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SPARKLE (Subtypes of Ischaemic Stroke Classification System), Incorporating Measurement of Carotid Plaque Burden: A New Validated Tool for the Classification of Ischemic Stroke Subtypes

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Key Words

Ischemic stroke · Etiological classification · Total plaque area · Validity · Reliability

Abstract

Background: Previous classification systems of acute ischemic stroke (Causative Classification System, CCS, of acute ischemic stroke, Trial of Org 10172 in Acute Stroke Treatment, TOAST) established the diagnosis of large artery disease (LAD) based on the presence or absence of carotid stenosis. However, carotid plaque burden is a stronger predictor of cardiovascular risk than stenosis. Our objective was to update definitions of ischemic stroke subtypes to improve the detection of LAD and to assess the validity and reliability of a new classification system: SPARKLE (Subtypes of Ischaemic Stroke Classification System). **Methods:** In a retrospective review of clinical research data, we compared three stroke subtype classifications: CCS, TOAST and SPARKLE. We analyzed a random sample of 275 patients presenting with minor stroke or transient ischemic attack (TIA) in an Urgent TIA Clinic in London, Ont., Canada, between 2002 and 2012. **Results:** There was substantial overall agreement between SPARKLE and CCS ($\kappa = 0.75$), with significant differences in the rate of detection of LAD, cardioembolic and undeter-

mined causes of stroke or TIA. The inter-rater reliability of SPARKLE was substantial ($\kappa = 0.76$) and the intra-rater reliability was excellent ($\kappa = 0.91$). **Conclusion:** SPARKLE is a valid and reliable classification system, providing advantages compared to CCS and TOAST. The incorporation of plaque burden into the classification of LAD increases the proportion of cases attributable to LAD and reduces the proportion classified as being of 'undetermined' etiology.

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Introduction

Classification systems for stroke are dynamic approaches that improve over time with better understanding of the pathogenesis of cerebrovascular disease and with improvements in investigation. In clinical practice, a simple and informative classification system enables early initiation of appropriate treatment to reduce recurrent stroke [1].

In 1978, the Harvard Cooperative Stroke Registry classification was introduced, at a time when only 3% of pa-

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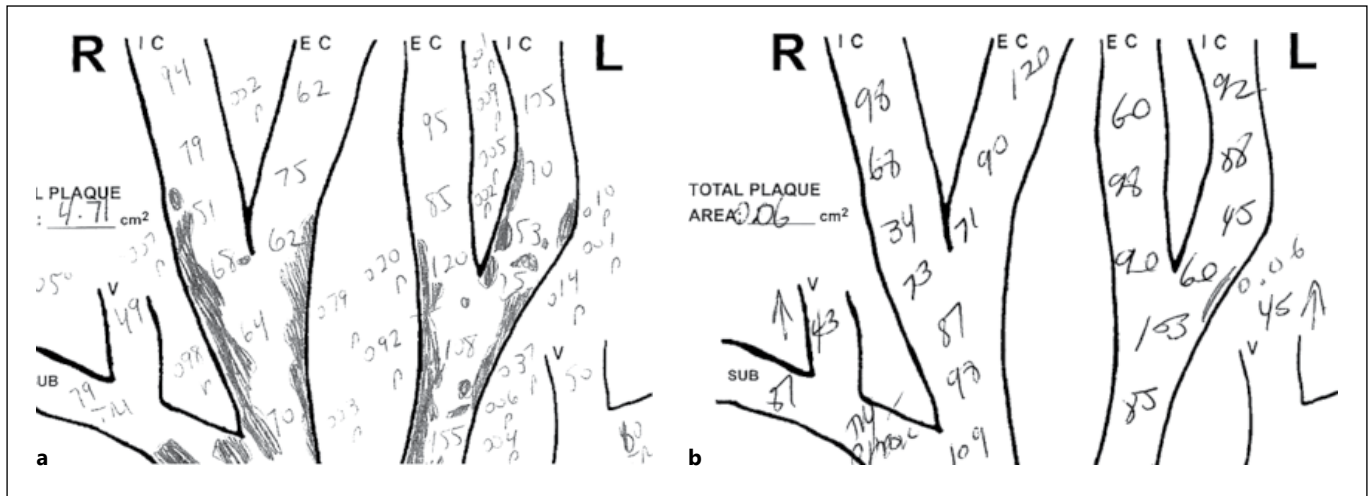


Fig. 1. Measurement of plaque burden adds to the diagnosis of stroke subtype. **a** Although it may be intuitive that patients without stenosis do not have much plaque, in fact many patients without carotid stenosis of 50% or more have LAD with a high TPA. This is thought to be due to compensatory enlargement of the artery, as described by Glagov et al. [40]. This composite drawing of carotid plaques from the ultrasound report of a normotensive 79-year-old woman with atherosclerotic stroke shows a very high plaque burden (TPA = 4.71 cm², approximately 9 times normal for age and

sex); the peak velocities (numbers written into the lumen) show that there was no internal carotid stenosis. **b** In contrast, this composite drawing shows almost no plaque (TPA = 0.06 cm²) in a normotensive 72-year-old man with no carotid stenosis and cryptogenic stroke (normal TPA for age and sex would be more than 10 times higher – 0.8 cm²). The absence or near absence of plaque in a normotensive patient without diabetes raises the suspicion of a cardioembolic source, dissection or other unusual cause of stroke.

tients were assessed with CT [2, 3]. This classification was replaced in 1988 by the Stroke Data Bank classification system, by which point 97% of patients received CT, and the pathogenesis of ischemic stroke subtypes was better understood [3, 4]. MRI and echocardiography were then added to the assessment procedures. With these enhanced imaging modalities, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) provided a more comprehensive etiological grouping of ischemic stroke subtypes with similar management [5]. However, the TOAST system classified cases with more than one cause of stroke as being of ‘undetermined’ etiology; hence, cases with well-defined yet multicausal etiologies were pooled under the broad undetermined category. In 2005, the Causative Classification System (CCS) of acute ischemic stroke was developed, allowing for classification of patients with multiple causes of stroke according to the ‘most probable’ cause of the presenting cerebrovascular event [6].

All these classification systems have been developed using data from patients with ischemic stroke. However, TOAST has been used by many studies with patients presenting with transient ischemic attack (TIA) [7–9]. In addition, a study by Amort et al. [10] showed that TOAST and CCS provide a similar distribution of ischemic stroke subtypes in patients with TIA to patients with ischemic stroke.

In the TOAST and CCS classification systems, large artery disease (LAD) is limited to patients with carotid stenosis, thus excluding patients who may have severe plaque burden [2, 4–6]. Figure 1 shows that this approach is problematic. Atherosclerosis burden, measured as total plaque area (TPA), strongly predicts stroke, death or myocardial infarction [11]. Indeed, TPA is a stronger predictor of stroke, myocardial infarction or death than carotid stenosis [12]. Moreover, after risk assessment based on risk factors, the addition of TPA increases the area under the curve for the prediction of cardiovascular events [13]. Thus, a classification system of ischemic stroke should include a measurement of plaque burden in the definition of LAD. Therefore, our main objective in this study was to revisit the definition of ischemic stroke subtypes, including ultrasound assessment of the burden of atherosclerosis measured by TPA [14–16]. We hypothesized that SPARKLE (Subtypes of Ischaemic Stroke Classification System) would classify correctly patients with LAD who are missed by TOAST and CCS.

Based on the results of our 2002 study, in our source population (among whom only 19% had experienced a prior stroke) TPA ≥ 1.19 cm² was associated with a 19.5% 5-year risk of stroke, death or myocardial infarction, after

adjustment for coronary risk factors [11]. Consequently, we included in our definition of LAD a high risk TPA $\geq 1.19 \text{ cm}^2$ in the top quartile of that study population, acknowledging that this value might differ in populations with different distributions of stroke risk factors and demographic characteristics.

We additionally sought to assess the validity of this new classification system, SPARKLE, compared to the former classifications (CCS and TOAST). We hypothesized that the use of the SPARKLE system would lead to fewer patients being assigned to the undetermined category compared to CCS and TOAST. Our third objective was to assess the reliability of SPARKLE. We expected that SPARKLE would emerge as a reproducible classification system demonstrating consistent results both between and within raters.

Patients and Methods

Sample

We conducted a retrospective analysis of data collected from patients referred to the Urgent TIA Clinic at the University Hospital in London, Ont., between 2002 and 2012. Eligible patients were included if they experienced their first lifetime minor stroke or TIA. Patients were excluded if they had a documented history of stroke/TIA before 2002 or if their final diagnosis was a stroke mimic such as a seizure or brain tumor. Data used in this study are part of a retrospective study assessing secular trends in ischemic stroke subtypes in the Thames Valley area of Ontario that was approved by the Research Ethics Board of the Western University of Health Sciences.

The total study sample consisted of 275 patients, comprising random samples of 25 patients per year seen between 2002 and 2012. Ischemic stroke subtypes for all cases were classified by a physician (C.B.) based on information collected from patient medical charts, according to the criteria presented in table 1.

The SPARKLE System

SPARKLE is a novel classification system that was developed as an adaptation of the CCS algorithm [6], by including TPA measurements [11] in the definition of LAD.

The SPARKLE system classifies patients with multiple etiologies of cerebrovascular disease and more than one 'evident' cause of stroke/TIA based on the most 'probable' stroke/TIA subtype. Cases with more than one 'possible' cause of stroke/TIA are classified according to the most possible stroke/TIA subtype. The identification of clinical outcomes and the assignment of cases in the most probable or most possible cause of stroke/TIA rely on information from the patients' history showing a close temporal relationship between the onset of a stroke-related medical condition to the onset of stroke/TIA symptoms and a mechanism of disease explaining the presenting stroke/TIA. 'Incomplete investigation' is assigned to patients who have an indication for additional investigation and who do not attend their appointment or for whom additional tests are not performed.

SPARKLE consists of five ischemic stroke/TIA subtypes: LAD, cardioembolic, small vessel disease (SVD), other rare or unusual etiology, and undetermined etiology. Diagnostic criteria and definition of ischemic stroke/TIA subtypes are provided in table 1. High-risk cardiac sources of embolism, classified as evident cardioembolic, and low-risk cardiac diseases, classified as possible cardioembolic causes of stroke/TIA, are provided in online supplementary table 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000362417).

Procedures

A stroke expert (J.D.S.) examined all patients at the clinic, at the time of the referral, between 2002 and 2012. J.D.S. performed basic standardized clinical assessment (medical history, physical examination, examination of brain and vascular imaging) and ordered additional investigation where needed (e.g. cardiac investigations were ordered when there was evidence or suspicion of cardiac sources of embolism). Subsequently, a final clinical diagnosis of the ischemic stroke subtype was confirmed or altered after receiving results from all additional laboratory diagnostic tests.

During the second half of 2012, the first author (C.B.) collected all eligible cases and classified them according to SPARKLE, CCS and TOAST at baseline, and also recorded recurrent stroke/TIA events based on SPARKLE and CCS. At the same time, C.B. determined SPARKLE classification at the 1-year follow-up after the first stroke/TIA (for patients who had at least 1 year of follow-up) to validate the classification as more information was accumulated (table 1). Finally, C.B. repeated the classification of all baseline stroke/TIA based on SPARKLE, with a period of more than 6 months between the first and second assessment, in order to evaluate consistency in rating clinical data using the SPARKLE classification system at different times of assessment.

A second physician (T.W.) assessed independently the same 275 cases at baseline using SPARKLE to determine the inter-rater reliability between C.B. and T.W.

To assess the relationship between carotid stenosis and TPA, we queried our current database of 7,217 patients with measurement of both TPA and carotid stenosis by Doppler peak velocity.

Statistical Analysis

Results from the assignment of cases based on SPARKLE, CCS and TOAST at baseline were analyzed using McNemar's test for the comparison of discordant dependent cases [17]. Alpha was set at 0.05. Cohen's kappa was used to assess agreement.

Agreement was assessed between SPARKLE and CCS at baseline and between SPARKLE and TOAST at baseline. Agreement was also measured between baseline and 1-year follow-up adjudication of cases as well as between baseline and recurrent events based on SPARKLE. Also, agreement was assessed between baseline and recurrent events based on CCS. Finally, Cohen's kappa was used to measure the agreement between the two raters and derive the intra- and the inter-rater reliability of SPARKLE [18].

The strength of the agreement was interpreted based on the criteria of Landis and Koch [19] as poor ($\kappa = 0.00$), slight ($\kappa = 0.00-0.20$), fair ($\kappa = 0.21-0.40$), moderate ($\kappa = 0.41-0.60$), substantial ($\kappa = 0.61-0.80$) and excellent ($\kappa > 0.80$) agreement. Analyses were performed using R version 2.15.2 [20].

Table 1. The SPARKLE System

Subtypes	Definitions	
LAD	Clinical criteria	(1) Fluctuating symptoms with varying periods of gradual worsening and improvement, involving cerebral, cortical, cerebellar or brain stem dysfunction [34] (2) Amaurosis fugax can be present (3) Symptoms suggesting subclavian steal syndrome [35] (4) Cardiac sources of embolism must be excluded
	Laboratory criteria	(1) CT or MRI indicating infarction ≥ 2 cm or normal imaging [6] (2) Carotid and/or transcranial Doppler ultrasound (3) Angiography, in the presence of significant carotid or intracranial stenosis
	Evident etiology	(1) Ipsilateral internal carotid or intracranial stenosis $\geq 50\%$, or (2) TPA ≥ 1.19 cm ² with absence of evidence of acute infarction in vascular territories other than the symptomatic vascular territory (3) Microemboli detection on continuous transcranial Doppler monitoring [36, 37] (4) Subclavian steal syndrome on carotid Doppler ultrasound [35]
	Probable etiology	(1) Presence of another evident cause of stroke, other than LAD (2) Presence of significant carotid and intracranial atherosclerosis ipsilateral to the vascular territory generating stroke symptoms, with confirmation of stroke signs through the neurological assessment (3) Past history of TIA or amaurosis fugax ipsilateral to the carotid or intracranial vascular territory having significant stenosis
	Possible etiology	(1) Presence of carotid atherosclerosis causing stenosis $< 50\%$, or (2) Presence of 0.12 cm ² \leq TPA < 1.19 cm ² indicating lower-risk carotid atherosclerotic lesions (3) Presence of any possible cause of stroke/TIA not related with symptom onset or presenting stroke/TIA
Cardioembolic	Clinical criteria	(1) Acutely developed cerebral or cortical symptoms of increased severity at the onset of the event with rapid clinical improvement [38] (2) Symptoms and signs indicate involvement of multiple vascular territories
	Laboratory criteria	(1) CT or MRI indicating cerebral or cortical infarction (2) Echocardiogram investigating high- and/or low-risk cardiac sources of embolism (3) Transcranial Doppler Bubble Study (4) Carotid ultrasound excludes presence of LAD
	Evident etiology	(1) Multiple territory acute infarcts in brain imaging or symptoms and signs suggesting multiple territory involvement (2) Presence of high-risk cardiac sources of embolism
	Probable etiology	(1) Presence of another evident cause of stroke other than a high-risk cardiac source of embolism (2) Presence of acute multiple territory infarctions strongly related to cardiac sources of embolism
	Possible etiology	(1) Multiple territory acute infarcts in brain imaging or symptoms and signs suggesting multiple territory involvement (2) Presence of low-risk cardiac sources of embolism (3) Presence of any other possible cause of stroke of stroke/TIA with a mechanism of disease not related with multiple territory acute stroke/TIA
SVD	Clinical criteria	(1) Presence of 1 of the 5 lacunar syndromes: pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, sensorimotor stroke, dysarthria-clumsy hand syndrome [39] (2) Absence of cortical or cerebral dysfunction
	Laboratory criteria	(1) CT or MRI indicating deep brain infarction ≤ 2 cm without focal stenosis or other vascular pathology (e.g. dissection, vasculitis) [6] (2) Carotid and transcranial ultrasound excludes LAD (3) Echocardiography excludes cardiac source of embolism
	Evident etiology	(1) Medical history and physical examination suggesting presence of a lacunar syndrome (2) CT or MRI confirms deep brain infarction of a diameter ≤ 2 cm [6]

Table 1. (continued)

Subtypes	Definitions
	Probable etiology (1) Presence of a typical lacunar syndrome (2) Presence of another evident cause of stroke/TIA with a mechanism of disease that cannot explain the presenting symptoms and signs
	Possible etiology (1) Clinical evidence of a lacunar syndrome with normal brain imaging (2) Presence of another possible cause of stroke/TIA unrelated with presenting stroke/TIA in terms of time to symptom onset and mechanism of disease
Other rare or unusual etiologies	Clinical criteria (1) Acute symptom onset after traumatic overextension or head and neck injury (2) Family history and/or clinical evidence of genetic or hematological disorders
	Laboratory criteria (1) CT or MRI (2) Carotid Doppler and/or angiography to differentiate arterial dissection from LAD (3) Blood test for genetic or hematological disorders (4) Urine drug testing, where applicable
	Evident etiology (1) Laboratory confirmation of a rare or unusual cause of stroke/TIA or mechanism of disease occurring immediately before symptom onset
	Probable etiology (1) Medical history suggesting mechanism of presence of an unusual or rare disease having a temporal relationship with the onset of the presenting stroke/TIA event, in the presence of another evident etiology of stroke/TIA unrelated with the presenting event
	Possible etiology (1) Medical history supporting a rare or unusual cause of stroke/TIA with negative investigation or delayed investigation that returned normal results
Undetermined etiologies	Clinical criteria (1) Evidence of stroke/TIA on medical history, physical examination and brain imaging with symptoms and signs not explained by 1 of the aforementioned categories
	Laboratory criteria (1) CT or MRI (2) Carotid and transcranial ultrasound (3) Echocardiogram and/or Holter (4) Blood tests for rare or unusual causes
	Unknown etiology (1) Evidence of a stroke/TIA with normal investigation for LAD, SVD, cardioembolic, and other rare or unusual etiologies
	Incomplete evaluation (1) Positive medical history for 1 of the aforementioned categories, with lack of additional investigation or loss of follow-up

Results

Among the 7,217 cases in the Stroke Prevention and Atherosclerosis Research Centre (SPARC) database, 1,535 (21%) had internal carotid stenosis $\geq 50\%$ on either side and 2,391 (33%) had a TPA ≥ 1.19 cm². Of the cases with TPA ≥ 1.19 cm², 1,535 (21%) had a stenosis of 50% or greater of either internal carotid artery. Among the 1,535 cases with stenosis, 1,170 (76%) had TPA ≥ 1.19 cm². Online supplementary figure 1 shows the distribution of carotid stenosis by TPA; the Pearson correlation coefficient between the percent stenosis of the internal carotid artery with the more severe stenosis and TPA was 0.55 ($p = 0.0001$).

Baseline characteristics of the 275 patients are provided in online supplementary table 1. At baseline, the agree-

ment between SPARKLE and CCS was substantial ($\kappa = 0.75$) and the agreement between SPARKLE and TOAST was fair ($\kappa = 0.38$). There was a significant difference between SPARKLE and both CCS and TOAST in LAD, cardioembolic and undetermined cause of stroke/TIA (table 2). No significant differences were found between SPARKLE and CCS or between SPARKLE and TOAST in patients with SVD and other rare or unusual cause of stroke/TIA (table 2).

Figure 2 presents Venn diagrams for the five ischemic stroke/TIA subtypes comparing SPARKLE, CCS and TOAST at baseline. The three classification systems exhibited nonsignificant differences concerning SVD with only 3 cases falling under the undetermined etiology in TOAST in the presence of multiple causes of

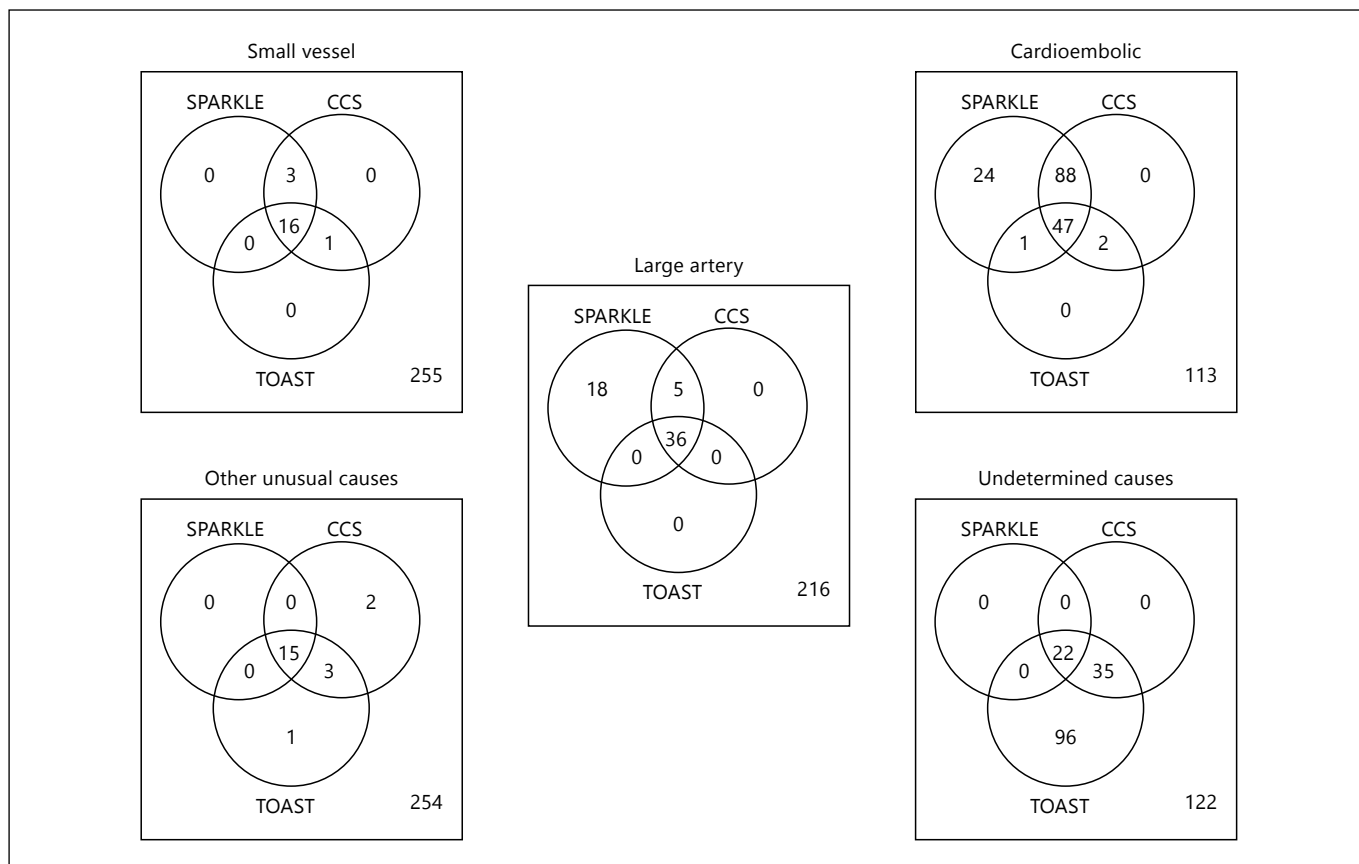


Fig. 2. Venn diagrams showing the agreement/discordance among the 3 classification systems. SPARKLE identified significantly more patients with LAD and cardioembolic stroke/TIA compared to CCS and TOAST. By classifying fewer patients under the unde-

termined category, SPARKLE offers the opportunity for more appropriate treatment to reduce the risk of recurrent stroke. The bottom right number in the Venn diagrams denotes the number of cases not classified under each ischemic stroke subtype.

Table 2. Comparison of SPARKLE, CCS and TOAST

	SPARKLE		CCS		TOAST		SPARKLE vs. CCS p value	SPARKLE vs. TOAST p value
	n	%	n	%	n	%		
LAD	59	22	40	15	36	13		
Cardioembolic	160	58	138	50	50	18	<0.001	<0.001
SVD	19	7	20	7	17	6	1	0.63
Other	15	6	20	7	19	7	0.13	0.06
Undetermined	22	8	57	21	153	56	<0.001	<0.001
Total	275		275		275			

stroke/TIA. There were 18 patients with LAD in SPARKLE who were classified as undetermined in CCS and TOAST in the absence of TPA criterion. Also, 131 cases with either multiple causes of stroke/TIA or high TPA without carotid stenosis and otherwise LAD in

SPARKLE were classified under the undetermined category in TOAST.

Additional analysis showed an excellent agreement in SPARKLE between the first adjudication of stroke/TIA and the 1-year follow-up adjudication ($\kappa = 0.95$) and sub-

stantial agreement between baseline and recurrent events ($\kappa = 0.71$). Similarly, substantial agreement was shown between baseline and recurrent events based on the CCS classification ($\kappa = 0.68$). In patients who had recurrent events, SPARKLE classified fewer cases in the undetermined category compared to CCS.

Finally, the assessment of reliability of SPARKLE showed an excellent rater consistency over time ($\kappa = 0.91$) and substantial inter-rater agreement ($\kappa = 0.76$).

Discussion

We propose that SPARKLE may be useful in informing the medical management of patients with acute stroke/TIA using minimal diagnostic tests and accommodating the latest in diagnostic tools [1]. It introduces a diagnostic tool for atherosclerosis (TPA), which is easy to measure with a regular ultrasound machine and without specific software requirements [11].

In their recently published population-based study, Palm et al. [21] used CCS with the addition of a criterion for 'probable atherosclerosis', suggesting the need for more precise criteria for LAD diagnosis. In SPARKLE, we quantified plaque burden based on stratified high (TPA $\geq 1.19 \text{ cm}^2$) and low (TPA $< 0.12 \text{ cm}^2$) stroke risk. Using a TPA $\geq 1.19 \text{ cm}^2$ to identify LAD resulted in the detection of 33% of cases with LAD compared to only 21% based on stenosis. Limiting the diagnosis to cases with stenosis underestimates the presence of high-risk LAD and potentially limits more intensive medical treatment that can significantly reduce the risk of recurrent stroke [14].

SPARKLE classified fewer cases into an undetermined category, thereby potentially enhancing preventive therapy.

Adams et al. [5] discussed the similarity of risk factors for SVD and LAD. The differential diagnosis of hypertensive, atherosclerotic or even cardioembolic origin of small subcortical infarcts is challenging. A genetic analysis in patients with SVD showed that 34% of cases had a genetic profile similar to cardioembolic stroke, 13% had a genetic profile of LAD and 47% were predicted to have SVD [22]. However, based on current knowledge, we decided to retain the description of the classical clinical lacunar syndromes referred to as SVD as previously described, acknowledging that this subtype of stroke/TIA might change in the future when new evidence emerges.

Although SPARKLE did not provide a better description of SVD and of other rare or unusual causes of stroke/TIA than CCS or TOAST, it introduced more informa-

tion for the classification of cases into LAD and cardioembolic stroke/TIA subtypes. Indeed, with the inclusion of the TPA criterion, SPARKLE identified 18 more cases with LAD that would have been missed in CCS and classified 20 more cases with possible cardioembolic stroke/TIA than did CCS. These results verify the content validity of SPARKLE by including all dimensions of ischemic stroke/TIA subtypes [23]. Moreover, the substantial agreement between SPARKLE and CCS supports the construct validity of SPARKLE [23]. Finally, SPARKLE showed an excellent agreement between baseline and 1-year follow-up adjudication of stroke/TIA that indicates the validity of diagnosing cases as more information is accumulated.

The inter-rater reliability of SPARKLE ($\kappa = 0.76$) was not substantially different from that for CCS ($\kappa = 0.8$) [24]. The greatest disagreement between the two raters occurred when information from the medical history was overlooked.

There was no significant difference in follow-up events between SPARKLE and CCS other than CCS classifying more cases under the undetermined category.

First and foremost, an unavoidable limitation of all stroke classification systems is the inability to compare the results with a gold standard, which ideally is the pathological examination [25]. Instead, Ay et al. [6] proposed the most accurate classification system to date (CCS), based on evidence from a 2% stroke risk threshold, to differentiate an evident from a possible cause of stroke. However, the ideal application of CCS requires a full set of diagnostic investigations, which is currently not available in all stroke patients in all clinical settings.

Another issue is that of the cutoff we used to define LAD. We chose a TPA of $\geq 119 \text{ mm}^2$ of plaque, which was the top quartile in our study in 2002 [11], that predicted a 19.5% 5-year risk of stroke, death or myocardial infarction, after adjusting for age, sex, blood pressure, smoking, cholesterol, diabetes, homocysteine and treatment of blood pressure and lipids. In 2004 we reported that TPA was a stronger predictor of risk than stenosis [26]. We acknowledge that this criterion might be different in other populations with different distributions of stroke risk factors and demographic characteristics. Indeed, a multicenter trial would provide the best source of evidence regarding the cutoff values of TPA to define high-risk LAD patients in multiple populations and clinical settings. A final limitation concerns the generalizability of this classification system.

Results from the Northern Manhattan Study [27], the Tromsø study [28, 29] and the High-Risk Plaque Study

[30] show that plaque burden is currently measured in other clinical settings with similar results to those in our source population. It is expected that as the advantages of measuring plaque burden [31] become more widely appreciated, this will become the standard of care. As a result, we believe that there is a considerable potential for the use of SPARKLE in different clinical settings to provide the opportunity for early diagnosis and appropriate treatment of LAD.

Whether subtype classifications should be limited to patients with stroke or should include patients with TIA is an issue that some readers may question. In this study, 165 patients (60%) had a stroke at baseline and 111 patients (40%) had TIA (data included in online suppl. table 1). A number of studies used the TOAST system for subtype classification of patients with TIA, as well as a combined population of patients with TIA and minor stroke [7–9]. Furthermore, a recent study comparing TOAST, CCS and ASCO showed a similar distribution of ischemic stroke subtypes in patients with TIA compared to studies using only stroke patients [10]. The most appropriate and effective therapy to reduce the risk of recurrent stroke is the therapy that specifically targets the underlying cause; for example, a patient with giant cell arteritis needs high-dose corticosteroids, and patients with cardioembolic stroke need anticoagulants [32]. The greatest opportunity for prevention is in patients who have not yet had a devastating stroke; therefore subtype classification is particularly useful in patients with TIA or minor stroke. This is supported by the results of the EXPRESS study, where intensive and early medical treatment of patients with TIA/minor stroke resulted in an 80% reduction of the risk of recurrent stroke [33].

SPARKLE reflects current clinical practice and can be used in all clinical settings and in further epidemiological

studies. However, confirmation of the reliability of this new classification system is required in multiple centers and from different raters. Moreover, a cluster-randomized clinical trial would provide the best evidence on the performance of SPARKLE compared to CCS by randomizing patients to clinical care with and without measurement of TPA. This could also be accompanied by genetic profile assessment to confirm which classification system can better identify patients of a particular stroke/TIA subtype. A clinical trial of this design could assess the prognostic value of each classification system.

Conclusion

Initial findings suggest that SPARKLE is a valid and reliable ischemic stroke classification system. Incorporating plaque burden into the definition of LAD reduces the proportion of cases classified as of undetermined etiology and thus permits more specific treatment of the underlying causes of cerebrovascular disease in order to reduce recurrent strokes.

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Disclosure Statement

None of the authors has a conflict of interest in connection with the content of this paper.

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