Is the future of symptomatic intracranial atherosclerotic stenosis management promising?

Dacheng Liu,[1] Jingyi Liu,[1] Yuan Cai,[1] Ka Sing Lawrence Wong,[2] Liping Liu [1,3]

Intracranial atherosclerotic stenosis (ICAS) is one of most common causes of stroke; it has the highest rate of recurrence compared with other aetiologies.[1] ICAS is especially more prevalent among the Asians.[2] The results of the Chinese Intracranial Atherosclerosis Study indicated that the prevalence of symptomatic ICAS (sICAS) is as high as 46%.[1] The 1-year stroke recurrence rate with sICAS is reported to be 12.2% and 15%.[3 4] We understand, the following pathological reasons could account for the high recurrence rate in sICAS. First, patients with ICAS are prone to encounter hypoperfusion haemodynamics, especially under poor collateral conditions.[5] Studies on the association of blood pressure (BP) control in the acute stage and clinical outcomes are contradictory, supporting this hypothesis.[6] Second, plaques in stenotic arteries are usually highly vulnerable (due to large lipid cores, thin fibrous caps and intraplaque haemorrhage).[7] These plaques are prone to rupture into downstream arteries, leading to embolic stroke in the territory of the responsible artery.[5] Furthermore, these patients are often comorbid with heightened risk factors strongly correlated with stroke recurrence, including hypertension, metabolic disorders, dyslipidaemia.[8]

Therefore, there is an urgent need to standardise assessment and management of sICAS. The treatment of sICAS nowadays primarily focuses on secondary prevention to reduce stroke recurrence. Therapeutic methods include antiplatelet therapy, interventional therapy and control of risk factors.[9] Two milestone trials, the Warfarin Aspirin Symptomatic Intracranial Disease (WASID)[3] Trial and the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)[4] Trial aim to provide an updated strategy for clinical practice.

The WASID Trial, with a double-blind, multicentre, randomised control clinical trial design, aimed to evaluate the efficacy and safety of warfarin over aspirin among patients with 50%–99% degree of ICAS. Aspirin proved to be equally efficient and safer. This led to the investigation of a dual-antiplatelet therapy for secondary prevention in patients with sICAS. The Clopidogrel Plus Aspirin versus Aspirin Alone for Reducing Embolization in Patients with Acute Symptomatic Cerebral or Carotid Artery Stenosis[10] Trial indicated that in patients in the sICAS group, dual-antiplatelet therapy reduced microembolic signals detected by transcranial Doppler ultrasound (TCD) (31% vs 54%, relative risk reduction 42.4%, 95% CI 4.6% to 65.2%, p=0.025) at day 2 of enrolment, which may further reduce the recurrence of artery-origin embolic stroke in these patients. The Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events[11] Trial published in 2013 first verified the benefit of dual-antiplatelet therapy for minor strokes and high-risk transient ischaemic attacks. It showed that combined use of clopidogrel and aspirin started within 24 hours and continued to 21 days was superior to aspirin monotherapy in reducing the risk of stroke in the first 90 days. In the ICAS subgroup analysis,[12] it was found that dual-antiplatelet therapy had a tendency to reduce stroke recurrence over monoantiplatelet therapy at 90 days, but was not statistically significant due to the limited number of participants enrolled.

Interventional therapy beyond the conventional reperfusion therapeutic time window in acute ischaemic stroke (AIS) is considered to modify stenotic status, improve haemodynamics and further reduce stroke recurrence, but its efficacy remains controversial. In the SAMMPRIS Trial, Chimowitz and colleagues[4] attempted to observe whether angioplasty or stenting plus medical therapy is beneficial for patients with sICAS over medical therapy alone. 451 patients with sICAS of 70%–99% stenosis within 30 days of onset enrolled. During the 30-day follow-up, 14.7% in the stenting group reached primary end points of stroke recurrence or death, versus only 5.8% in the medical management group (p=0.002). Interestingly, the authors further analysed the outcome for those patients who met the SAMMPRIS criteria from the WASID Trial:[13] the 30-day and 1-year stroke recurrence and death rates in the WASID Trial are much higher than those in the SAMMPRIS Trial (10.5% vs 5.8%, 21.9% vs 12.6%, respectively, p=0.009). Interpreting the results, the authors found that aggressive control of risk factors and the ideal target in the SAMMPRIS Trial medical group may contribute to the difference. Therefore, aggressive medical treatment is still the main therapeutic strategy for secondary prevention of sICAS.

Despite the emerging research results, there still persist lots of problems and concerns in clinical practice. Risk factor management targets have not yet been verified. Most of the risk factors of sICAS are managed according to SAMPRIS standards: systolic blood pressure (SBP) ≤140 mm Hg (≤130 mm Hg if diabetes), low-density lipoprotein cholesterol (LDL-C) level reduced by 50% or <1.8 mmol/L. Increased SBP is strongly associated with a high recurrence rate in ICAS.[14] However, for patients with AIS with large intracranial vessel stenosis, and potential for hypoperfusion disorders, the ideal BP target and treatment initiation timing remains unclear. It is reasonable to assume that many physicians are cautious about antihypertension treatment in patients with ICAS, especially during the acute stage.

As for dyslipidaemia, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)[15] Trial provided evident reduction in the rate of stroke recurrence with intensive statin therapy. But since SPARCL did not specially focus on patients with ICAS, this result should be interpreted with caution. The significance of statin therapy in reducing stroke recurrence in ICAS has only been reported in observational studies.[16]

Moreover, despite aggressive medical treatment, some patients with sICAS still face a high stroke recurrence rate. Many researchers have attempted to improve current medical treatment strategy. For example, resorting to new antiplatelet agents such as cilostazol[17]

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]Division of Neurology, Department of Medicine and Therapeutics, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China
[3]China National Clinical Research Center for Neurological Diseases, Beijing, China

Correspondence to Dr Liping Liu, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China; lipingsister@gmail.com

J Neurol Neurosurg Psychiatry: first published as 10.1136/jnnp-2019-321564 on 9 January 2020. Downloaded from http://jnnp.bmj.com/ on December 1, 2020 by guest. Protected by copyright.

and ticagrelor.[18] But the efficacy of these antiplatelet medicines hasn't been established yet. Besides, some patients with ICAS fail to have satisfactory lowering of LDL-C with intensive statin therapy. Thus, proprotein convertase subtilisin-kexin type 9 inhibitors, such as alirocumab,[19] which could lower LDL-C levels significantly, could be the alternative choice. But their application in ICAS treatment still has a long way to go.

In addition, the role of surgical methods, such as intervention in sICAS, remains uncertain. Reperfusion therapy has been the first-line treatment for AIS with large artery occlusion within the therapeutic time window, from recent successful randomised controlled trials (RCTs).[20] But for sICAS at the subacute stage, the SAMMPRIS Trial and the Vitesse Intracranial Stent Study for Ischaemic Stroke Therapy[21] Trial failed to prove the importance of priority of stenting over aggressive medical treatment. Some concerns emerged regarding the results of these two trials: participants were selected only through severe stenosis, regardless of their perfusion or collateral circulation status; the relative limited experience of the subcentres; the second-line devices used in these trials may not be ideal for all complex vascular situations. In a recent Chinese sICAS Registry (NCT01968122),[22] all participants were enrolled for hypoperfusion aetiology with poor collaterals within 90 days after onset, and received individualised endovascular treatment. Patients had 4.3% and 8.1% of stroke recurrence at 30 days and 1 year, respectively,[22 23] which is quite lower than in the SAMMPRIS Trial. Despite ethnic differences between various trials, we believe that the results of the Chinese Trial were better mainly due to the highly selective patient enrolment. Future RCTs comparing individually tailored stenting versus medical therapy in a specially selected cohort of patients are particularly needed. Another surgical alternative that should be considered is extracranial-intracranial (EC-IC) bypass surgery. In a recent cohort study,[24] the superficial temporal artery-middle cerebral artery bypass in carefully selected patients with severe intracranial stenoocclusive disease could improve cerebral haemodynamic parameters, which further prevent recurrence of ischaemic stroke during a follow-up of 34 months. However, there is a lack of high-level evidence of an RCT on individual assessment, and the indication and efficacy of EC-IC bypass is still controversial.

Lastly, the process of recognition and assessment of features of ICAS are still under progress. Commonly used methods for vascular and perfusion assessments include TCD, MR angiography, arterial spin labelling, CT angiography, CT perfusion, digital subtraction angiography. Compared with the above imaging methods, high-resolution MRI (HR-MRI), which could provide additional valuable information on the diagnosis of ICAS and plaque, has been further studied and is widely used. HR-MRI could particularly detect plaque components, vessel wall morphology and luminal thrombus.[7] Clinical researchers have considered variation of plaque characteristics on HR-MRI as the primary end points, for further use in clinical practice. Trials detecting the effect of medical therapy guided by HR-MRI in ICAS should be one of the directions in future[25] . Furthermore, recent research on the computational fluid dynamics (CFD)[26] technique providing non-invasive utilisation of dynamic features such as translesional pressure ratio and translesional wall shear stress ratio and clinical relevance of patients with ICAS, might be a promising and helpful guide to a better individualised secondary prevention strategy.

In conclusion, sICAS has been one of the top burdens of stroke, worldwide. Antiplatelet therapy, interventional therapy and control of critical risk factors are the major therapeutic approaches on hand. To further reduce the recurrence of stroke and improve outcome, the potential management strategy could be alternative drugs for antiplatelet and lipid lowering, more precise targets for control of risk factors, and validating particular patients benefiting from interventional therapy. New imaging techniques, such as HR-MRI and CFD, may provide detailed understanding of the pathology and mechanism, significant for governing the risk factors, and reducing risk of recurrent stroke in sICAS. In future, larger-scale studies with more specific patient data are warranted for individualised secondary prevention.

Contributors DL, JL and YC collected data and drafted the manuscript, KW revised the manuscript. LL designed and revised the manuscript.

Funding This work was supported by the National Key R&D programme of China (2016YFC1307301) and National Natural Science Foundation of China (81820108012).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

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Check for updates

To cite Liu D, Liu J, Cai Y, *et al*. *J Neurol Neurosurg Psychiatry* 2020;**91**:122–124.

Received 8 August 2019
Revised 18 November 2019
Accepted 26 November 2019
Published Online First 16 December 2019

Linked

► http://dx.doi.org/10.1136/jnnp-2019-320893

J Neurol Neurosurg Psychiatry 2020;**91**:122–124. doi:10.1136/jnnp-2019-321564

ORCID iD
Liping Liu http://orcid.org/0000-0003-2943-055X

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