Oxfordshire Community Stroke Project Clinical Stroke Syndrome and Appearances of Tissue and Vascular Lesions on Pretreatment CT in Hyperacute Ischemic Stroke Among the First 510 Patients in the Third International Stroke Trial (IST-3)

Adam Kobayashi, MD, PhD; Joanna M. Wardlaw, MBChB, MD, FRCR, FRCP, FMedSci; Richard I. Lindley, MD, FRCP, FRACP; Steff C. Lewis, PhD, MSc; Peter A.G. Sandercock, DM, FRCPE, FMedSci; Anna Czlonkowska, MD, PhD; on behalf of the IST-3 Collaborative Group

Background and Purpose—The Oxfordshire Community Stroke Project (OCSP) clinical stroke syndrome classification correlates well with the stroke lesion in established ischemic stroke, but there are few data in patients with hyperacute stroke. We wished to assess whether the OCSP correlated with the site and size of the ischemic lesion and location of cerebral vessel lesion on computed tomography (CT) in hyperacute stroke.

Methods—Prospective study of ischemic stroke patients presenting within 6 hours of onset in the Third International Stroke Trial (IST-3), a randomized, controlled trial of rt-PA. OCSP syndrome was assigned by a computer-based algorithm. The CT assessment was made by a neuroradiologist blinded to clinical details.

Results—We assessed baseline data and CT findings for the first 510 patients; early tissue ischemic changes were present in 329/510 (65%) total anterior circulation syndrome (TACS) - 79%; partial anterior circulation syndrome (PACS) - 57%, lacunar syndrome (LACS) - 40%; posterior circulation syndrome (POCS) - 33%. The site and size of ischemic change on CT was compatible with the clinical syndrome in 79%, 37%, 2%, and 14%, respectively. Assuming that all patients with a normal CT scan will develop an incompatible lesion these numbers reflected the “worst possible scenario.” For the “best possible scenario” we presumed that those with a normal CT will develop concordant ischemic change and the proportions were 100%, 80%, 62% and 81%, respectively. The hyperattenuated artery sign was seen in 206/510 (40%); (TACS 54%; PACS 35%, LACS 5%, and POCS 19%).

Conclusions—Within 6 hours of stroke, in patients with a nonlacunar syndrome, the OCSP syndrome correlated well with the pattern of ischemic change on CT. For clinicians who wish to restrict the use of thrombolytic therapy to large-artery ischemic stroke, concordance of clinical and CT appearances may give greater confidence in making therapeutic decisions in hyperacute stroke. In centers where immediate access to MR is limited, use of the classification may help focus use of MR on patients with suspected LACS and POCS. The utility of the classification may further increase if IST-3 establishes that the OCSP syndrome significantly modifies response to thrombolytic therapy. (Stroke. 2009;40:00-00.)

Key Words: acute stroke ■ OCSP classification ■ computed tomography ■ ischemic change ■ hyperattenuated artery sign

The Oxfordshire Community Stroke Project (OCSP) clinical classification is a simple classification for acute stroke and can be based either on the clinical syndrome alone, or a combination of clinical and imaging findings. Previous studies have shown that the OCSP clinical syndrome diagnosed in the hyperacute phase of stroke correlates with clinical outcome, and, when applied within 48 hours of stroke, with the underlying computed tomographic (CT) lesion. Furthermore, its simplicity makes it appealing for use in routine clinical practice, in large-scale observational studies and clinical trials.
However, with the advent of thrombolytic therapy, it is necessary to assess and scan patients within the first few hours of stroke onset. At this stage of stroke evolution, the clinical symptoms are often quite unstable and the CT appearances are more subtle; both factors might considerably reduce the utility of the classification. Although the NINDS trial showed having a favorable effect of thrombolysis in all subtypes of ischemic stroke (e.g., large artery stroke versus small vessel stroke), this subgroup analysis was based on small numbers of patients with some subtypes (e.g., lacunar). Because the analyses were not powered to detect moderate treatment subtype interactions, it may be premature to conclude that thrombolytic therapy will be equally effective in all ischemic stroke subtypes. Hence, if the OCSP clinical syndrome does help improve diagnostic certainty or predict response to thrombolytic or other acute treatment, its simplicity would make it potentially useful both for clinical practice and research in this setting.

Recent surveys have demonstrated that although many hospitals that admit patients with acute stroke do not have rapid access to advanced imaging techniques for these patients, almost all do have CT scanning. CT scanning is therefore likely to remain a key imaging method for patients being considered for thrombolysis in many hospitals.

We therefore tested the hypothesis that the OCSP clinical syndrome would correlate well with the site and extent of early ischemic change and the presence and site of large artery occlusion (the hyperattenuated artery sign). If so, the OCSP clinical classification might aid diagnosis and management decisions in the acute phase of stroke. We also wished to identify when the findings were most likely to be discordant. We analyzed clinical and imaging data from patients with ischemic stroke who had CT as their prerandomisation imaging modality in the Third International Stroke Trial (IST-3).

Materials and Methods
We have described the rationale for IST-3 and published the full protocol in detail elsewhere (www.ist3.com). Briefly, the IST-3 is a prospective multicenter randomized controlled, open, blinded endpoint (PROBE) trial of intravenous rt-PA (alteplase). Patients with acute ischemic stroke, aged over 18 years, in whom treatment can be started within 6 hours of symptom onset, are eligible. Intracerebral hemorrhage (ICH) and structural brain lesions that can mimic stroke (e.g., brain tumor, cerebral abscess, etc) must be excluded with brain imaging before randomization. Written informed consent is taken from the patient or relative according to the trial protocol. The baseline clinical data are collected centrally (automated touch tone telephone system or via secure internet website), validated, and a computer-based randomization algorithm allocates patients either to “standard care” or to “standard care” plus rt-PA (0.9 mg/kg with 10 mg bolus and the remainder infused over 1 hour, maximum dose 90 mg). The prerandomization clinical examination includes the National Institutes of Health Stroke Scale (NIHSS) and 8 easily recognizable clinical signs:

- Unilateral weakness (or sensory deficit) affecting face,
- Unilateral weakness (or sensory deficit) affecting arm or hand,
- Unilateral weakness (or sensory deficit) affecting leg or foot,
- Dysphasia,
- Homonymous hemianopia,
- Visuospatial disorders affecting face (e.g., sensory or visual inattention, unable to copy pictures),
- Brain stem or cerebellar signs,
- Other neurological deficit,

ie, independent of the clinician’s own OCSP clinical syndrome diagnosis to minimize bias in the assignment of the syndrome by knowledge of the CT appearances by the treating clinician. The randomization system assigns the OCSP subtype according to a validated computer algorithm using the 8 clinical signs. All patients must have prerandomization brain imaging with noncontrast CT or MRI. A follow-up scan is performed 24 to 48 hours after randomization in all patients.

All brain images were assessed centrally by a single experienced neuroradiologist (J.M.W.) blinded to clinical details, treatment allocation, follow-up scans, and later clinical events. The presence, location, and extent of any early ischemic changes, hypodensity, or swelling were recorded on a standard proforma according to a validated classification. The location of any hypoattenuated artery was noted. Table 1 shows which brain scan appearances we considered to be consistent with each OCSP clinical syndrome.

The protocol permits the use of either CT or MR prerandomization, but the present analysis was confined to those patients assessed with CT scanning, as CT is the most commonly available scanning technique for acute stroke. The analysis was restricted to the prerandomization CT, since: (1) we wished to focus on the type of diagnostic information that would be available when making treatment decisions, (2) the post randomization scans would be confounded by the effects of thrombolytic treatment, and (3) we did not wish to risk any unblinding of the trial data.

We used descriptive statistics to calculate the frequency of any early ischemic change and site and size of ischemic lesion for each syndrome. We calculated a “best possible scenario” as the sum of the number of patients with that clinical syndrome whose CT appearance was compatible plus the number with no visible ischemic changes assuming that a compatible lesion will develop on follow-up. A “worst possible scenario” was equivalent to the percentage of patients with a relevant ischemic lesion on baseline CT, assuming that in patients with no apparent lesion on baseline scanning, a lesion would later appear as incompatible to the OCSP syndrome. All analyses were performed with SPSS 13.0 for Windows software package.

Role of the Funding Source
The study is designed, conducted, analyzed, and reported independently of the sponsors and funding agencies.

Results
We extracted data from the 575 patients who had been randomized in IST-3 by July 18, 2006. Data on 510 patients met the criteria for this analysis (diagnosis of ischemic stroke and the baseline imaging method was CT). The remaining 65 had either an MRI scan performed, or the neuroimaging studies were not yet available at the time of data extraction.

Compatibility of Site and Size of Early Ischemic Change on CT With OCSP Clinical Syndrome
Overall tissue changes suggestive of early ischemic change were present in 329/510 (64%). The distribution of the ischemic brain tissue change on the baseline CT and its compatibility with the patient’s clinical syndrome is given in Table 1. In patients with TACS, the site and size of the CT abnormality was compatible with the OCSP syndrome in 79% and not compatible in only 1% of those with visible ischemic change. In patients with lacunar syndromes, 60% had no visible ischemic change; 5% showed a lacunar infarct, and in 35% the radiological picture was not compatible with the syndrome. These numbers also reflect the “worst possible
scenario” taking into account the assumption that the patients with a normal baseline CT scan then develop an ischemic lesion not relevant to the clinical syndrome on the follow-up scan. The “best possible scenario” assumed that all patients with a normal CT scan might have an infarct of a clinically predicted size and location. For this “best possible scenario,” in patients with TACS, PACS, LACS, and POCS the proportions with an appropriate radiological picture were 100%, 80%, 62%, and 81%, respectively, with an overall figure of 87%.

**Frequency of Indicators of Ischemic Stroke in Different OCSP Syndromes**

The presence of any indicator of an ischemic stroke (ie, loss of gray-white matter differentiation, hypoattenuation, swelling, or the presence of the hyperattenuated artery sign) is given in Table 2. The frequency of any of these signs of an ischemic lesion was highest for TACS (84%) and lowest for LACS (40%).

**Clinical and Radiological Features in Patients Whose Clinical Syndrome and CT Did Not Appear Compatible**

The CT appearances and the clinical syndromes of the patients whose syndrome and CT were not compatible are given in Table 1. There were no incompatible CT changes found in the patients with TACS. Among the patients with PACS the most common reason for incompatibility was the finding of more extensive middle cerebral artery (MCA) infarcts than expected from their clinical deficit. All patients with LACS and POCS and incompatible CT appearances had MCA territory (nonlacunar) infarcts.

**Relation of the Clinical Syndrome to the Presence/Absence of a Hyperattenuated Artery**

The hyperattenuated artery sign was seen in 206/510 patients (40%). The number and percentage in patients with each clinical syndrome was: TACS 132/246 (54%); PACS 64/183 (35%); LACS 3/60 (5%); and POCS 4/21 (19%; Figure).

**Compatibility of the Clinical Syndrome and Vascular Territory of a Visible Hyperattenuated Artery**

The location of the hyperattenuated artery was relevant in all patients with TACS (Figure). Likewise, in patients with LACS and POCS and compatible CT appearances had MCA territory (nonlacunar) infarcts.

**Table 1. Site and Size Classification of Ischemic Change on CT Scan and OCSP Clinical Syndrome, Showing Which Are Considered to be Appropriate to That Appearance**

<table>
<thead>
<tr>
<th>Site and Size of Change on CT</th>
<th>TACS (n=246)</th>
<th>PACS (n=183)</th>
<th>LACS (n=60)</th>
<th>POCS (n=21)</th>
<th>Total (n=510)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large MCA infarct (whole peripheral MCA territory, whole peripheral MCA territory and ipsilateral basal ganglia, or all MCA territory)</td>
<td>91 (37%)</td>
<td>30 (16%)</td>
<td>4 (7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infarct of less than 1/2 of MCA territory</td>
<td>57 (23%)</td>
<td>42 (23%)</td>
<td>7 (11%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Borderzone infarct</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Small cortical infarct</td>
<td>12 (5%)</td>
<td>11 (6%)</td>
<td>4 (7%)</td>
<td>2 (9%)</td>
<td></td>
</tr>
<tr>
<td>Subcortical infarct &gt;2×2×2 cm (basal ganglia or white matter)</td>
<td>29 (12%)</td>
<td>12 (7%)</td>
<td>8 (13%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>ACA territory infarct</td>
<td>0</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lacunar infarct (internal capsule, lentiform nucleus, internal border zone, centrum semiovale)</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lacunar infarct (thalamus)</td>
<td>0</td>
<td>3 (2%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Occipital (PCA territory), cerebellar or brain stem infarct</td>
<td>4 (1.5%)</td>
<td>4 (2%)</td>
<td>0</td>
<td>3 (14%)</td>
<td></td>
</tr>
<tr>
<td>No visible ischaemia</td>
<td>52 (21%)</td>
<td>79 (43%)</td>
<td>36 (60%)</td>
<td>14 (67%)</td>
<td>181 (36%)</td>
</tr>
<tr>
<td>Compatible with this syndrome</td>
<td>194 (79%)</td>
<td>67 (37%)</td>
<td>1 (2%)</td>
<td>3 (14%)</td>
<td>267 (52%)</td>
</tr>
<tr>
<td>Not compatible with this syndrome</td>
<td>0</td>
<td>37 (20%)</td>
<td>23 (38%)</td>
<td>4 (19%)</td>
<td>62 (12%)</td>
</tr>
<tr>
<td>Best possible scenario*</td>
<td>100%</td>
<td>80%</td>
<td>62%</td>
<td>81%</td>
<td>88%</td>
</tr>
<tr>
<td>Worst possible scenario†</td>
<td>79%</td>
<td>37%</td>
<td>2%</td>
<td>14%</td>
<td>52%</td>
</tr>
</tbody>
</table>

*Loss of grey/white matter differentiation or hypoattenuation or swelling, or hyperattenuated artery sign.

Text in bold typeface indicate the situations where the CT change were not compatible with the clinical syndrome. MCA indicates middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

For the “best possible scenario” we assumed that those with a normal CT will develop concordant ischaemic change on a follow-up CT.

For the “worst possible scenario” we assumed that all patients with a normal CT scan will develop an incompatible lesion on a follow-up CT.
PACS, the hyperattenuated artery was compatible in all but two patients; one had a hyperattenuated posterior cerebral artery (PCA) and one a hyperattenuated internal carotid artery (ICA) and anterior cerebral artery (ACA). Of the patients with a lacunar syndrome, one had a hyperattenuated sylvian branch of the MCA with a small cortical infarct. The other two had a hyperattenuated MCA, one with a coexisting whole MCA territory and the other with a striatocapsular infarct. In all cases the appearance of the brain tissue ischemia was also not relevant to LACS (Figure). One patient with POCS had a hyperattenuated MCA, which is incompatible with the clinical syndrome (Figure).

Discussion

This study showed that the OCSP clinical syndrome usually correlated well with the site and size of ischemic tissue lesion and the likely arterial lesion, especially with TACS and PACS, in more than 500 patients with acute stroke assessed within 6 hours of onset. Thus, if a patient assessed within the first 6 hours of symptom onset, has a concordant OCSP clinical syndrome and CT appearances, this should give the clinician greater confidence in making treatment decisions, especially if they do not have rapid access to more advanced imaging techniques. Hence, for example, the clinician, faced with a patient who has a partial anterior circulation clinical syndrome, may then feel more confident in deciding about treatment whether the CT shows either appropriate tissue changes or a relevant hyperattenuated artery, because involvement of a relevant large artery (eg, thrombotic occlusion) is more likely to be present. Since the CT findings—as expected—were less often consistent in patients with LACS and POCS, it may be that, in this situation, MR imaging with diffusion-weighted imaging may be very helpful as it is more likely than CT to show small ischemic cortical, subcortical, and posterior fossa lesions. Patients with milder strokes are more likely to be able to tolerate MR in the hyperacute phase than patients with TACS. Thus, where rapid access to advanced MR imaging is restricted, use of MR could be focused on patients with suspected subcortical or posterior fossa (LACS or POCS) strokes who are being considered for thrombolysis.

The strengths of the study are the prospective design, large sample size, the categorization of the OCSP syndrome unbiased by the clinician’s individual opinion, a blinded review of the CT by an expert, and that both clinical and radiological examinations were performed close in time in real-life situations. The overall frequency of early ischemic changes on CT of 70% is close to the 60% observed in the reanalysis of the National Institute of Neurological Disorders and Stroke (NINDS) trial and other acute stroke and thrombolysis studies. The high frequency is most likely explained by the high proportion of TACS and the recruitment of the majority of patients at more than 3 hours after stroke onset (hence allowing more time for changes of ischemia to become visible).

The OCSP clinical syndromes most commonly associated with large artery occlusion, total and partial anterior circulation syndromes, not surprisingly, most frequently had identifiable and appropriate early ischemic change on CT. Previous studies have showed that the frequency of early ischemic change on CT performed on the first day of stroke in patients with TACS was more than 80%, which is consistent with our results. In the International Stroke Trial (IST), when imaging was performed within 48 hours, an infarct was visible in 61% of TACS overall (45% within 6 hours), but the CT assessment was performed by the randomizing clinician not
blinded to the clinical details. Visible early ischemic change was seen in PACS in over 50%. In lacunar infarcts the lesions are usually smaller and often harder to identify within 6 hours of stroke onset. The low frequency of compatible lesions in patients with lacunar syndromes in IST-3 is therefore not surprising; and it was less frequent than previous studies, mostly likely because patients were scanned earlier in the present study. It is also well recognized that, in the hyperacute phase of stroke, not all clinical deficits that are the hallmark of large artery occlusion are apparent on initial clinical examination (eg, perhaps because of good cortical collateral supply). Another factor is that, in certain circumstances, the inability of the computer algorithm to differentiate very focal weakness (eg, affecting the hand only) from weakness affecting the whole upper limb may—in the occasional patient—diminish its ability to differentiate lacunar from nonlacunar clinical syndromes. Our finding that about one third of the patients presenting with what appeared clinically to be a lacunar syndrome in fact had a pattern of ischemic tissue change suggesting large artery pathology is again not surprising. About 20% of patients with a clinical lacunar syndrome have a cortical or large subcortical (striatocapsular) lesion on imaging consistent with a partial anterior circulation infarct. Our findings are similar to a study of CT up to 48 hours after symptom onset, in which 14% of patients with lacunar stroke had a relevant radiological picture and in 44% CT showed cortical or large subcortical involvement.

The hyperattenuated cerebral artery sign is a well established radiological marker of artery occlusion by thrombus in acute ischemic stroke. Its most frequent location is the MCA and its branches. Leys et al found the hyperattenuated MCA sign in 27% of patients with a CT scan done within 12 hours of stroke onset. An analysis from the European-Australian Collaborative Acute Stroke Study (ECASS) trial, where the time window was 6 hours as in our study, 19% of patients had a hyperattenuated MCA sign. In the NINDS trial, where all baseline neuroimaging was performed up to 3 hours after onset at latest, 15% had a hyperattenuated artery with no location specified. We found it in 40% of patients, which is more than reported previously. The higher frequency of this sign may be because IST-3 has included patients with more severe strokes, and reflects the increased sensitivity of current CT scanning technology. The sign was most common in TACS, less common in PACS and POCs, and least common in LACS.

Finally, the authors of the original report of the OCSP classification pointed out that in an individual patient, the OCSP subtype assigned might need to be modified in the light of further clinical or radiological information. The data from IST3 indicate the circumstances where imaging data are likely to provide reassurance in correctly assigning an OCSP subtype in patients with hyperacute stroke, and suggest that MR imaging with diffusion imaging, a more limited resource, could be most useful in suspected lacunar and posterior circulation strokes.

Conclusions
These data support the notion that the OCSP clinical syndrome may be useful in the hyperacute phase of stroke as well as in the acute phase, especially in patients with nonlacunar hemispheric strokes, in whom the concordance between the clinical presentation and imaging findings is higher. In patients with ischemic stroke, concordance between the OCSP clinical syndrome and CT features may help improve diagnostic confidence, especially if no additional imaging is rapidly available. Furthermore, if IST-3 establishes that any one of the clinical syndromes or individual imaging features examined clearly modifies the response to thrombolysis, these data may prove useful in patient selection. For research studies, these data confirm the need to combine clinical and CT data to provide the most accurate subtyping of ischemic stroke.

Acknowledgments
The authors thank Dr John Bamford from the University of Leeds for his kind comments.

Sources of Funding
Adam Kobayashi is supported by the Polish School of Medicine Memorial Fund at the University of Edinburgh Scholarship Programme and the British-Polish Young Scientists Programme. Richard I. Lindley is supported by an infrastructure grant from NSW Health. IST-3 is an independent, investigator-led trial. It is supported by grants from: the UK Medical Research Council, the Health Foundation (a UK medical research charity); the Stroke Association of the United Kingdom; Chest, Heart, and Stroke Scotland (RES0007); University of Edinburgh; Polish Ministry of Science and Higher Education (grant no. 2PO5B10928); Norwegian Research Council; AFA Insurances (Sweden); The Swedish Heart Lung Fund; The Australian Heart Foundation; The Australian NHMRC; DesAcc Inc; and the Dalhousie University Internal Medicine Research Fund (Canadian center support). In the initial double-blind phase, drug and placebo for the first 300 patients were supplied by Boehringer Ingelheim, The University of Edinburgh and the Lothian Health Board act as joint sponsors.

Disclosures
None.

References
Oxfordshire Community Stroke Project Clinical Stroke Syndrome and Appearances of Tissue and Vascular Lesions on Pretreatment CT in Hyperacute Ischemic Stroke Among the First 510 Patients in the Third International Stroke Trial (IST-3)

Adam Kobayashi, Joanna M. Wardlaw, Richard I. Lindley, Steff C. Lewis, Peter A.G. Sandercock and Anna Czlonkowska

on behalf of the IST-3 Collaborative Group

Stroke, published online January 8, 2009;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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/early/2009/01/08/STROKEAHA.108.526772.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/