

Supplementary Methods

Magnetic resonance–based stroke subtype classification

The magnetic resonance (MR)–based stroke subtype classification that we previously developed¹⁸ is composed of the five following steps: (1) consideration of other determined etiology of stroke, (2) screening for small vessel occlusion (SVO) on diffusion-weighted image (DWI), (3) consideration of relevant artery stenosis or occlusion, (4) consideration of recanalization status after thrombolytic therapy, and (5) consideration of follow-up recanalization status without thrombolytic therapy.

Step 1. Consideration of other determined etiology of stroke

The other causes category includes patients with a diverse array of stroke mechanisms. Disorders included in this category are difficult to categorize into more homogenous groups. A patient who has a rare cause of ischemic stroke would be classified as "other determined cause" or "two or more undetermined causes (UD ≥ 2)," according to coexistence of other stroke etiology such as large artery atherosclerosis (LAA), SVO, and cardioembolism.

Step 2. Screening for SVO using DWI

A single lesion with the largest diameter of ≤ 20 mm in an axial DWI for penetrating artery infarction of the basal ganglia, corona radiata, thalamus, or pons would be classified as a SVO. If high-risk cardioembolic sources coexist, the subtype is classified as UD ≥ 2 . If accompanied by relevant stenosis of a corresponding cerebral artery on angiographic evaluation, including CT angiography, MR angiography, or conventional angiography, then it is classified as a "large artery atherosclerosis with lacunae." Infarctions in the midline extending from the base of the pons into the tegmentum without significant relevant artery stenosis would be classified as "branch atheromatous disease (LAA-BR)."

Step 3. Consideration of relevant artery stenosis or occlusion

Relevant arterial pathology was defined as stenosis or occlusion of arteries supplying the vascular territory of acute ischemic lesions detected on DWI. Stenosis less than 50% was also regarded as being relevant when clinical syndromes, lesions patterns on DWI, and new imaging techniques such as high-resolution wall imaging supported its relevance. In cases of a single lesion with the largest diameter >20 mm or multiple lesions with no steno-occlusion of relevant artery on angiographic evaluation, a possibility of cardioembolic stroke should be considered. "Exten-

sive embolic source evaluation," including 24-h Holter monitoring (24-h Holter), transthoracic echocardiography, and transesophageal echocardiography are recommended. Infarctions in which a definite cardioembolic source is not revealed despite a comprehensive work-up would be classified as "undetermined negative (UD-negative)." However, when relevant lesions are located at the anterior choroidal artery territory, single territory of cerebellum, or medulla oblongata, where SVOs do not seem to be causing infarctions, traditional MRI techniques cannot detect vascular pathologies of a relevant artery, and atherosclerosis may be a dominant vascular pathology, the infarctions are classified as "large artery atherosclerosis with normal angiography" instead of "UD-negative."

When a relevant pathology of a corresponding artery is observed, it is divided into stenosis and occlusion. If medical history or electrocardiography identifies high-risk cardioembolic sources with coexistence of relevant stenosis, then that infarction is classified as "UD ≥ 2 ." When there is evidence of chronic occlusion, or no or low risk cardioembolic source with relevant stenosis, it is classified as "LAA." Occlusion on pre-stroke angiographic evaluation, border zone infarction with clinical settings suggestive of hemodynamic failure, or recent (within 1 month of stroke onset) transient ischemic attack corresponding to occlusion site is considered as evidence for chronic occlusion.

Step 4. Consideration of recanalization status of occluded artery after recanalization therapy

If there is occlusion but no evidence of chronic occlusion and recanalization therapy, including mechanical thrombectomy, is performed, then the recanalization status after recanalization therapy should be considered. When residual stenosis exists, or angioplasty or stenting is performed for atherosclerotic stenosis, the underlying vascular pathology is considered primarily as atherosclerotic. When occlusion is resolved completely, comprehensive cardioembolic work-up is recommended. In this situation, low-risk cardioembolic sources are regarded as explaining the etiology of stroke.

Step 5. Consideration of follow-up recanalization status of occluded artery without recanalization therapy

When there is occlusion and recanalization therapy is not performed, follow-up angiographic evaluation is recommended and recanalization status on that evaluation guides further investigation and determination of stroke subtypes.