Current Management in Intracranial Atherosclerotic Disease

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Abstract

Intracranial atherosclerotic disease (ICAD) is one of the most common cause of stroke worldwide. Known risk factors are hypertension, hyperlipidemia, smoking and its prevalence also differs among ethnic groups. In the symptomatic group, due to the progressive nature of the disease, treatments primarily aim to prevent stroke and disabilities. In the asymptomatic group, however, its natural history remains largely unknown.

The main therapeutic approach is intensive medical therapy with lifestyle and risk factors modification. Other treatment options are surgical interventions which include endovascular angioplasty with stenting and surgical revascularization. The roles of surgical and endovascular treatments are still controversial due to lack of supporting evidences. Nonetheless, patients who are refractory to medical therapy can benefit greatly from surgical intervention. The purpose of this study is to review the management of ICAD and identify the role of surgical intervention in selected patients. Further studies are required to better identify the patients' conditions and tailor effective treatments as needed.

Keywords: Stroke, Intracranial atherosclerotic disease, Intracranial stenosis (J Thai Stroke Soc. 2022;21(1):26–42)

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การรักษาโรคหลอดเลือดสมองตีบในปัจจุบัน

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บทคัดย่อ

โรคหลอดเลือดสมองอุดตัน (Ischemic stroke) ยังคงเป็นสาเหตุหลักของการเสียชีวิต และพิการของประชากรโลกในปัจจุบัน สาเหตุที่พบบ่อยที่สุด คือ ภาวะหลอดเลือดสมองตีบ (intracranial atherosclerotic disease) โดยปัจจัยเสี่ยงที่สำคัญ ได้แก่ ผู้สูงอายุ การสูบบุหรี่ โรคความดันโลหิตสูง เบาหวาน และภาวะไขมันในเลือดสูง นอกจากนี้ยังพบความเกี่ยวข้องกับกรรมพันธุ์ และเชื้อชาติ การรักษาภาวะหลอดเลือดสมองตีบในปัจจุบัน เป็นการป้องกันการเกิดโรคซ้ำของกลุ่มที่มีอาการ ในขณะเดียวกันยังไม่มีการรักษาชัดเจนในกลุ่มที่ไม่มีอาการ เนื่องจากข้อจำกัดของข้อมูลในกลุ่มดังกล่าว การรักษาในปัจจุบันประกอบด้วยการรักษาด้วยยาละลายลิ่มเลือด และควบคุมปัจจัยเสี่ยง รวมถึงการปรับเปลี่ยนพฤติกรรม ต่อมาได้มีการศึกษาการรักษาด้วยวิธีการผ่าตัด ได้แก่การผ่าตัดต่อหลอดเลือดสมอง (Extracranial–Intracranial (EC–IC) Bypass) และการักษาด้วยการใส่สายสวนหลอดเลือดสมอง (Endovascular treatment) ซึ่งอาจได้ประโยชน์ในกลุ่มที่ไม่ตอบสนองต่อยา เป้าหมายของบทความนี้จึงเป็นการรวบรวมแนวทางการรักษาของโรคหลอดเลือดสมองตีบในปัจจุบัน และสรุปข้อมูลของกลุ่มที่อาจได้รับประโยชน์จากการรักษาด้วยการผ่าตัด

คำสำคัญ: โรคหลอดเลือดสมองตีบ, สมองขาดเลือด, โรคหลอดเลือดสมองอุดตัน (J Thai Stroke Soc. 2022;21(1):26–42)

Introduction

Intracranial atherosclerotic disease (ICAD) is one of the most common causes of stroke worldwide, and is the second most common cause of disability and death. In Thailand, stroke is the highest cause of death for females and third-highest for males of all age groups.[1] Since a stroke has devastating consequences, preventing recurrent stroke has become the primary aim of managing the disease.

Treatments of stroke consist of medical therapy using risk factors modification and surgical intervention which may require in selected patients with evidence of cerebral hypo-perfusion. Although endovascular treatment has become an option over the past few decades with the development of angioplasty and stenting, surgical intervention is in many aspects still controversial as there is no evidence supporting the benefit of bypass surgery (extracranial-intracranial bypass). Nevertheless, the standard treatments for ICAD are still in the process of evolution. This article intends to review and summarize the clinical evidences from recent studies, and update on the best practice for disease management.

Epidemiology and risk factors

Intracranial atherosclerosis is the cause of 30% to 50% of strokes in Asia[2] and 8% to 10% in North America. In Thailand, ICAD was found to be 47% in stroke patients.[3] From most studies, ICAD is particularly most prevalent in Asians, followed by African-Americans, Hispanics, and Caucasians. In 1998, the study showed the prevalence of stroke in Thailand at 690/100,000 of population (age over 20 years)[4] which is estimated to be 2.7% among the elderly (age over 65 years old)[1], with ischemic being 70% to 80%. Stroke is the leading cause of death in Thailand, claiming 50,000 lives annually.[5]

Risk factors for symptomatic and asymptomatic ICAD had age, ethnic group (Asian and black), hypertension, diabetes mellitus, hyperlipidemia, metabolic syndrome, smoking, and sedentary lifestyle.[6] Some studies suggest that biomarkers for intracranial atherosclerosis correspond to the inflammation and plaque formation, e.g. Adiponectin, IL-6, C-reactive protein and matrix metalloproteinase.[7]

Natural history

Symptomatic intracranial atherosclerotic disease

Atherosclerosis is a progressive disease and many studies have established data on the natural history of symptomatic intracranial atherosclerotic disease. A higher degree of stenosis is believed to correlate with a higher recurrence rate of ischemic events.

The GESICA (Groupe d'Etude des Sténoses IntraCrâniennes Athéromateuses symptomatiques) study was a multi-center, prospective trial focused on the natural history of ICAD in patients who were refractory to medication. One hundred and two medical-treated symptomatic ICAD patients with ≥ 50% stenosis enrolled within 6 months after the events, diagnosed either by magnetic resonance angiography (MRA) or traditional angiography. With a mean follow-up of 23.4 months, 38.2% experienced recurrent events, 25% had new transient ischemic attack (TIA) and 14% had ischemic stroke. About 50% of all recurrences occurred within 2 months.[8]

In the WASID study[9], 569 patients enrolled with symptomatic 50% - 99% stenosis within 90 days after ischemic events. During a follow-up of 1 to 8 years, 21% had recurrent ischemic events. However, since the recurrence rate was highest

in a group enrolled within 17 days after the first events, selection bias in timing of enrollment may have affected the incidence of recurrence. WASID results also demonstrated the risk of stroke in stenotic territory was highest with severe stenosis (≥ 70%).

One study comprised 705 patients with acute ischemic stroke who enrolled within 7 days after the onset of ischemic events.[10] At 1 year, the rate of ischemic event was 17.1% for ICAD compared to 24.3% for both intracranial and extracranial atherosclerosis, but with only 10.9% for patients without ICAD. The authors concluded that concurrent extracranial atherosclerotic stenosis was a predictor for higher cerebrovascular events. Another study found via follow-up magnetic resonance imaging (MRI) that 19% of patients with symptomatic ICAD developed a new lesion at 7 months.[11] However, only one-quarter of the patients have had symptoms.

Gao et al. evaluated 114 patients with ischemic stroke in middle cerebral artery (MCA) stenosis. Micro-emboli signals (MES) were detected in 25 (22%) of patients, and were more commonly found in cases with severe stenosis ($p = 0.02$). With a mean follow-up of 13.6 months, the authors found that presence of MES was a predictor of ischemic stroke or TIA.[12]

The Chinese Intracranial Atherosclerosis (CICAS) study evaluated symptomatic cerebral ischemia in 2,864 patients (46% had ICAD) within 7 days of an onset. After 12 months follow-up, recurrence rate of stroke was 3.34% in patients without ICAD, 3.82% for 50% - 69% stenosis, 5.16% for 70% - 99%, and 7.40% for total occlusion.[13]

Asymptomatic intracranial atherosclerotic disease

According the WASID trial, a risk of new ischemic event was 3.5% per year in territories, supplied by 85 asymptomatic stenosis cases.[14] Kern et al. evaluated 102 patients with MCA stenosis, and found the overall stroke risk was 12.5% per year, compared to only 2.8% in asymptomatic group ($p < 0.01$).[15] For symptomatic MCA stenosis, the authors found an 8-fold increased risk for an ischemic event. Borozan et al. also found similar results, in a study comprising 93 patients with 24% symptomatic ICAD. All of the patients had at least 20% intracranial atherosclerotic stenosis. The overall annual stroke risk was 5.1%, but subgroup analysis showed 6.4% in symptomatic and 3.5% in asymptomatic group.[16] Cerebral reactivity impairment was noted to be one of the stroke predictors in asymptomatic ICAD patients. There were 107 ICAD patients (48 had carotid occlusion and 56 had ≥ 70% stenosis) and the mean follow-up was 635 days. Exhausted cerebral reactivity, determined by more than 20% increase in MCA velocity in response to 8% carbon dioxide, was found to be correlated with future ischemic events (11 patients, 6 strokes, and 5 TIAs) for carotid occlusion and stenosis.[17]

In one study in Japan with 2,807 healthy volunteers (mean age 62 years), asymptomatic ICAD was detected in 166 participants (5.9%). Forty-two had moderate stenosis (≥ 50%) and 124 had mild stenosis. The majority was MCA stenosis (110 patients). Mean follow-up time was 64.5 months, in which 32 participants (1.1%) had cerebrovascular events. The risk factors were age, hypertension, and dyslipidemia.[18]

The natural history of asymptomatic ICAD were largely unknown, in spite of data established by various studies. Moreover, the

high-risk features to predict a future ischemic event are yet to be determined.

Pathophysiology of intracranial atherosclerotic disease and mechanisms of stroke

Intracranial atherosclerotic disease is mostly found in patients from 60 to 70 years of age, in contrast to stenosis in the extracranial artery which is usually found years earlier. Commonly affected locations are the anterior circulation, especially the MCA, followed by internal catered artery and posterior circulations. Rarely it is found in cerebellar or communicating arteries.[19]

There are anatomical differences between intracranial and extracranial vasculature. Intracranial vascular structures have denser internal elastic lamina, without an external elastic lamina or vasa vasorum, the latter of which is associated with inflammatory process.

"Athero-" means "fat," and "sclerosis" means "hardening." This process consists of the thickening and hardening of arterial walls, primarily affecting the intima. Pathogenesis of atherosclerosis occurs first by deposition of cholesterol, which subsequently causes dysfunction of endothelium. Afterwards, there will be emigration of smooth muscle cells and the activation of macrophage, engulfing lipid and forms the fibrofatty atheroma, which causes stiffness, loss of compliance of the arteries, and eventually leads to lumen narrowing and thrombosis or embolic events. There are three main mechanisms of stroke related to ICAD.[6, 20] Low-flow hemodynamic impairment (hypo-perfusion), artery-to-artery embolism, and plaque extension over small penetrating arteries or "branch atheromatous disease," or a combination of these mechanisms.

Diagnostic imaging

Mechanisms of the stroke may not be clinically determined but can be discovered by imaging. Infarction pattern noted on MRI would reflect the etiologies.[2] Branch occlusion from a perforator infarction would have created a "perforator pattern" on MRI, where the infarction of the subcortical area is noted. A wedge-shaped territorial infarction would indicate an artery-to-artery embolism. Meanwhile, a watershed distribution or "border zone" pattern of infarction would suggest a hypoperfusion mechanism.

In diagnosing ICAD, the gold standard is a digital subtraction angiography (DSA). Despite being more invasive, DSA is not only able to diagnose, but also identify the quantification of luminal stenosis which is one of the prognostic indicators and the mandate for identifying the severity and make therapeutic judgement.

The Stroke Outcome and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial showed that transcranial doppler ultrasonography (TCD) and MRA yielded highly negative predictive value (86% - 91%) with low positive value (36% - 59%). They concluded that TCD may appropriate for screening but inefficient to confirm the diagnosis or identifying severity. Moreover, the limitation of TCD is dependent on its operator. Meanwhile, MRA showed benefit in identification of degree of narrowing but limit to case with near or total occlusion.[21] Compared to the standard DSA, CTA (computed tomography angiography) has fewer risks, less expensive, and more available where studies showed CTA might be the desirable option for ICAD screening, especially in case with significant intracranial stenosis (≥ 50 % stenosis) in particular.[22, 23] CTA has high negative predictive value in detecting 50-99% stenosis at 73%[22] and

99.8%[23], respectively. Perfusion-based imaging had been recently used to predict future stroke risk which was increase in cases with impaired distal blood flow.[24] Moreover, evaluating of the leptomeningeal collaterals is crucial where rapid filling of distal collateral vessels was related to less stroke recurrence.[25]

High resolution MRI (HR-MRI) can proficiently demonstrate the arterial plaque characteristics, inflammatory activities, and the location of the plaque related to adjacent perforator arteries which help in predicting the progression and prognosis of the disease.[26] Optical coherence tomography (OCT), which had been used with coronary arteries, is now being used with cerebral arteries as well. It has an ability to use low-coherence light from an intra-arterial catheter to capture three-dimensional image of the vessel wall, for identifying plaque and stent apposition.[27]

Treatment of intracranial atherosclerotic disease Antithrombotic therapy (Antiplatelet and anticoagulants)

Aspirin

For decades, antithrombotic therapy has been a mainstay treatment for TIA and stroke. In 2005, WASID trial (Warfarin vs. Aspirin for Symptomatic Intracranial Disease), a multi-center randomized controlled trial, published data comparing warfarin to high-dose aspirin in patients with TIA or intracranial stenosis 50% - 99%. After an early phase with 569 patients, enrollment discontinued. The result showed that warfarin was no better than high-dose aspirin, and with warfarin there was a higher bleeding complication. Despite this shortcoming, however, the failure of warfarin therapy was not the lack of efficacy. In patients who maintained international normalized ratio (INR) at therapeutic window (2.0 - 3.0), the risk of 1-year recurrent stroke was reduced by 5.1% compared to patients with INR < 2.[9] Since the new oral anti-coagulants (NOACs) have comparable efficacy and less bleeding risk than warfarin, future studies comparing NOACs to antithrombotic therapy should be conducted.

Clopidogrel

The benefit of reducing recurrent stroke from a combination of aspirin and clopidogrel was demonstrated in patients with intracranial arterial stenosis in the CLAIR study (Clopidogrel plus Aspirin vs. Aspirin alone for reducing embolization in patients with acute symptomatic cerebral or carotid artery stenosis). The data published in 2010 showed the combined group having higher efficacy in reducing micro-emboli signals from transcranial doppler ultrasound.[28] Advantages of clopidogrel plus aspirin were also shown in SAMMPRIS trial (Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis), a randomized controlled trial published in 2011, studying patients with ≥ 70% intracranial stenosis within 30 days after a stroke event. Risk factors were strictly controlled; systolic blood pressure < 140 mmHg, LDL < 70 mg/dL. They were administered a combination of 75 mg clopidogrel plus 325 mg aspirin for 90 days, then later 325 mg aspirin alone. The results from SAMMPRIS showed 30-day mortality and recurrent stroke was only 5.8% compared to 10.7% from the WASID trial.[14]

In 2013, CHANCE trial (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events) investigated 5,170 patients presented with TIA or minor stroke. Patients were assigned at random either a combination therapy

(clopidogrel plus aspirin) or aspirin alone within 24 hours after onset. Using recurrent stroke within 90 days as a primary endpoint, data showed 8.2% in combination group and 11.7% in monotherapy group (HR, 0.68; 95% CI 0.57–0.81, p < 0.001).[29] Furthermore, in the subgroup of 481 patients with ICAD, combination therapy tended to have more favorable outcome (recurrent stroke at 90 days) but not statistically significant.[30]

Cilostazol

Cilostazol is a phosphodiesterase III (PDE–III) inhibitor, which causes an elevation of cyclic adenosine monophosphate (cAMP) and reduce platelet aggregation. In 2000, Cilostazol Stroke Prevention Study (CSPS) investigated 1,095 patients, comparing 200 mg cilostazol with placebo. Result showed significantly reduced recurrent stroke (relative RR, 41.7%; 95% CI 10.3–62.9, p = 0.0127) with considerable safety.[31] Later in 2010, CSPS 2 trial, a non–inferiority trial in 2,757 patients with non–cardioembolic stroke, compared 200 mg cilostazol to 81 mg aspirin. After a mean follow–up of 29 months, cilostazol was found to have higher efficacy in reducing recurrent stroke (HR, 0.734; 95% CI, 0.56–0.98; p = 0.0357) and had less bleeding complication (HR, 0.458; 95% CI, 0.296–0.711; p = 0.0004).[32]

In the Trial of Cilostazol in Symptomatic Intracranial Stenosis I (TOSS I) published in 2005, 135 patients were either given 200 mg cilostazol plus 100 mg aspirin, or aspirin alone. Primary endpoint was measured by the progression of symptomatic stenosis using MRA, and the secondary outcome with TCD. Result showed no hemorrhagic complication in both groups. The combination group (cilostazol plus aspirin) had a progression of disease at 6.7% compared to 24.4% in aspirin alone. The authors concluded that cilostazol in combination with aspirin was beneficial in reducing progression of symptomatic intracranial stenosis (p = 0.008).[33]

In 2011, TOSS II studied 457 intracranial arterial stenosis patients, comparing a combination of 200 mg cilostazol plus 75 – 125 mg aspirin to 75 mg clopidogrel plus 75 – 125 mg aspirin. Primary outcome was measured by the progression of symptomatic stenosis using MRA, and secondary outcome measured by new lesion from MRI. Results showed no significant difference between two groups in terms of efficacy, cardio vascular events, and hemorrhagic complication. However, the results were not measured by clinical outcome.[11] A recent study by CSPS.com was conducted in 2019. It was an open–label, randomized controlled trial. 1,884 patients with high–risk non–cardioembolic stroke and intracranial arterial stenosis ≥ 50% were divided into four groups. Two groups received monotherapy (81 – 100 mg aspirin, or 50 – 75 mg clopidogrel) and two groups received dual therapy (200 mg cilostazol plus either aspirin or clopidogrel). Results showed that dual therapy group had higher efficacy in stroke reduction (HR, 0.49; 95% CI, 0.31–0.76; p = 0.001), with less severe bleeding complication but not significant statistically.[34] However, the studies of cilostazol were mainly conducted in Asian population and thus cilostazol is not yet widely accepted or recommended by the American Heart Association (AHA) guidelines 2014.[35] However, recent studies on anti–platelet therapy especially for Cilostazol and Ticagrelor were published after that and according to the AHA guideline of 2021, the recommendations for ICAD are as follows[36]

- For patients with recent stroke or transient ischemic attack (within 30 days) that is attributed to severe stenosis (70% – 99%) of a major intracranial artery, addition of clopidogrel

75mg/day to aspirin for 90 days is reasonable (Class IIa, Level B)

• For symptomatic major intracranial arterial stenosis (50%–99%), consider 325 mg aspirin over warfarin (Class I, Level B) and may consider additional cilostazol 200 mg/day to aspirin or clopidogrel (Class IIb, Level C)

• Addition of Ticaglelor 90 mg twice daily to aspirin for up to 30 days might reduce the stroke risk (Class IIb, Level B) in patients with recent (within 24 hours) minor stroke or high-risk TIA with concomitant ipsilateral >30% stenosis of major intracranial artery or symptomatic major intracranial arterial stenosis (≥ 50%),

Risk factors modification

Hypertension, diabetes mellitus, and dyslipidemia are all significant risk factors for a stroke. According to the SAMMPRIS trial, an intensive risk factors modification comprising blood pressure < 140/90 mmHg (<130/80 mmHg if diabetic), low-density lipoprotein < 70 mg/dL, and blood sugar control including lifestyle change had a large impact on stroke reduction. Additionally, post-hoc analysis showed 40% reduction in stroke recurrence after achieving physical activity target.[23] There are various recent studies on targeted therapy on inflammatory cascade of atherosclerotic disease, although they are mainly focused on coronary heart disease.[37, 38]

Surgical or endovascular treatments

Stenting

Angioplasty was used for treatment of recurrent stroke in ICAD but due to high rate of complications, the stents, which has been recognized in coronary diseases, are now being used in treating ICAD instead.[20] Wingspan stent was approved by FDA in 2005 with the following on-label criteria, age 22 – 80 years old, symptomatic intracranial atherosclerotic stenosis of 70% – 90% and had ≥ 2 strokes in vascular territory of stenotic lesion, with at least one stroke while on medical therapy.

In the SAMMPRIS trial, usage of wingspan stent was compared with dual antiplatelet therapy plus intensive risks control. While the study was halted after 451 patients enrollment, result showed 30-day mortality rate of 14.7% in stenting group and 5.8% in the medical therapy group.[14] The trial faced criticisms for its enrollment of off-labeled patients, the operators' level of experience, and stent placement within 7 days of a stroke which current reports suggest an increased risk. However, the 30-day stroke-related death was lower in the stenting group, at 2.2% in contrast to 6.2% in medical group. This result may indicate a possible benefit of stenting if a lower complication rate can be achieved.[39]

WEAVE trial (Wingspan Stent System Post Market Surveillance), published in 2019, studied 152 patients with ≥ 70% stenosis and compared stenting with medical therapy. Unlike SAMMPRIS trial, WEAVE trial enrolled only on-label cases, employing more experienced operators, and performed stenting only after 7-days post stroke events. Results showed only 2.6% periprocedural complication rate at 30 days.[40] The National Institutes of Health (NIH) registry for wingspan stent study group revealed that complications were associated with posterior circulation stenosis and placement of stent within 10 days after a stroke.[41] Furthermore, the AHA guidelines suggest that for patients with severe stenosis (70% – 90%), endovascular procedures (both angioplasty and wingspan stent) are not recommended for initial treatment (Class IIb, Level C).[36, 42] Therefore, in patients who suffer

from acute, recurrent stroke despite medical therapy and intensive risk factors modification, endovascular treatment may find its place to shine in selected patients.

However, this does not mean that intracranial stenting is immediately favorable when the patients are refractory to medical therapy. Whether or not the patients will benefit from the procedure, several factors must also be considered; the anatomy of vessels (e.g. wall pathology and tortuosity), plaque characteristic, and mechanisms of the stroke.

Direct cerebral revascularization

The purposes of cerebrovascular bypass surgery are either flow augmentation, to assist the blood-flow for cerebral hemodynamic impairment, e.g. intracranial arterial stenosis, moyamoya disease, or preventive bypass in complex cerebrovascular diseases or flow preservation, e.g. in complex intracranial aneurysms, or a skull-base tumor surgery.

The international extracranial-intracranial (EC-IC) bypass trial, published in 1985, was the first study of flow augmentation surgery in ICAD patients. It failed to indicate the benefit of surgery over medical therapy. No significant difference was found in recurrence rate of stroke at an average follow-up duration of 55.8 months, which was 31% in surgical and 29% in medical group.[43] Despite the result, an interest was sparked, focusing on what were the best criteria to select patients for surgery.

According to the stages of cerebral hemodynamic impairment, stage II hemodynamic failure, or "misery perfusion," is characterized by a loss of cerebrovascular reserve and an increase in oxygen extraction fraction (OEF). If the cerebral perfusion pressure (CPP) is reduced to the point where both cerebral autoregulatory vasodilation and OEF are in decline, then ischemia occurs. In 1988, St. Louis Carotid Occlusion Study (STL-COS) by Grubb et al. found that a stage II hemodynamic failure, determined by increased OEF using positron emission tomography (PET), that is distal to a symptomatic extracranial internal carotid artery (ICA) occlusion was a predictor for subsequent ischemic stroke. With 26.5% ipsilateral stroke at 2 years, compared to 5.3% in patients without stage II impairment.[44] Previous studies had also established that EC-IC bypass surgery can improve and normalize hemispheric OEF ratio.[45, 46]

A subsequent study, the Carotid Occlusion Surgery Study (COSS), was a prospective, multi-center randomized trial that enquired whether a superficial temporal artery to middle cerebral artery (STA-MCA) bypass is superior to medical therapy in stroke prevention. Patients with ipsilateral to contralateral hemispheric OEF ratio > 1.13 were enrolled (derived from retrospective STLCOS subgroup analysis identifying high-risk patients). COSS was halted after it had enrolled 97 patients in surgical and 98 in medical group. The 2-year ipsilateral stroke rate for surgical group was 21% while the medical group was 22.7% ($p = 0.78$), but perioperative ipsilateral stroke (within 30 days) in surgical group was 14.4% compared to medical group's 2%, excluding the benefit of surgery from the final results.[47]

The first study to demonstrate benefits of EC-IC bypass in stroke prevention was published in 2006 by the Japanese EC-IC Bypass Trial (JET), a multi-center randomized controlled trial. Patients enrolled were with at least grade I cerebral hemodynamic impairment, with a total of 196 patients equally divided into surgical and medical group. after 15 months

follow-up, they found significant reduction of major stroke and death; 5.1% in surgical compared to 14.3% in medical group.[48] The indication for surgery was cerebral blood flow (CBF) < 80% and cerebrovascular reserve (CVR) < 10%. However, no 30-day endpoint data was published. Subsequently, the JET-2 study aimed to determine the true threshold for risk of future stroke. All patients had CBF > 80% and CVR > 10%, and the authors stratified patients according to their CBF and CVR values into four groups. Between these groups, no difference in endpoint was found. Nonetheless, comparing the endpoint rate of JET-2 to the medical group from JET study there were major differences. Primary endpoint (stroke, death, MI) was 7.0% in JET-2 and 16.6% in the medical group of JET (p = 0.02). Secondary end point (ipsilateral stroke) was 3.9% in JET-2 and 10.3% in the medical group of JET (p = 0.04).[49]

The authors concluded that resting CBF < 80% and CVR < 10% were the threshold of hemodynamic compromise. For patients indicated for surgery, EC-IC bypass is unlikely to benefit those with rest CBF > 80% or CVR > 10%.[49] Moreover, for 50% - 99% stenosis patients with stroke or TIA, EC-IC bypass surgery is not recommended (Class III, Level B).[35, 36]

Depending on mechanisms of the stroke, flow augmentation surgery should prove beneficial in patients with hypoperfusion or low-flow hemodynamic impairment. There are still no studies to established the relationship between treatments and various stroke etiologies. Therefore, these data should be focused on as they may be the answer to inconsistent results among various ICAD studies.

Indirect cerebral revascularization

Indirect cerebral revascularization has proven its benefits in moyamoya patients, but is still largely ineffective on non-moyamoya vasculopathy due to the absence of angiogenic milieu.[50, 51] Recently published in 2020, phase II data from the Encephaloduroarteriosynangiosis revascularization for Symptomatic Intracranial Arterial Stenosis (ERSIAS) trial comprising [52] patients, showed that patients treated with encephaloduroarteriosynangiosis (EDAS) surgery had significantly lower rate of recurrence at 11%, compared to 37% from the medical group of SAMMPRIS which had comparable population (OR, 0.21; 95% CI, 0.05-0.84; p = 0.02).52 Among 52 patients, 35 were presented with stroke and amidst these 35 patients, 28 had border-zone pattern infarction. 15 (54%) had exclusive border-zone ischemia, while the other 13 (46%) had mixed pattern that included border-zone type. Absolute risk reduction was 26%. The authors proposed that EDAS may generate new collaterals to ischemic territories. Despite the small number of participants, the results were encouraging, and may further support the use of flow augmentation surgery to help patients with cerebral hypoperfusion who also have border-zone pattern infarction. Further studies should be conducted with larger population and longer follow-up time to determine the benefits in preventing stroke and complications between direct and indirect cerebral revascularization. Major trials in surgical therapy and endovascular stenting are listed in [Table 1.].

Table 1. *Major clinical trials in surgical therapy and endovascular stenting in intracranial atherosclerotic stenosis.*

Surgical trials	Year	Sample size	Intervention	Mean follow-up time	Outcome
International cooperative study of extracranial / intracranial arterial anastomosis (EC-IC Bypass)[43]	1985	1,377	STA-MCA bypass vs. medical therapy	55.8 months	No difference in rate of stroke
The Carotid occlusion surgery study (COSS) [47]	2003	195	STA-MCA bypass vs. medical therapy	2 years	No difference of 2-year stroke rate but surgical group carried more 30-day perioperative stroke
Japanese EC-IC bypass (JET) study[48]	2006	196	STA-MCA bypass vs. medical therapy	15 months	Major reduction of stroke in surgical group
Japanese EC-IC bypass-2 (JET-2) study[49]	2015	132	STA-MCA bypass vs. medical therapy	2 years	Lower rate of recurrence stroke compared to medical arm of JET study
Encephaloduro-arteriosynangiosis Surgery Averts Stroke in Atherosclerotic Patients with Border-Zone Stroke (ERSIAS)[52]	2020	52	Indirect cerebral bypass vs. medical therapy (SAMMPRIS cohort)	Phase II trial preliminary reported	Lower rate of recurrence stroke in surgical group compared to historical control
Stenting trials					
Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS)[14]	2011	451	Angioplasty with stenting vs. medical therapy	11.9 months	Higher 30 days stroke and death rate in stent group

Surgical trials	Year	Sample size	Intervention	Mean follow-up time	Outcome
The Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT)[53]	2015	112	Balloon-expandable stent vs. medical therapy alone	12 months	Increased 30-day and 12 -months risk for stroke or TIA in stent group
Vertebral artery stenting trial (VAST)[54, 55]	2015	115	Stenting vs. medical therapy	12 months	More adverse outcome in stent group and stenting did not lower risk of stroke
Stenting for symptomatic vertebral artery stenosis (VIST)[55]	2017	182	Stenting vs. medical therapy	3.5 years	Stenting did not lower risk of stroke
Wingspan Stent System Post Market Surveillance (WEAVE)[40]	2019	152	Single arm wingspan stenting	72 hours post procedure	Low periprocedural complication for stenting

Discussion

Controversy in management makes Intracranial atherosclerotic disease (ICAD) the topic of interest. From literatures review, these conditions are common problem in Asian population (30%-70%). Most of the negative results for surgical intervention were conducted in either Europe or America, meanwhile results from Japan showed benefit of revascularization intervention in selected patients.

Regarding the pathophysiology of ICAD, there are multiple mechanisms of stroke. Branches occlusion, embolic phenomenon, hypo-perfusion and combined mechanisms. In our opinion, difference mechanism needs its own distinct management. Therefore, mechanism of the stroke in individual patients are to be defined. For instance, ICAD patients with hypo-perfusion stroke may benefit from revascularization. Nevertheless, studies for exact benefit of surgical revascularization (low or high-flow bypass) in these conditions are needed particularly with patient selection. Although the role of surgical intervention in stroke treatment is limited and still under enquiry, a growing list of evidences supporting their benefits has expanded substantially, particularly endovascular treatment with wingspan stent. These procedures may be the future trends due to emerging technologies which could reduce the perioperative complications.

Technological developments such as high-resolution MRI, and knowledge such as vessels wall pathology have helped to identify lesion characteristics and predict any subsequent

stroke. Following developed imaging modalities, we can clearly define the pathophysiology of ICAD where suitable treatment could be guided. For treatment, antithrombotic therapy together with intensive risk factors modification are still the anchor of therapeutic options. Aspirin combined with Clopidogrel show promising result in severe ICAD patients (≥ 70% stenosis) with acute stroke. Data on Cilostazol are emerging and becoming more widely used, although primarily in Asian population. Other potential antiplatelet agents and targeting biomarkers are under investigation. Further studies on antiplatelet regimens with distinct stroke mechanisms, population, and duration of dual antiplatelet are required.

Nonetheless, previous ICAD studies often incorporated varied stroke etiologies, different population, and assortments of therapeutic options. In our opinion, further studies with a focus on Asian population, mechanisms of stroke in an effort to create evidence for suitable treatment in each individual patient are to be performed.

Conclusion

ICAD is a progressive disease leading to devastating consequences and, despite the progress made in both diagnostic and treatment methodologies, it remains the major cause of stroke and disabilities worldwide. Presently, there is still inadequate data on the natural history of the disease, and no consensus regarding the best treatment procedure. A proper management should be tailor-made according to the patient's baseline characteristics, stroke etiologies, mechanisms, and severity of stenotic lesions.

Knowledge gaps and future research

Despite standard medical therapy for intracranial atherosclerotic disease, current studies showed growing evidences in benefit of revascularization surgery in highly-selected patients. However, further researches in identification of high-risk medical refractory patients where surgical intervention might be advantage are needed with emerging imaging technologies to determine individual stroke mechanism and prediction of stroke recurrence.

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