期内共有 568 名新发的缺血性脑卒中病例。454 名病例由影像学资料（98.9%；449/454）或者病理资料（1.1%；5/454）确诊为缺血性脑卒中。其中 83.9%（381/454）为首次发病，从而被
纳入了亚型分类体系的比较研究。这381名病例中，共354例（92.9%）入院治疗，而其中的27例（7.1%）在社区接受治疗。队列中的人口学资料、危险因素和检查情况列于表1。心源性脑栓塞患者的年龄较大，其发病前冠心病罹患率较高，而吸烟比例最低（以上P<0.01；表1补充版可见于http://stroke.ahajournals.org）。大动脉病变中男性比例较高，并且吸烟率最高（P<0.01）。CCS和ASCO体系的小血管病变中糖尿病（并不患高血压）更为常见，P值分别于0.05和0.08。

基于人群的队列研究中TOAST分型和CCS分型的比较

TOAST分型体系将39.4%（150/381）归类于不明病因（见表2）。其中36.7%的患者（55/150）存在多种竞争致病机制，35.3%（53/150）完善检查仍无因可循，而28%（42/150）的患者所行的检查尚不完善。CCS分型与TOAST分型相比显著增加了各明确病因组的病例数（所有组间比较的P<0.01；Bonferroni显著性阈值为0.0125），而且不明病因组的病例数也减少了33.3%（P=0.000001），以上两种情况完全吻合。我们可以看到，CCS分型十分显著地增加了病因明确的病例数，分别体现于其他病因组（相对增加了91.7%，P=0.001），大动脉粥样硬化组（相对增加了44.1%，P=0.00006），小动脉闭塞性（相对增加了27.3%，P=0.00006）以及心源性或心主动脉性脑栓塞组（相对增加了6.9%，P=0.004）。

TOAST分型与ASCO分型的一致性为佳（其他病因组和不明病因组到极佳（心源性或心主动脉性脑栓塞组；见表3）。

TOAST分型和ASCO分型在以人群为基础的队列中的比较

与TOAST分型相比，在符合ASCO1级证据明确为单病因的患者中，我们发现小动脉病变组的患者比例变小（相对减少了29.1%，P=0.007；见表2），而大动脉/粥样硬化血栓形成的患者显著增加（相对增加了27.3%，P=0.00006）以及心源性或心主动脉性脑栓塞组（相对增加了6.9%，P=0.004）。

TOAST分型和ASCO分型在以人群为基础的队列中的一致性

与TOAST分型相比，在具有ASCO1级或ASCO2级证据的患者中，我们发现不明病因组的患者比例变小（相对减少了18.7%，P=0.0001），而小动脉病变组的患者相对增加了27.3%（P=0.0001）。以上两种情况相互吻合。大动脉/粥样硬化血栓形成组和其他病因组的患者增加得较少，分别相对增加了20.6%（P=0.02）和50%（P=0.03），但经Bonferroni校正后均无统计学上的显著差异。TOAST分型和ASCO分型（1级证据）的一致性研究列于表3。纳入选ASCO2级证据分析后，ASCO分型1级证据和2级证据相结合的评价方法与TOAST分型之间的一致性
性除在小动脉病变组显著高于 ASCO 分型 (1 级证据) 与 TOAST 分型之间的一致性 (κ 值从 0.61 变为 0.86) 外，在其他组均无明显差异。

CCS 分型和 ASCO 分型在以人群为基础的队列中的比较

CCS 分型与 ASCO 分型 (1 级证据) 相比增加了小动脉病变组 (相对增加了 79.5% ; P < 0.000001) 和心源性栓塞 / 心主动脉性组 (相对增加了 11.2% ; P = 0.004) 的患者比例，大动脉病变组的患者比例有增大的趋势 (相对增加了 22.5% ; P = 0.06)；而不明病因组的患者比例则相应地变小 (相对减少了 37.9% ; P = 0.0005 ; 见表 2)。CCS 和 ASCO 分型 (1 级证据) 之间的一致性水平波动于优至极佳之间 (见表 3)。

ASCO 分型提供的额外信息

我们将 ASCO 分型应用于整个队列 (381 例) TOAST 体系中不明病因组的患者 (150 例) 后得到了一些额外信息。

我们在队列中应用 ASCO 分型后得到了 97 种的组合模式 (共有 625 种可能的组合模式)。我们根据病因检出与否将这些组合分门别类以显示 ASCO 表型的分布频率 (表 4)。

TOAST 分型体系中不明病因的患者共有 150 名，其中有 104 名 (69.3%) 接受了心脏检查 (超声心动图和心电图或便携式监测仪)，122 名 (81.3%) 接受了血管检查 (颅内血管或颅外血管)。15.3% (23/150) 为心源性脑栓塞的高危患者 (C1)，而 31.1% (47/150) 的患者有心源性脑栓塞的潜在风险 (C1/C2/C3)。16.7% (25/152) 为病灶同侧动脉粥样硬化的高危患者 (A1)，而 73.3% (110/152) 的患者有大动脉或者主动脉粥样硬化的证据 (A1/A2/A3)。15.3% (23/150) 为小动脉病变证据确凿的患者 (S1)，而 64.7% (97/150) 的患者有小动脉病变的证据 (S1/S2/S3)。8% (23/150) 为有其他病因证据的患者 (O1/O2/O3)。

不同分类方法在住院患者群中的比较

我们在住院患者群 (n=354) 中重复了 CCS 分型和 ASCO 分型分别与 TOAST 分型的比较，这是因为在社区接受诊疗的患者所完成的检查相对较少 (见表 1)。住院患者群与以普通人群为基础的队列相比，其所应用的每一种分类方法中的心源性脑栓塞 / 心主动脉性病变组、大动脉病变组和其他明确病因组的患者比例均有增加 (见表 5)，而小动脉病变组和不明病因组的患者比例则略微减少 (见表 5)。两种队列中亚型分类间的差别很小 (绝对差的范围为 -1.6% - +0.8%)。

我们重新分析了那些至少都做过头颅影像、ECG 或便携式监测、超声心动图和颅外血管影像的患者 (共 259 名)。我们再次发现，与 TOAST 相比，CCS( 而不是 ASCO1) 体系中不明病因组的患者比例有所减少，大动脉病变组和小动脉病变组的患者比例有所增加 (P 均 <0.001)，而其他病因以及心源性脑栓塞的患者有变多的趋势 (P 分别为 0.06 和 0.125)。

### 表 4 ASCO 表型在人口学队列分布的频率

<table>
<thead>
<tr>
<th>分型类型</th>
<th>ASCO1</th>
<th>ASCO2</th>
<th>ASCO3</th>
<th>不检查 (ASCO9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>动脉粥样硬化 (A)</td>
<td>79 (301/381)</td>
<td>0 (0/381)</td>
<td>21 (80/381)</td>
<td></td>
</tr>
<tr>
<td>小动脉病变 (S)</td>
<td>65.9 (251/381)</td>
<td>0 (0/381)</td>
<td>34.1 (130/381)</td>
<td></td>
</tr>
<tr>
<td>心源性栓塞 / 心主动脉性 (C)</td>
<td>52.5 (200/381)</td>
<td>28.6 (109/381)</td>
<td>18.9 (72/381)</td>
<td></td>
</tr>
<tr>
<td>其他病因 (O)</td>
<td>9.7 (37/381)</td>
<td>71.7 (273/381)</td>
<td>18.6 (71/381)</td>
<td></td>
</tr>
</tbody>
</table>

### 表 5 不同分类体系中卒中亚型的分布 : 住院患者队列

<table>
<thead>
<tr>
<th>亚型分类</th>
<th>TOAST</th>
<th>CCS</th>
<th>ASCO1</th>
<th>Δ</th>
<th>P</th>
<th>Δ</th>
<th>P</th>
<th>Δ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>心源性栓塞 / 心主动脉性</td>
<td>123/354</td>
<td>132/354</td>
<td>119/354</td>
<td>+7.3%</td>
<td>0.004</td>
<td>-3.3%</td>
<td>0.48</td>
<td>+10.9%</td>
<td>0.0002</td>
</tr>
<tr>
<td>大动脉 / 动脉粥样硬化</td>
<td>(34.7%)</td>
<td>(37.3%)</td>
<td>(33.6%)</td>
<td>(2.6, 12)</td>
<td>-10.1, 3.5</td>
<td>5.1, 16.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>血栓形成性</td>
<td>32/354</td>
<td>47/354</td>
<td>38/354</td>
<td>+46.9%</td>
<td>0.00006</td>
<td>+18.8%</td>
<td>0.03</td>
<td>+23.7%</td>
<td>0.02</td>
</tr>
<tr>
<td>小动脉闭塞 / 疾病</td>
<td>(9.0%)</td>
<td>(13.3%)</td>
<td>(10.7%)</td>
<td>(23.7, 70.1)</td>
<td>3.9, 33.7</td>
<td>(5.3, 42.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>其他明确病因</td>
<td>47/354</td>
<td>62/354</td>
<td>37/354</td>
<td>+31.9%</td>
<td>0.00006</td>
<td>-21.3%</td>
<td>0.08</td>
<td>+67.6%</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>不明确病因 / 无单一病因的</td>
<td>12/354</td>
<td>22/354</td>
<td>16/354</td>
<td>+83.3%</td>
<td>0.002</td>
<td>+33.3%</td>
<td>0.13</td>
<td>+37.5%</td>
<td>0.03</td>
</tr>
<tr>
<td>ASCO1 (1 级证据)</td>
<td>140/354</td>
<td>91/354</td>
<td>144/354</td>
<td>-35%</td>
<td>&lt;0.000001</td>
<td>+2.9%</td>
<td>0.68</td>
<td>-36.8%</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Δ 表示不同分类体系之间每一亚型的相对差异 (括号内为 95% 可信区间)。
体系之间的一致性没有变化。

评估者之间的可信度评估
尽管 CCS 分型和 ASCO 分型 (1 级证据) 的评估者之间可信度评估并非本项研究的主要目的，但我们仍对其进行了分析。一位受过培训的卒中内科医师 (M.M.) 和另一位非卒中专科医师 (C.D.) 回顾了缺血性脑卒中各个亚组中病例的原始资料之后对卒中亚型进行了分类。我们比较了这两位评估者的工作。虽然卒中专科医师知晓非专科医师的归类结果，但所有病例的分类都在资料整理后按 CCS 和 ASCO 分型的规定分析所得。

每位评估者根据 CCS 分型和 ASCO 分型分别对 38 例和 100 例患者进行分类。CCS 评估者间一致性除了在小动脉闭塞组 (κ=0.48) 和不明病因组 (κ=0.53) 为中等水平外，在其余组中均为佳到极佳，其中中心主动脉源性脑栓塞组、大动脉粥样硬化组和其他病因组的 κ 值分别为 0.87、1.0 和 0.65。ASCO1 评估者间一致性情况与此相似，仅在小动脉闭塞组 (κ=0.48) 和不明病因组 (κ=0.59) 为中等水平，而在心源性脑栓塞组 (κ=0.88)、大动脉粥样硬化组 (κ=0.79) 和其他病因组 (κ=0.66) 均为佳至极佳水平。

### 讨论

本研究描述了 CCS 和 ASCO 分型体系与 TOAST 分型相比在以人群为基础的缺血性脑卒中患者队列的
Marnane et al  Comparison of TOAST, ASCO, and CCS Subtyping

实践应用。曾有文献报道了 CCS 和 ASCO 的来历 [8,9,17], 但据我们所知, 尚无在大型卒中研究应用的报道。本研究肯定了两种分型体系的有效性, 但在更广泛地应用于流行病学研究和临床试验之前则需要对体系中的某些方面另作修改。

我们发现 CCS 分型和 TOAST 分型在所有卒中亚型的分类上的一致性均达到了很高的水平。心源性脑栓塞 / 心主动脉源性脑栓塞组合、大动脉病变组合和大动脉粥样硬化组合的一致性最好, 而其他病因组和不明病因组的一致性则保持良好水平。这并不在我们的意料之外, 因为 CCS 体系正是基于某些危险因素与缺血性脑卒中相关的证据而对 TOAST 分型作了补充和修改。

不仅如此, CCS 分型与 TOAST 分型相比还显著改善了各明确病因亚组的分类。TOAST 分型中某组别的患者绝不会被分配至 CCS 分型中的其他组别 (见图), 这提示体系间的一致性高是因 CCS 分型更为合理地分配每一种卒中亚型所致。其他病因、大动脉病变和小动脉病变的分类得到明显的改善 (见表 2), 而且归类于不明病因组的患者数量与 TOAST 相比减少了三分之一。CCS 分型与 ASCO 分型相比的情况与此相似。CCS 分型标准常改变 TOAST 和 ASCO 分型中亚型的分类, 其中最为多见的包括以下四点: (1) 全身性栓塞或者混合性主动脉粥样硬化 (心主动脉源性); (2) 入组前一个月内出现同一供血区域的 TIA 或卒中, 或者同侧内分水岭梗死, 或者多发生于病变动脉 (大动脉粥样硬化) 供血区域内的多发且各自独立的梗死灶; (3) 脑梗死灶 TIA 于一周内出现双侧出现, 或者出现经典腔隙性综合症 (小动脉病变); (4) 与缺血性脑卒中的发生在时间上或者空间上有着密切联系的特殊疾病过程, 例如动脉夹层或血管内血栓形成 (其他病因)。

ASCO1 分型与 TOAST 分型的一致性达到很高的水平 (很强的因果相关性), 尤其在心源性脑栓塞组、大动脉病变组和其他病因组。尽管如此, ASCO1 标准的应用并未改变归入这些亚组或者不明病因组的患者比例。两者间一致性在小血管病变的分类上最差 (κ=0.61), 这与 ASCO 分型显著减少归入小血管病变组的患者数量 (29%) 有关。这可能是由于 ASCO1 对于归入小动脉病变亚组的要求极为严格。ASCO1 标准要求在影像上能见到与症状相符的小的深部梗死灶并且符合一项以上的附加条件, 例如存在另一供血区域的腔隙性梗死, 同一供血区域的腔隙性 TIA, 或者在影像上有脑白质病变、微出血或血管周间隙扩张等证据。相比之下, TOAST 分型中只要符合传统的临床腔隙综合征并且头颅 CT/MRI 表现正常或者相应供血区域有脑干或皮层下小梗死这两个条件便可归入小动脉病变组。ASCO 分型 (2 级证据) 与 TOAST 分型相似, 如果在影像上有单一深穿支的梗死灶或者存在典型的脑干梗死, 就可将其归入小动脉病变组。如果我们联合应用 ASCO 1 级证据和 ASCO 2 级证据, 那么与 TOAST 分型之间的一致性就会大大升高, 而归入小动脉病变组的患者会增加 27%。除了上述的分类标准的限制性较小外, 这些病例的增加还可能是因为联合应用 ASCO1 1 级证据和 ASCO 2 级证据会将一些其他的临床综合症诊断为腔隙性脑卒中, 如单纯性脑梗死、皮质扩散和侧脑室扩散 [9]。

尽管 ASCO 分型体系并未明显增加明确病因组的患者比例, 但它为我们提供了 TOAST 分型和 CCS 分型所无法提供的附加信息。例如, 虽然只有 10.5% 的患者符合 ASCO1 关于大动脉病变的标准, 但 68.5% (261 名患者) 有动脉粥样硬化化的证据 (A1/A2/A3)。如此显著的增加也见于心源性脑栓塞组和大动脉病变组。TOAST 分型中部分患者被归入不明病因组, 这一组常常在临床试验的分析中被剔除, 但是 ASCO 分型对其做了更为深入的研究。例如, TOAST 分型中不明病因的患者中 15% 至 17% 的人有心源性脑栓塞、大动脉病变或小动脉病变的 ASCO1 级证据。此外, 尚有 31% 至 73% 的患者有着这些病因不同程度的证据 (ASCO 1 级至 ASCO 3 级)。ASCO 系统的这些特性可能会完善卒中遗传学研究中表型的定义, 或者为针对某特定致病机制的治疗性药物临床试验选择合适的患者。例如, 与 ASCO 分型的其他表型相比, 他汀类药物对于有动脉粥样硬化化的证据 (ASCO 1 级至 3 级) 的卒中或者 TIA 患者的裨益可能会更多。表型分类体系 (如 ASCO 分型) 也使对遗传学或者环境学中风险指标的研究更为方便。尽管如此, 我们仍然强调, 在临床研究和实践中由 ASCO 3 级信息所衍生的假说是需要进一步被证明的。
性卒中综合症的诊断经验不一致。κ值分别为 0.87、1.0 和 0.65。ASCO1 评估者间一致性情况与此相似，仅在小动脉闭塞组（κ=0.48）和不明病因组（κ=0.59）为中等水平，而在心源性脑栓塞组（κ=0.88）、大动脉粥样硬化组（κ=0.79）和其他病因组（κ=0.66）均为良好至优秀水平。我们认为要得出这些结论尚需进一步的证实，因为分析为回顾性研究，而且其样本量（尤其是 CCS 分型）也较小。当在样本量较小的情形下阐释可信度分析时，我们应该牢记观察的次数会影响 Kappa 值的大小。

本研究严格遵循了严谨的卒中流行病学研究的推荐标准，其优势正在于较大的样本量以及以人群为基础的队列设计[11]。然而并不是所有患者都接受了完善的检查，这是本研究的缺点。我们发现在其他人群和医院的研究中患者接受检查的比例与本研究相似。这也许在现实中是无法避免的，是观察研究的通病[2,18]。当我们在发现某高危因素时，常会中止对病例的检查（例如，若检查发现病变的动脉狭窄，那么就很可能不会对其进行超声心动图了）。而有些情况下追踪某病例的病因而是次要（例如，卒中十分严重，患者生命濒危）。我们为了解释了 ASCO 体系与 TOAST 分型和 CCS 分型有可比性，就根据简化的原则将病例分门别类（例如，若发现患者有某一病因范畴的 ASCO 证据，就会将其归入此类；这就包含了一部分未行针对其他潜在病因的检查的患者）。这种反映在实际研究中的临床决策（例如，缺血性卒中患者既往行金属人工瓣膜置换术而一直接受抗凝治疗，对这样的患者可能就不行颅内血管造影患者可能就会更少了。我们针对这个问题重复研究变，这就提示了本研究中部分病例的诊断性评估不完善对最终的结论并无很大影响，或许是因广泛分布于整个研究背景而致互相抵消。

本研究阐明了 CCS 体系和 ASCO 体系的几个特点。两者与 TOAST 分型之间有着很高的一致性。ASCO 分型（1 级证据）与 TOAST 分型在小动脉病变组的一致性最低。CCS 分型将更多的患者纳入明确病因组，同时减少了不明病因组的患者比例。这就说明了 CCS 分型法在亚型分类上有很高的特异性。不断有证据证实某些危险因素与卒中的发生密切相关，而 CCS 体系的衍生正是基于这些切实可靠的证据。CCS 体系的优势还在于其多人机交互界面，操作十分方便。ASCO 体系保留了一些与卒中病因潜在相关的信息，而这些信息是 TOAST 体系和 CCS 体系所不具备的。它们在一些研究中尚有用武之地。若我们判定为更为严格的标准，那么就会提高 ASCO 分型对小动脉病变分类的特异性，但 1 级证据的应用会降低其敏感性。

所有分类体系均有其独到的优势，同时为临床卒中研究制定统一的分型方法的呼声也很高，由此我们应该考虑制定一个能整合所有分类方法的优势于一身的分类体系。一方面为了提高亚型分类的整体特异性，应融入 CCS 分型的循证法；另一方面，为了最大限度地保留与某些研究相关的信息，也要为证据评定各种级别（类似 ASCO2, ASCO3 和 ASCO9）。另外还有一些问题需要研究者的共识，比如如何归类主动脉瓣的动脉粥样硬化病变[19]。这种整合体系的可行性应在未来的研究中得到检验。

参考文献