Management of carotid artery stenosis

Tsong-Hai Lee, MD, PhD

Acta Neurol Taiwan 2021;30:123-127

EPIDEMIOLOGY OF CAROTID ARTERY STENOSIS

The incidence of both ischemic and hemorrhagic stroke is more common in Asians compared to Caucasian [1]. It is found there is a decreased incidence of ischemic stroke in Northern America but increased incidence in Africa, Mongolia and southeast Asia. In the epidemiological study of carotid artery stenosis (CAS), Framingham study showed the prevalence of significant extracranial CAS was 7% in women and 9% in men [2]. Among all strokes in Caucasian population, 20–30% were due to extracranial CAS and 5–10% due to intracranial atherosclerosis [3,4]. Northern Manhattan stroke study also found intracranial atherosclerosis could be seen in 6–10% of ischemic strokes in white patients, but up to 29% among African Americans and Hispanics [5]. Intracranial artery stenosis was more frequently found in Chinese population than extracranial artery stenosis with the range of 3.7% - 70.4% of intracranial CAS and 1.5% - 49% of extracranial CAS [6]. Intracranial artery stenosis is more common in Asian, Hispanic, and African-American populations. In hospitalized patients with symptomatic intracranial stenosis, it was only 1% in non-Hispanic whites, while 50% in Asian populations. Population-based studies revealed the prevalence of symptomatic intracranial disease was 1 in 100,000 for whites to 15 in 100,000 for African Americans, but 7% of the population aged more than 40 years for Chinese [7]. Concurrent atherosclerosis of extracranial and intracranial arteries was also common in Asians. It was reported 10% to 48% in patients with symptomatic cerebrovascular disease, and 21% of stroke patients had concurrent stenoses in Hong Kong, 33% in China, 18% in Taiwan, and 48% of patients with more than 30% extracranial carotid stenosis had concurrent intracranial stenosis in South Korea [8]. The study of concomitant atherosclerotic arterial diseases showed in patients with ≥50% significant CAS, the most frequent artery was coronary artery disease which was found in 68% of patients, while renal artery stenosis and limb artery stenosis were found in 20% and 21% of patients, respectively [9]. Carotid artery stenosis of 70% or greater was detected in 37.7% patients with cerebrovascular disease, 24.5% patients with peripheral arterial disease, and 11.1% patients with coronary artery disease [10]. Significant extracranial carotid and vertebral artery disease (ECCVD) identified by duplex ultrasonography is not uncommon in Chinese patients with coronary artery disease (CAD), and 22.9% ECCVD was seen in patients with CAD, comparable with that reported in white populations [11]. In our Stroke Registry In Chang-Gung Healthcare System (SRICHS) from 2008 to 2011 (Fig. 1), we found large artery atherosclerosis (LAA) occupied 19.5% of total ischemic stroke patients and 3.1% had concurrent atrial fibrillation [12].

From the Department of Professor of Neurology Linkou Chang Gung Memorial Hospital Taoyuan, Taiwan.
Received August 26, 2020. Revised September 15, 2020.
Accepted October 28, 2020.
Correspondence to: Tsong-Hai Lee, MD, PhD. Professor of Neurology Linkou Chang Gung Memorial Hospital Taoyuan, Taiwan.
E-mail: thlee@adm.cgmh.org.tw.

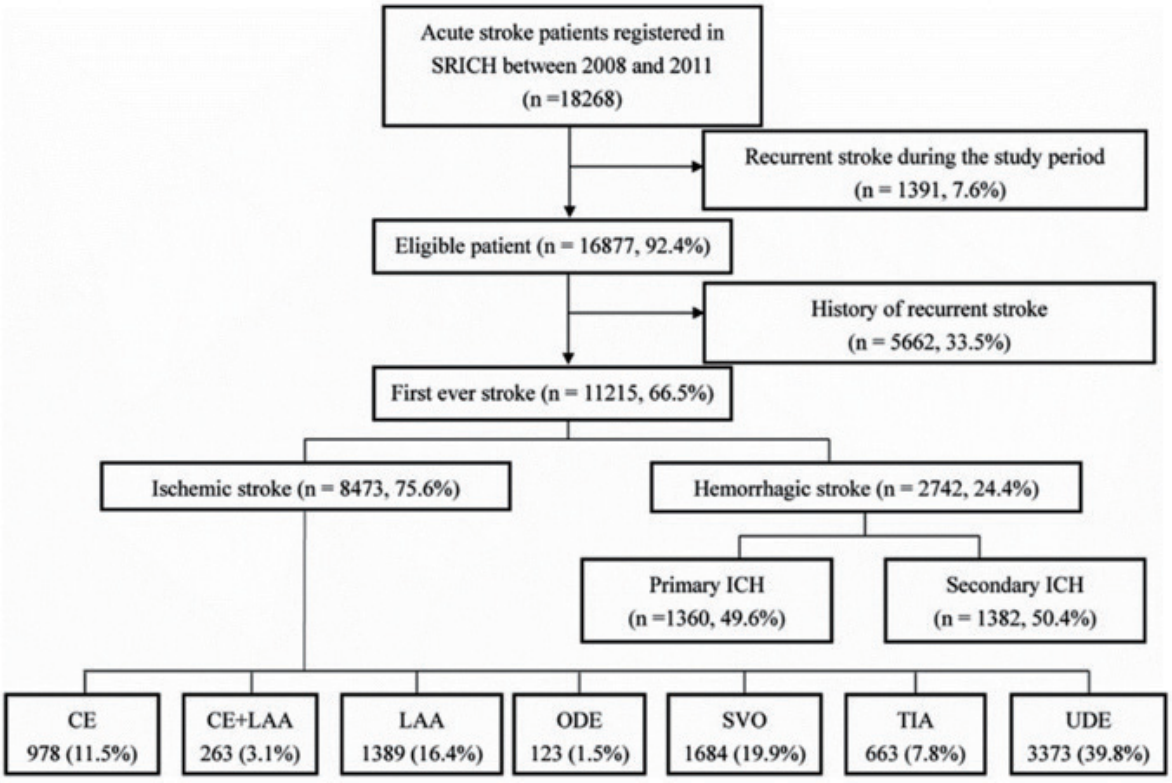

Fig. 1. Flowchart of the study patient selection. Patients with stroke registered in the Stroke Registry of Chang-Gung Healthcare System from 2008 to 2011 are recruited. Patients who have recurrent strokes during the study period and who have a history of previous stroke are excluded. The eligible first-ever stroke patients are analyzed according to stroke subtypes. CE indicates cardioembolism; LAA, large-artery atherosclerosis; LAA + CE, large-artery atherosclerosis and cardioembolism; ODE, stroke of other determined etiology; SVO, small-vessel occlusion; TIA, transient ischemic attacks; UDE, stroke of undetermined etiology; ICH, intracerebral hemorrhage. Reproduced with permission from Liu CH, et al. Angiology 2018.

GENETICS OF CAROTID ARTERY STENOSIS

Stroke is a multi-factorial disease, and the underlying genes and pathways are largely unknown. In a multiancestry genome-wide-association meta-analysis in 521,612 individuals (67,162 cases and 454,450 controls), a total of 32 stroke risk loci were found and 6 (3 novel) loci were associated with LAA with EDNRA and LINC01492 showing the association only with LAA [13]. Our previous genome-wide-association study in an independent Han Chinese population identified 5 single-nucleotide polymorphisms, including rs2415317, rs934075, rs944289, rs2787417, and rs1952706 (Fig. 2), at one novel locus on chromosome 14q13.3 within PTCSC3 (encoding papillary thyroid carcinoma susceptibility candidate 3) and also two other genes, HDAC9 and TWIST1, that were associated with LAA stroke at genome-wide significance [14]. As our previous study on Moyamoya disease (MMD) found atherosclerosis (32.4%) and thyroid disease (29.7%) were the leading coexisting diseases in quasi-MMD [15], we suggest it is possible that PTCSC3 could be a unique gene for intracranial LAA in Han Chinese. Future studies on the role of PTCSC3 in the pathogenesis of intracranial LAA are needed.

CEREBRAL PERFUSION IN CAROTID ARTERY STENOSIS

Amyloid plaque is suggested to be associated with dementia. We used [18F]AV-45, a positron emission tomography (PET) ligand, to bind to extracellular plaques

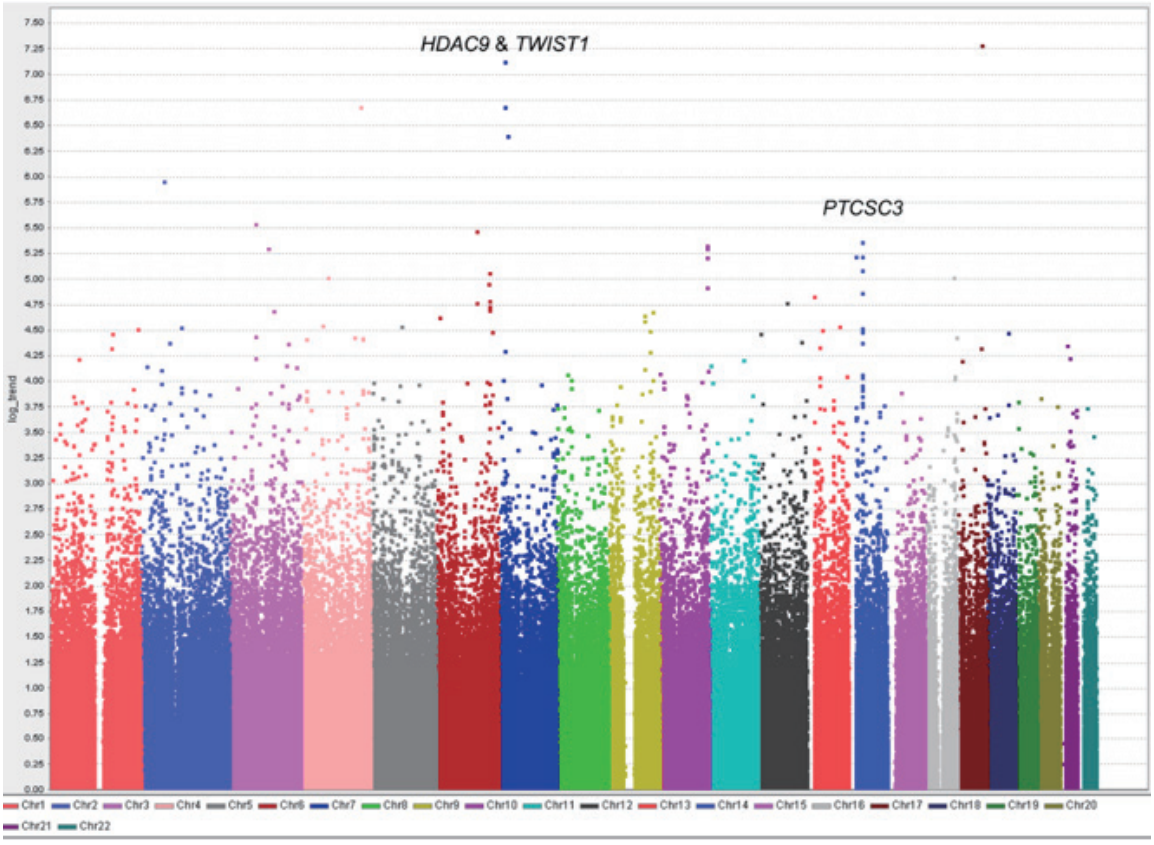

Fig. 2. Results of genome-wide association analysis shown in chromosomal order for 570,275 SNPs tested for association in 8 initial samples from 444 patients with LAA stroke and 1,727 controls. The x axis represents each of the SNPs used in the primary scan. The y axis represents the log10 P value of the trend test. Signals in HDAC9, TWIST1, and PTCSC3 loci are indicated. LAA, large artery atherosclerosis; SNPs, single-nucleotide polymorphisms. Reproduced with permission from Lee TH, et al. J Am Heart Assoc 2016.

(Fig. 3). We found that patients with dementia and unilateral CAS had a higher global [18F]AV-45 SUVR as compared with controls, suggesting that amyloid-related dementia may occur under cerebral hypoperfusion due to CAS [16]. In the study of the association between functional connectivity and cognitive decline in CAS patients, we found that the hemispheres ipsilateral to the CAS were significantly impaired in "degree" and "global efficiency" which was positively correlated with neuropsychological performances, whereas these relationships were not observed in the controls [17]. Our study suggests the analysis of brain connectivity may help to elucidate the relationship between hemodynamic impairment and cognitive decline.

Carotid artery stenting could cause a significant improvement of cerebral blood volume and time-to-peak in the middle cerebral artery territory in patients with unilateral CAS. Patients with reversed ophthalmic flow had better improvement of time-to-peak in both middle and posterior cerebral artery territories than patients with forward flow. Cerebral hemodynamics can be reconstituted within a few days after carotid revascularization, especially in patients with reversed ophthalmic flow. However, cerebral hemodynamics with prolonged time-to-peak in prestenting middle cerebral artery subcortical area may suggest a high risk of poststenting intracerebral hemorrhage [18]. Carotid artery stenting can also cause an increment of cerebral blood flow on the stenotic side, which was found significantly higher in the hemisphere with impaired cerebral vasoreactivity than that in the normal hemisphere. There was a significantly positive correlation between cerebral vasoreactivity impairment

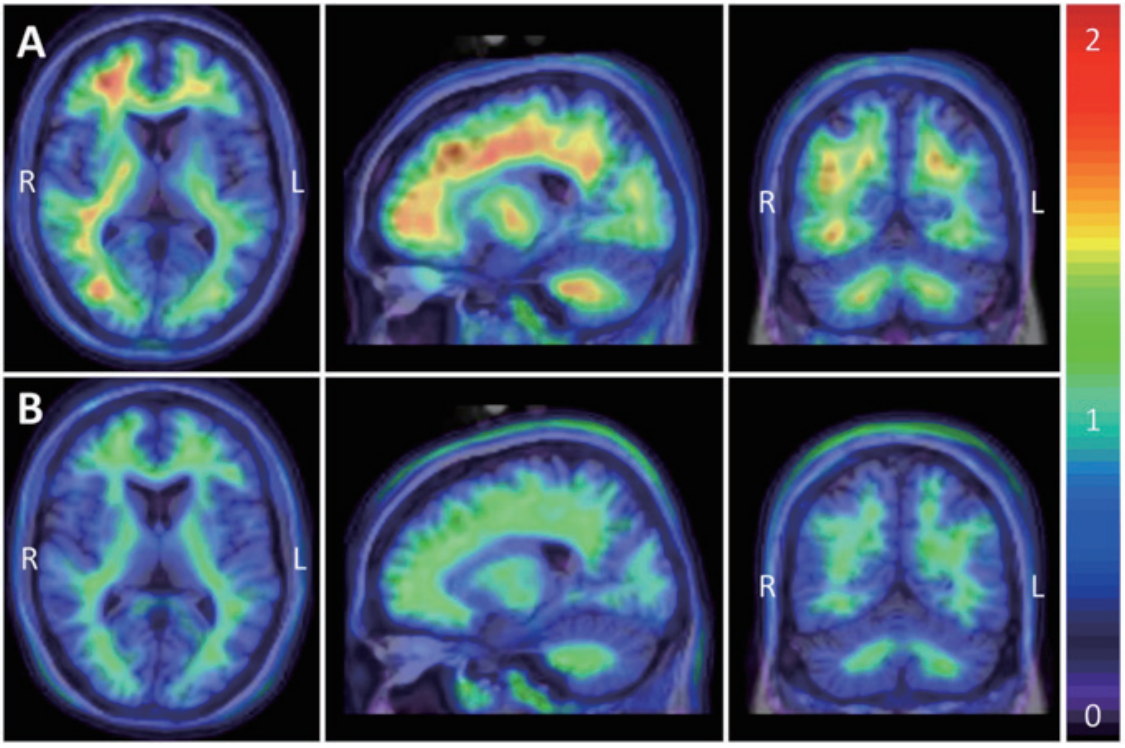

Fig. 3. [18F]AV-45 PET images of demented patients with unilateral carotid artery stenosis (A) and the elderly controls (B). Reproduced with permission from Huang KL, et al. J Neurol Sci 2012.

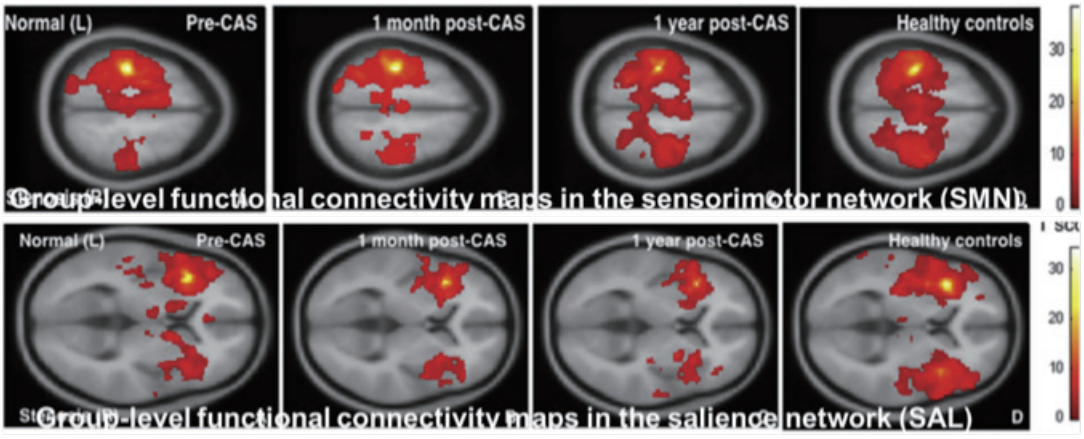

Fig. 4. Group-level functional connectivity maps in the sensorimotor network (SMN, upper column) and salience network (SAL, lower column). Four sets of one-sample SMN and SAL, seeded at left primary motor cortex (M1) and left insula, respectively. From left to right: carotid stenosis patients before carotid artery stenting (A), 1 month after stenting (B), 1 year after stenting (C), and healthy controls (HC) (D). Reproduced with permission from Huang KL, et al. Neuroimage Clin 2018.

and the cerebral blood flow increment [19]. Before carotid artery stenting, functional connectivity may decrease in the cerebral hemispheres ipsilateral but increase in that contralateral to CAS, compared with normal controls. These functional connectivity alterations were associated with poor cognitive performances but tended to recover after carotid artery stenting (Fig. 4), and the hyper-connectivity may serve as a compensation for neural

challenge [20]. The segments in the circle of Willis are not in a static feature and may be opened or closed after carotid artery stenting. Some segments of circle of Willis (A1, P1 and PCoA) may be blocked after stenting, and others may be opened to create a new willisian collateralization, either for relief of reperfusion pressure or for other hypoperfused areas [21].

OUTCOME OF CAROTID ARTERY STENOSIS

The long-term prognosis of patients with CAS is poor, and patients may have high risk of further vascular events or death. Previous study [22] showed the overall 5-year cumulative rates of mortality, re-stroke and poor outcomes were 31%, 41% and 51%, respectively. The corresponding rates were 13, 22 and 31% in patients without concurrent atherosclerosis, but more deaths, re-strokes and poor outcomes were seen in patients with concurrent atherosclerosis. Furthermore, ischemic stroke patients with concurrent stenoses and ischemic heart disease have an even worse prognosis with 5-year cumulative rates of mortality, re-stroke and combined poor outcomes 40%, 50% and 83%, respectively [23]. Our study showed patients with carotid artery stenosis have the highest mortality rate among the stroke subtypes if associated with atrial fibrillation [12].

MANAGEMENT OF CAROTID STENOSIS.

According to the Taiwan stroke treatment guideline, symptomatic CAS is advised to receive interventional treatment, either endarterectomy or stenting, if the stenosis degree is over 60%, while for asymptomatic stenosis, interventional treatment is suggested if over 80%. In the selection of either carotid stenting or endarterectomy for the treatment of extracranial CAS, the study of long-term follow-up of carotid stenting versus endarterectomy over 10 years has revealed there was no significant difference between patients receiving stenting and those receiving endarterectomy with respect to the risk of periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke in patients with CAS [24] or asymptomatic CAS [25]. Also, the postprocedural ipsilateral stroke rate was not different between the two groups. For intracranial artery stenosis, previous clinical trials including SAMMPRIS [26] for intracranial CAS, and VAST [27], VISSIT [28] and VIST [29] for intracranial vertebral artery stenosis have found a significantly higher rate of stroke occurrence in patients treated with stenting within 30 days of treatment compared to medical therapy. Based on SAMMPRIS, the current American Heart Association guidelines for secondary stroke prevention in patients with recent stroke or transient ischemic attack that is attributed to severe stenosis (70%–99%) of a major intracranial artery, dual antiplatelet therapy for 90 days is suggested to be more reasonable than interventional treatment [30]. However, the most recent study, Wingspan Stent System Post Market Surveillance (WEAVE), suggests that with experienced interventionalists and proper patient selection following the on-label usage guidelines, the use of Wingspan stent for intracranial CAS can demonstrate a low periprocedural complication rate and excellent safety profile [31] compared to previous clinical trials.

REFERENCE LIST

1. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: Findings from the global burden of disease study 2010. Lancet Glob Health. 2013;1:e259-281
2. Fine-Edelstein JS, Wolf PA, O'Leary DH, Poehlman H, Belanger AJ, Kase CS, et al. Precursors of extracranial carotid atherosclerosis in the framingham study. Neurology. 1994;44:1046-1050
3. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: A population-based study of incidence and risk factors. Stroke. 1999;30:2513-2516
4. White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, et al. Ischemic stroke subtype incidence among whites, blacks, and hispanics: The northern manhattan study. Circulation. 2005;111:1327-1331
5. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The northern

manhattan stroke study. Stroke. 1995;26:14-20
6. Liu CY, Chen CQ. Intra- and extracranial atherosclerotic stenosis in china: Epidemiology, diagnosis, treatment and risk factors. Eur Rev Med Pharmacol Sci. 2014;18:3368-3379
7. Suri MF, Johnston SC. Epidemiology of intracranial stenosis. J Neuroimaging. 2009;19 Suppl 1:11S-16S
8. Man BL, Fu YP. Concurrent stenoses: A common etiology of stroke in asians. World J Clin Cases. 2014; 2:201-205
9. Wu YW, Lin MS, Lin YH, Chao CL, Kao HL. Prevalence of concomitant atherosclerotic arterial diseases in patients with significant cervical carotid artery stenosis in taiwan. Int J Cardiovasc Imaging. 2007;23:433-439
10. Cheng SW, Wu LL, Lau H, Ting AC, Wong J. Prevalence of significant carotid stenosis in chinese patients with peripheral and coronary artery disease. Aust N Z J Surg. 1999;69:44-47
11. Chen WH, Ho DS, Ho SL, Cheung RT, Cheng SW. Prevalence of extracranial carotid and vertebral artery disease in chinese patients with coronary artery disease. Stroke. 1998;29:631-634
12. Liu CH, Lin JR, Liou CW, Lee JD, Peng TI, Lee M, et al. Causes of death in different subtypes of ischemic and hemorrhagic stroke. Angiology. 2018;69:582-590
13. Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. Nat Genet. 2018;50:524-537
14. Lee TH, Ko TM, Chen CH, Lee MT, Chang YJ, Chang CH, et al. Identification of ptcsc3 as a novel locus for large-vessel ischemic stroke: A genome-wide association study. J Am Heart Assoc. 2016;5:e003003
15. Wei YC, Liu CH, Chang TY, Chin SC, Chang CH, Huang KL, et al. Coexisting diseases of moyamoya vasculopathy. J Stroke Cerebrovasc Dis. 2014;23:1344-1350
16. Huang KL, Lin KJ, Ho MY, Chang YJ, Chang CH, Wey SP, et al. Amyloid deposition after cerebral hypoperfusion: Evidenced on [(18)f]av-45 positron emission tomography. J Neurol Sci. 2012;319:124-129
17. Chang TY, Huang KL, Ho MY, Ho PS, Chang CH, Liu CH, et al. Graph theoretical analysis of functional networks and its relationship to cognitive decline in patients with carotid stenosis. J Cereb Blood Flow Metab. 2016;36:808-818
18. Chin SC, Chang CH, Chang TY, Huang KL, Wu TC, Lin JR, et al. Brain computed tomography perfusion may help to detect hemodynamic reconstitution and predict intracerebral hemorrhage after carotid stenting. J Vasc Surg. 2012;56:1281-1290
19. Chang TY, Liu HL, Lee TH, Kuan WC, Chang CH, Wu HC, et al. Change in cerebral perfusion after carotid angioplasty with stenting is related to cerebral vasoreactivity: A study using dynamic susceptibility-weighted contrast-enhanced mr imaging and functional mr imaging with a breath-holding paradigm. AJNR Am J Neuroradiol. 2009;30:1330-1336
20. Huang KL, Chang TY, Ho MY, Chen WH, Yeh MY, Chang YJ, et al. The correlation of asymmetrical functional connectivity with cognition and reperfusion in carotid stenosis patients. Neuroimage Clin. 2018;20:476-484
21. Chuang YM, Lin CP, Wong HF, Chang YJ, Chang CH, Chang TY, et al. Plasticity of circle of willis: A longitudinal observation of flow patterns in the circle of willis one week after stenting for severe internal carotid artery stenosis. Cerebrovasc Dis. 2009;27:572-578
22. Man BL, Fu YP, Chan YY, Lam W, Hui CF, Leung WH, et al. Use of magnetic resonance angiography to predict long-term outcomes of ischemic stroke patients with concurrent stenoses in hong kong. Cerebrovasc Dis. 2009;28:112-118
23. Man BL, Fu YP, Chan YY, Lam W, Hui CF, Leung WH, et al. Long-term outcomes of ischemic stroke patients with concurrent intracranial and extracranial stenoses and ischemic heart disease. Cerebrovasc Dis. 2010;29:236-241
24. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med. 2016;374:1021-1031
25. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis.

N Engl J Med. 2016;374:1011-1020
26. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011;365:993-1003
27. Compter A, van der Worp HB, Schonewille WJ, Vos JA, Boiten J, Nederkoorn PJ, et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: A randomised open-label phase 2 trial. Lancet Neurol. 2015;14:606-614
28. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: The vissit randomized clinical trial. JAMA. 2015;313:1240-1248
29. Markus HS, Larsson SC, Kuker W, Schulz UG, Ford I, Rothwell PM, et al. Stenting for symptomatic vertebral artery stenosis: The vertebral artery ischaemia stenting trial. Neurology. 2017;89:1229-1236
30. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the american heart association/ american stroke association. Stroke. 2014;45:2160-2236
31. Alexander MJ, Zauner A, Chaloupka JC, Baxter B, Callison RC, Gupta R, et al. Weave trial: Final results in 152 on-label patients. Stroke. 2019;50:889-894