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Editorial: minor stroke is not minor

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Defining minor stroke can be complicated. A minor stroke can be called a mini or small stroke. It is often defined by the severity of neurological deficit, size of ischaemic lesion(s) on neuroimaging, and level of disability. The definition of minor stroke is often tangled with that of transient ischaemic attack (TIA).Minor stroke and TIA are often investigated together in observational and therapeutic studies. There has been voice in retiring the definition of TIA and minor stroke, and considering the two as a composite of 'acute ischaemic cerebrovascular syndrome', due to the commonality of the two in brain damage and future stroke risks.[1] In this editorial, we shall discuss the outcomes, associated factors and medical treatments in minor stroke and TIA patients, based on articles published in this journal and closely relevant studies published in other journals in recent years. Regarding the severity of the neurological deficit, a minor ischaemic stroke is usually defined with a National Institute of Health Stroke Scale (NIHSS) ≤3 or ≤5 in previous studies. Minor strokes discussed in this article are of non-cardioembolic origin and with an NIHSS score of ≤3, if not specified.

Patients with minor stroke or TIA are at a considerable risk of four types of outcomes: significant disability (about 28% not ambulating independently at discharge and 28% not discharged home),[2] recurrent stroke and other cardiovascular events, intracranial haemorrhage (ICH) and cognitive impairment.

As of the functional outcome, around 7% of 5131 minor stroke and TIA patients in the Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial were functionally dependent (modified Rankin Scale, mRS ≥3) at 3 months.[3] With an NIHSS ≤5 to define minor stroke, the rates of functional dependency at 1 and 3 months could be up to 30% and 25%, respectively, among 1339 patients in the Mild and Rapidly Improving Stroke Study.[4] Severe cerebral small vessel disease (SVD) and presence of intracranial arterial stenosis seem to associate with more severe disability by mRS at 3 months, according to the imaging-subgroup analysis of the CHANCE trial.[5]

The 1-year rates of composite cardiovascular events and all-cause mortality were respectively 6.2% and 1.8%, and the 5-year risks reached 12.9% and 10.6%, respectively, in 4789 patients with minor stroke or TIA (median age 66 years) enrolled in the TIAregistry.org project in 2009–2011.[6 7] The 1-year rate of composite major vascular events and death reached 15.9% in 40 825 Medicare beneficiaries hospitalised for a TIA in the USA in 2011–2014, with a median age of 80 years.[8] For those with multiple acute infarctions, which usually indicates artery-to-artery embolism in non-cardioembolic strokes, the 1-year rate of ischaemic stroke was 15.2% and a composite of cardiovascular events and vascular death was 17.3%.[9] In addition to conventional vascular risk factors included in commonly used risk stratification tools, higher inflammatory level is also associated with higher risks of stroke relapse in TIA and minor stroke patients.[9] For instance, in a subgroup analysis of the CHANCE trial, TIA and minor stroke patients with elevated high-sensitive C reactive protein (hsCRP, a marker of inflammation) had higher risks of ischaemic stroke (12.5% vs 9.3%) and a composite of cardiovascular events and vascular death (13.6 vs 9.7%) within 1 year, compared with otherwise. Further, a combination of elevated hsCRP and presence of multiple acute infarctions was associated with a highest risk of ischaemic stroke (16.7%) and a composite of cardiovascular events and vascular death (19.0%) within 1 year, in patient groups with different hsCRP levels and numbers of acute infarction(s).[9]

The risk of major bleeding within 5 years after a minor stroke or TIA was 1.5%, including a 1.1% risk of ICH, among 3847 patients in the TIAregistry.org project.[7] Severe cerebral SVD significantly increases the risk of developing ICH. With untreated hypertension, cerebral small vessels develop hyalinosis and small aneurysms that are at risk of causing haemorrhage. In addition, cerebral amyloid angiopathy (CAA) is a common cause of small vessel stroke.[10] While lobar haemorrhage is more likely related to CAA (24%), deep ICHs are likely related to lacunar changes (15%).

Enlarged perivascular space, another sign of SVD, is also related to ICH.[11] In the CHANCE trial, any bleeding was increased in patients with severe SVD treated with either single or dual antiplatelet therapy.[5] Furthermore, anticoagulation in patients with signs of microbleeds or severe white matter hyperintensities on MRI, also signs of SVD, may predispose such patients to ICH by 3–6 folds.[12]

The incidence of postevent dementia at 1 year after minor stroke and TIA were respectively 8.2% (95% CI 6.2% to 10.2%) and 5.2% (95% CI 3.4% to 7.0%), in the population-based Oxford Vascular Study.[13] Compared with the general population in the UK, the prevalence of dementia in 1-year survivors after minor stroke/TIA was brought forward by approximately 4 years in those who had a minor stroke, and 2 years in those who had a TIA.[13] SVD is a well-established risk factor for developing cognitive dysfunction. The underling mechanisms are multifactorial. Microangiopathy causes subcortical ischaemic changes. SVD-related ICH and CAA also predispose patients to long-term cognitive disorders.[14 15]

The best primary and secondary prevention strategies for minor stroke and TIA include management of hypertension, hyperlipidaemia and diabetes, and healthy lifestyles. For instance, targeting the low-density lipoprotein cholesterol (LDL-C) level to be <1.8 mmol/L (70 mg/dL) is recommended to reduce the risk of major cardiovascular events for all ischaemic stroke and TIA of atherosclerotic origin, in the 2021 secondary stroke prevention guideline from American Heart Association/American Stroke Association.[16] Particularly in non-cardioembolic minor stroke and TIA patients, the higher risk of ischaemic stroke in those with higher baseline LDL-C level could be neutralised by lipid-lowering treatment. In the CHANCE trial, baseline LDL-C≥ 2.6 mmol/L was associated with an increased risk of ischaemic stroke in patients without lipid-lowering treatment (adjusted HR 1.35; p<0.001), but not in those with lipid-lowering treatment (adjusted HR 0.99; p=0.91; p for interaction=0.007).[17]

For secondary prevention in minor stroke and TIA patients, aspirin plus clopidogrel for those with high-risk TIA or minor stroke for 21–90 days have been proven effective in two pivotal clinical trials.[18 19] The nation-wide Clinical Research Collaboration for Stroke-Korea registry found aspirin plus clopidogrel effective in lowering the 90-day stroke risk, compared with aspirin or other dual antiplatelet therapies (mostly aspirin plus cilostazol), in over 10 000 minor stroke patients.[20] Among Chinese minor stroke and TIA patients with CYP2C19 loss-of-function alleles (expected to have a diminished response to clopidogrel) in the CHANCE-2 trial, ticagrelor plus aspirin was more effective in reducing 90-day stroke risks than clopidogrel plus aspirin (6.0% vs 7.6%; HR 0.77; 95% CI 0.64 to 0.94; p=0.008), with similar risks of moderate or severe bleeding (0.3% in both treatment arms) but a higher risk of any bleeding (5.3% vs 2.5%).[21] For those with a TIA or minor stroke with an NIHSS score ≤5 in the Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death trial, ticagrelor plus aspirin significantly reduced 30-day risk of stroke or death compared with aspirin alone (5.5% vs 6.6%; HR 0.83; 95% CI 0.71 to 0.96; p=0.02), but with a significantly higher risk of severe bleeding (0.5% vs 0.1%; p=0.001).[22]

In summary, minor strokes are not minor. Patients with a minor stroke have considerable risks of stroke relapse, ICH, cognitive impairment and significant disability. Aggressive control of vascular risk factors and wise use of antiplatelet therapy could help reduce recurrent strokes.

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