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Research Article

Intracranial Atherosclerotic Stenosis: An Up-to-Date Review

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Abstract

In this review, we discuss recent clinical assays that have contributed to understanding the disease process associated with ICAD, risk factors associated with CVA recurrence in this subgroup of patients, imaging characteristics related to the prognosis, and an update on the treatments that reduce CVA recurrence.

Key words: intracranial atherosclerotic stenosis; cerebrovascular accident; ischemic stroke

Abbreviation

ICAD: intracranial atherosclerotic disease

CVA: cerebrovascular accident

IS: ischemic stroke

TIA: transient ischemic attack

TCD: transcranial doppler

MCA: middle cerebral artery

MRA: magnetic resonance angiography

A-ICAS: asymptomatic intracranial atherosclerotic stenosis

S-ICAS: symptomatic intracranial atherosclerotic stenosis

CTA: computerized tomography angiography

DSA: digital subtraction angiography

HRMRI: high-resolution magnetic resonance imaging

ICA: internal carotid artery

AMT: aggressive medical treatment

PTAS: percutaneous transluminal angioplasty and stenting

PTA: percutaneous transluminal angioplasty

ICH: intracerebral hemorrhage

ACA: anterior cerebral artery

PCA: posterior cerebral artery

EICS: elective intracranial stenting

Introduction

Cerebrovascular accidents (CVA) or strokes are one of the main mortality and morbidity causes around the world. Large-vessel atherosclerosis represents 20% of ischemic strokes (IS), 50% are intracranial, and it is associated with a high risk of recurrent CVA compared with other CVA subtypes, despite even the best medical care [1]. Intracranial atherosclerotic disease (ICAD) is one of the main causes of IS, representing almost 5-10% of intracranial atherosclerotic strokes in the USA, and up to 50% in Asia [2].

Materials and Methods

A search was made in the databases of PubMed (http: //www.ncbi.nlm.nih. Gov / PubMed / medline.html), OVID (http://www.ovid.com/), Ebsco (http : //www.ebsco.com) with the following terms: intracranial atherosclerotic disease, ischemic stroke,

symptomatic intracranial atherosclerotic stenosis, medical treatment, endovascular treatment

Epidemiology

ICAD causes between 5 and 10% of IS in white people, between 20 and 30% of transient ischemic attacks (TIA) or CVA in black people, and up to 30 to 50% of CVA in Asian people (3)(4). From a total of 900,000 CVA or TIA that occur each year in the USA, approximately 70,000-90,000 are caused by intracranial atherosclerotic stenosis [3,5]. The risk of recurrent CVA in these patients could be as high as 15% per year [6,7], and on other studies in patients with high-grade S-ICAD (stenosis: 70-99%), up to 23% per year despite aggressive antithrombotic therapy and standard vascular risk factor management [8,9]. Due to this elevated recurrence rate, there are alternative therapeutic options for the prevention of recurrent CVA in patients with severe ICAD that do not respond to medical treatments such as balloon angioplasty or stent placement [9,10].

Risk Factors

Symptomatic and asymptomatic ICAD risk factors include:

-Age

-Race: Afro American, Hispanic, and Asian compared to white people. [4,11].

-Cardiovascular risk pathologies:

*High blood pressure: In the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) study, the most important modifiable risk factor that increases the risk of recurrent CVA and cardiovascular events (acute myocardial infarction and vascular death) associated with ICAD is high blood pressure (Systolic arterial pressure ≥ 140 mm Hg, HR= 1.79, p = 0.0009) [12].

*Diabetes Mellitus: High levels of A1C hemoglobin are not correlated to the severity of the ICAD, but diabetes mellitus remains as an independent risk factor [13].

*Hyperlipidemia: Those that are associated to a higher risk of recurrent CVA and ICAD progression are: total cholesterol serum levels ≥ 200 mg/dl (WASID study: Warfarin Aspirin Symptomatic Intracranial Disease, HR= 1.44, p = 0.048) (5)(12), increase in the apolipoprotein B (apoB)/apolipoprotein A-I (apoAI) rate (TOSS-2 study: Trial of cilOstazol in Symptomatic intracranial Stenosis 2), decrease in serum levels of high-density lipoprotein cholesterol- HDL [14].

*Metabolic syndrome [15,16].

-Sedentary lifestyle and diet [17]

-Smoking [18].

-Morphological characteristics of the stenosis: The risk of CVA in the territory of the stenotic artery was higher in severe stenosis ≥ 70% (HR= 2.03, p = 0.0025) [19].

-Collateral circulation: The presence of good collaterality in patients with stenosis ≥ 70% decreases the risk of recurrent CVA, making the extension of collaterality a predicting factor of CVA in asymptomatic arterial territory (HR= 4.36, p = 0.0001) [20]. Collateral circulation is a potent determinant of the risk of CVA in ICAD, evidencing a protective role with severe stenoses and identifying more unstable minor stenoses (50-69%).

Biomarkers

Other biomarkers associated with a higher risk of recurrent CVA or ICAD progression are (21)(22)(23):

-Reduction: adiponectin

-Increase: phospholipase-A2 associated with Lipoprotein-Associated Phospholipase A [2] (Lp-PLA2), C-reactive protein (CRP), Plasminogen activator inhibitor-1 (PAI-1), and lipoprotein (A).

Physiopathology of CVA in ICAD

The three main physiopathological mechanisms of ICAD-related CVA include [24]:

1. Hemodynamic: Distal hypoperfusion (ischaemic infarcts in a watershed distribution on brain imaging)
2. Embolic: artery-artery (distal wedge-shaped territorial infarct or multiple cortical infarcts on brain imaging)
3. Branch atheromatous disease: extension of the atherosclerotic plaque to the ostium of small perforating arteries (lacunar infarctions on brain imaging)

These CVA mechanisms in the ICAD context can happen in isolation or combined, Caplan and Hennerici [25,26] suggested interrelated and complementary occurrences of hypoperfusion and embolia, stating that the decrease of distal arterial perfusion to high grade stenosis limits the capability of the embolus formed in the stenotic atherosclerotic area to be washed out of cerebral circulation, and thus, lead to accumulation in the regions of less perfusion pressure, i.e., in the areas of terminal supply and border zone areas [25].

The mechanism of initial CVA inicial in the context of ICAD is a predictor of the CVA subsequent physiopathological mechanism or the risk of recurrence. The risk of recurrent CVA in patients who presented a lacunar CVA in the WASID study was 18%, which is higher than expected of ICAD were an unrelated asymptomatic spectator [27], compared with the annual recurrence rate after a lacunar CVA in a population study that was 2% to 3%.

Some studies have evaluated the correlation between the CVA pattern (hemodynamic, artery-artery embolic, or branch or performing vessel atheromatous disease) with CVA recurrence rates in relation to anatomy, distribution, and the presentation of underlying stenosis. As such, basilar artery stenosis has more probability of presenting as a performing vessel CVA, and less probability or recurring. Patients with suboptimal medical treatments have double the probability of suffering a recurrent CVA. Among patients with optimal medical treatment, no recurrent CVAs were observed with an embolic artery-artery pattern, while there was a recurrence rate of 57% in patients with a watershed infarct pattern. We suggest that CVA due to ICAD with a hemodynamic mechanism could respond less to medical therapy, while ICAD caused by the destabilization of the plaque or in perforating territories could benefit from aggressive medical therapy and late or step by step endovascular treatment [28].

Some patients with ICAD present a lacunar type CVA fairly close to the ICAD, which poses the question of whether the infarction is caused by the stenosis or if it is a result of a small perforating vessel disease coexisting with asymptomatic ICAD. In the latter, a low risk of recurrent CVA in the territory of the stenotic artery could be expected, while for the former, a higher risk could be expected. The distinction between these two scenarios could be relevant to characterize the physiopathology, and more importantly, to determine the prognosis and treatment [29,30].

Khan et al [30] assessed the probability of a lacunar CVA lacunar vs a recurrent non-lacunar posterior to a first lacunar CVA secondary to ICAD, and they concluded that in patients with symptomatic ICAD (S-ICAD), the risk of recurrent CVA was similar among patients who started with lacunar or non-lacunar CVA (recurrence risk with lacunar index event 18% vs non-lacunar 22%, HR 0.79), and the recurrent CVA in patients who stated with lacunar CVA was typically non-lacunar and distal to the stenotic intracranial artery.

Diagnosis: The Role of Imaging

Diagnostic tools used to identify ICAD include:

Non-invasive methods:

- Transcranial Doppler (TCD): It is superior when providing flow information in real time and evidencing the direction of flow, collaterality, embolization (microembolic signs are an independent predictor of recurrence of CVA in patients with S-ICAD), and steal phenomenon, compared with static CT and MRA images [31]. It is useful for the standardized exploration protocol of Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) criteria to identify stenosis ≥ 50% stenosis. The optimal combined criteria for stenosis ≥ 70% were MCA average velocity >120 cm/s, or a stenosis/pre-stenosis ratio ≥3, or average-low velocity. In vertebral artery/basilar artery it varies >110 cm/s or stenotic/prestenotic ratio ≥ 3 [32].

- Magnetic resonance angiography (MRA): TOF-MRA is a flow sequence, accentuating hemodynamic characteristics and, as such, it generally overestimates the grade of stenosis, especially in cases with low distal flow to the ICAD location. The advantage of this sequence is that it makes it possible to evaluate the hemodynamic impact of the lesion [33].

Measurement techniques like the WASID Measurement Technique have been developed. Two measurements for each intracranial ACI are taken: 1) a linear measurement at the location of the most severe stenosis in the images either the MIP or axial source images; and 2) a linear measurement of the widest normal, non-tortuous portion of the petrous ACI parallel to the location of the stenosis. Using these measurements, we calculated the WASID grade of stenosis using the following equation (Figure 1): Percentage of stenosis = [(1 - [D stenosis / D normal])] x 100, where D stenosis is the diameter of the artery at the location with the most severe grade of stenosis and D normal is the diameter of the proximal artery in its widest, non-tortuous normal segment [34].

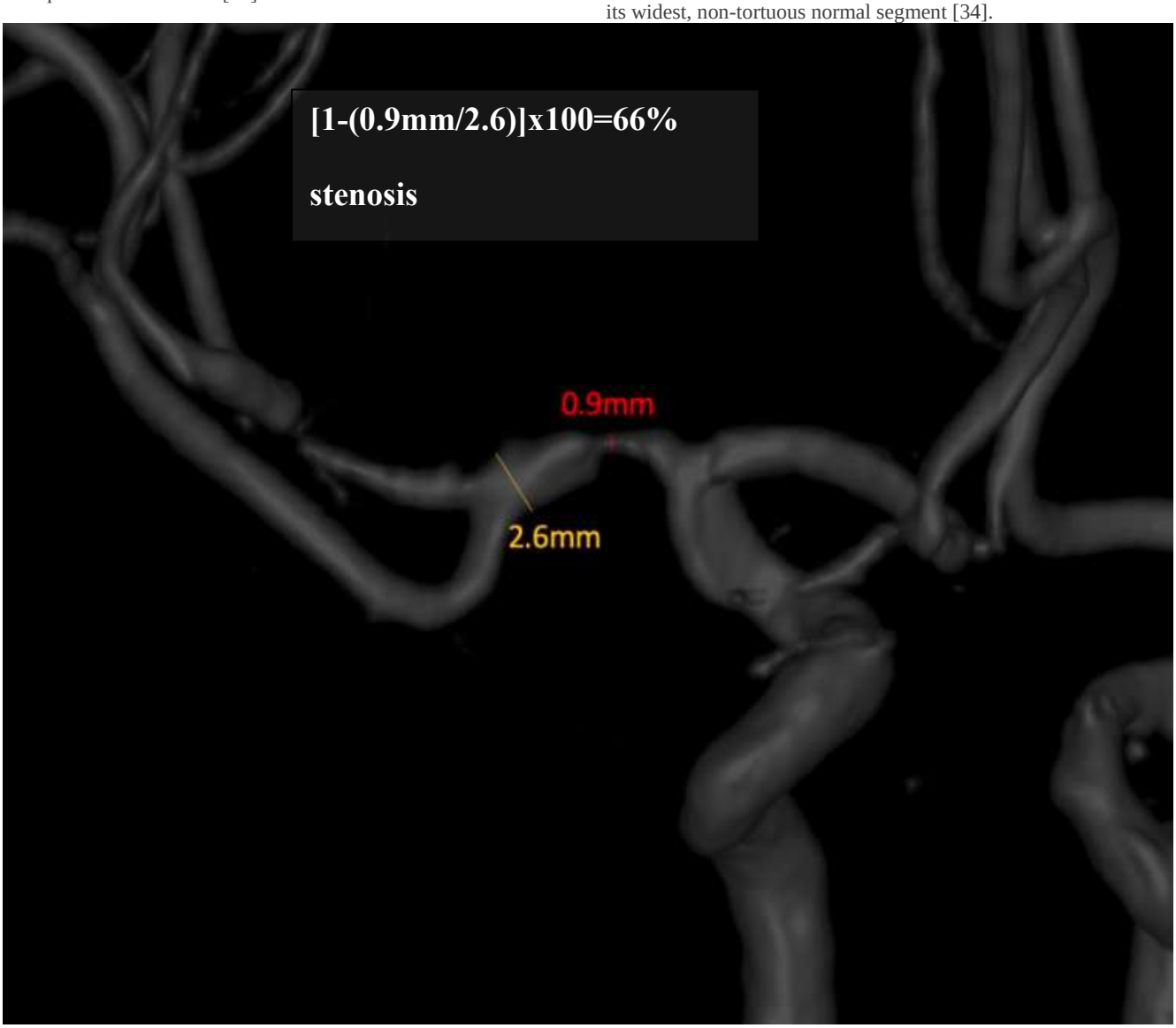

Figure 1: *WASID Measurement Technique: MRA MIP images demonstrating high-grade stenosis of the right intracranial MCA. For an accurate measurement of the grade of Warfarin-Aspirin Symptomatic Intracranial Disease Stenosis, we made a linear measurement of the most stenotic portion of the MCA, in this case 0.9 mm. A second "normal" measurement was made at the widest, non-tortuous, normal portion of the MCA that had margins parallel with the location of the stenosis, in this case 2.6 mm. The ratio of these two measurements was then used to calculate the WASID stenosis, in this case [1-(0.9 mm/2.6)]x100= 66% stenosis.*

- Computerized tomography angiography (CTA): It provides a better delimitation of the anatomy of intracranial arteries, which allows for higher diagnostic precision of luminar stenosis in ICAD compared to the TCD and MRA, with a sensitivity >95% in the diagnosis of ICAD (35) using DSA as the reference standard, even though the visualization of petrous and the cavernous segments of the internal carotid artery (ICA) by CTA could be affected by bone artifacts. Recently, CTA has been used more and more to evaluate collaterality in ICAD, including the leptomeningeal collaterals, which have been correlated to the risk or recurrent events, and recurrent CVA rates have been reported in patients with high grade stenosis (70-99%) of none vs good collaterality: HR= 4.60, and poor vs good collaterality: HR= 5.90 [3637]. Consequently, collateral flow is one of the most essential mediators in cerebral ischemia due to ICAD, making it an important indicator in the prediction of risk and the assignment of treatment in patients with symptomatic ICAD.

The anterograde and collateral blood flow (AnCo) scoring system is useful as a score to predict the state of anterograde and collateral blood flow in patients with S-ICAD of the MCA. The AnCo scoring system consists of the anterograde score (AnS) and the collateral score (CoS) [38].

Bash et al, after analyzing 115 sick vessels, found that CTA has higher sensitivity than MRA to detect ICAD (98% vs 70%, p <0,001), and occlusion (100% vs 87%, p 0,02). CTA had a positive predictive value higher than MRA, both for stenosis and occlusion. CTA was superior to DSA in the detection of the permeability of the vessel. In conclusion, CTA has higher sensitivity and positive predictive value than MRA and is recommended over the TOF sequence of the MRA to detect intracranial stenosis and occlusion. CTA is superior to DSA to assess steno-occlusive disease of posterior circulation when there is slow flow [34]. In another study that compared DSA and CTA, they found that CTA has high sensitivity and specificity to detect stenosis ≥ 50% in large intracranial segments [39].

-High-resolution magnetic resonance (HRMRI): It help in the assessment of the morphology of the intracranial plaque and the adjacent arterial wall, revealing the morphology and components of the plaque, including intraplaque, lipidic nucleus, and fibrous layer hemorrhage [37].

-Perfusion images (PerfuMRI or PerfuCT): this imaging modality makes it possible to identify potentially recoverable tissue or ischemic penumbra, so that they could be used to quantify the real collateral flow in the context of ICAD [40].

Invasive methods:

-Digital subtraction angiography (DSA): It is currently considered as the reference standard for the diagnosis of intracranial vascular diseases, including ICAD, because of its excellent spatial and contrast resolution to represent the vessels, and its capability to reveal temporal information about anterograde and collateral flow. A disadvantage as an invasive method is that it may lead to complications during the procedure, with rates of 1:1000 general neurological complications being reported (close to 2% in patients with ICAD) [33]. Therefore, DSA should not be routinely used to diagnose ICAD.

A challenge posed by these diagnostic tests is their limited capability to differentiate between an atherosclerotic plaque and other pathologies such as partially occlusive thrombus, vasospasm, vasculitis, or even preocclusive Moyamoya disease. Lately, high-resolution images of the vessel wall have been used to identify substenotic but active atherosclerotic plaques. In patients with ICAD, eccentric arterial thickening, and fibrous cap thickening in the image of the vessel wall could favor atherosclerosis of the thrombus or vasculitis [41].

The SONIA (Stroke Outcomes and Neuroimaging of Intracranial Atheroclerosis) study assessed the precision TCD and MRA compared to DSA, and it concluded that both have high negative predictive values (86 and 91%, respectively), but low positive predictive values (36 and 59%, respectively). Both techniques identify 50 to 99% of stenoses of large intracranial vessels non-invasively with substantial negative predictive value. This means that TCD and MRA are efficient for the exclusion of ICAD, but are less useful to establish a diagnosis of ICAD and to estimate the severity of the stenosis. Additionally, abnormal findings in TCD and MRA require a confirmation test, such as DSA, to reliably identify stenosis [31].

DSA is the diagnostic test that more precisely measures the grade or percentage of intracranial stenosis, above non-invasive tests. In conclusion, DSA is the gold standard for diagnosis and quantification of luminal stenosis of intracranial circulation, which is an independent predictor of recurrent CVA in the context of ICAD [41]. However, the grade of stenosis is not the only determining factor. Other factors are collateral circulation (hemodynamic impact), and morphological characteristics of the atherosclerotic plaque (plaque components) [33].

Treatment

There are three types of treatment for ICAD: Medical, endovascular, and surgical treatment.

Medical treatment

In 1995, Chimowitz et al (Warfarin-Aspirin Symptomatic Intracranial Disease Study Group: WASID) published the multicentric and retrospective study: the "Warfarin-Aspirin Symptomatic Intracranial Disease Study", to compare the efficacy of warfarin vs aspirin in the prevention of major vascular events (CVA, AMI or sudden death) in patients with S-ICAD. Seven centers and 151 patients participated; 88 were treated with warfarin and 63 with aspirin. The follow-up median was 14.7 months (warfarin group), and 19.3 months (aspirin group). Kaplan-Meier analysis showed a significantly higher percentage of patients free of major vascular events among patients treated with warfarin (p = 0,01). The relative risk of an important vascular event for these patients was 0.46 (95%CI: 0.23-0.86) as opposed to patients treated with aspirin. Important hemorrhagic complications occurred in three patients treated with warfarin (including two deaths) in 166 patients-year of follow-up, and none in the patients treated with aspirin in 143 patients-year of follow-up. This study suggests a favorable risk-benefit relation for warfarin, compared to aspirin for the prevention of major CVA in patients with S-ICAD [43]. This resulted in anticoagulation being informed for the first time as treatment for S-ICAD. Figure 2.

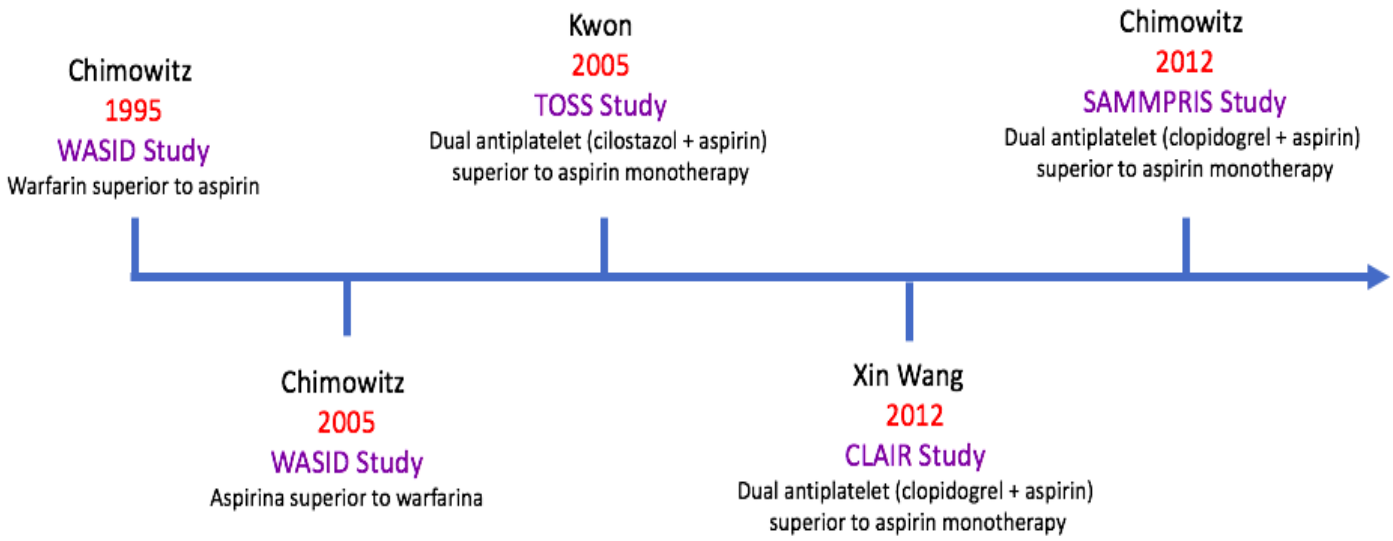

Figure 2: *Timeline for pharmacological treatment in patients with ICAD.*

Later on in 2005, Chimowitz et al (Warfarin-Aspirin Symptomatic Intracranial Disease Study Group: WASID) published the multicentric blind clinical trial: "Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis", where they randomized patients with these inclusion criteria: age ≥ 40 years, non-incapacitating TIA or CVA occurring 90 days before randomization, and which was attributable to a 50-99% stenosis verified by DSA in a main intracranial artery, a modified Rankin score ≤ 3, in two groups: warfarin 5 mg per day (INR objective 2.0-3.0) vs aspirin (total dosis per day: 1300 mg, 650 mg every 12 hours). In total, 569 patients were randomized, the study was stopped because of the worry regarding the safety profile of the arm of patients assigned to warfarin. During an average follow-up period of 1.8 years. The death ratio due to vascular causes was 3.2% aspirin vs 5.9% warfarin ($p = 0.16$); the death ratio due to non-vascular causes was 1.1% vs 3.8%, respectively ($p = 0.05$). In conclusion, warfarin was associated with significantly higher rates of adverse effects and did not provide any benefits compared to aspirin in this study. Aspirin should be preferably used instead of warfarin in patients with ICAD. A subanalysis was performed in the following contexts: severe stenosis (70-99%), vertebrobasilar stenosis or CVA symptoms in patients with antithrombotic treatment (therapeutic failure or failure in the response), who were previously thought to be benefitting from anticoagulation therapy. However, the WASID study findings showed that none of these subgroups have a significant benefit with warfarin [5].

In 2009, Turan et al published "Failure of Antithrombotic Therapy and Risk of Stroke in Patients With Symptomatic Intracranial Stenosis", where they compared CVA or vascular death rates in ON vs OFF patients (patients in antithrombotic treatment or warfarin at the time when the index event occurred to be included in the WASID study vs patients without treatment). Concluding, patients with S-ICAD who fail in antithrombotic therapy do not have a higher risk of CVA than those that do not fail with this therapy. Given the fact that patients with antithrombotic treatment ON and OFF have a higher risk of CVA in the territory, the intracranial stent placement assays should not be limited to only those who fail in this therapy [44].

In 2012, Xin Wang et al, published "The effectiveness of dual antiplatelet treatment in acute ischemic stroke patients with intracranial arterial stenosis: a subgroup analysis of CLAIR study", where they carried out an analysis of subgroups of the CLAIR study in patients with CVA or TIA with ICAD and microembolic signs confirmed with TCD recorded on days 1, 2, and 7. They included patients during the first seven days after the onset of symptoms, randomizing in two groups: group 1, clopidogrel (day 1: 300 mg and subsequently 75 mg/day plus aspirin (75-160 mg/day) for seven days (dual treatment), or just aspirin (75-160 mg/day) for seven days (monotherapy). They included 70 patients, 34 in the dual treatment dual and 36 in the monotherapy group. To conclude, dual treatment with clopidogrel and aspirin for seven days is more effective than only aspirin for reducing microembolic signs in patients with S-ICAD [45].

In 2012, the "Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis, SAMMPRIS Trial Investigators" was published, supporting the use of dual antithrombotic in the short term with aspirin and clopidogrel, followed by just aspirin. In this study they compared the aggressive medical treatment (AMT) vs percutaneous transluminal angioplasty and stenting (PTAS) to prevent recurrent CVA. The AMT in the SAMMPRIS study included:

-Dual antithrombotic therapy: aspirin 325 mg/day + clopidogrel 75 mg/day for 90 days after enrollment and subsequently, aspirin 325 mg/day during the rest of the assay.

-Control of primary risk factors: blood pressure <140/90 mm Hg (<130/80 mm Hg in case of patients with diabetes) and cholesterol levels LDL < 70 mg/dl.

-Control of secondary risk factors: diabetes mellitus, elevated non-high-density lipoprotein (non-HDL) cholesterol, smoking, obesity, and sedentarism aided by a lifestyle modification program.

The common practice of keeping blood pressure slightly high in patients with S-ICAD to reduce the risk of CVA by distal hypoperfusion, and increasing the systolic arterial pressure during follow-up in WASID did not reduce the risk of CVA in the stenotic artery territory, but in fact it increased the risk of recurrent CVA.

Patients who had had a recent (30 days) TIA or CVA attributed to 70-99% stenosis of the diameter of a major intracranial artery with AMT or AMT plus PTAS with a Wingspan stent were randomly assigned. The primary

outcome was CVA or death within the following 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period or the CVA in the territory of the qualifying artery after the 30 days. The study stopped at the beginning of 2011, regardless of the fact that follow-up will finish in 2013. In total, 451 were randomized, because the rate of CVA or death at 30 days was 14.7% in the PTAS group (12.5% non-fatal CVA and 2.2% fatal CVA), and 5.8% in the medical treatment group (5.3% non-fatal CVA and 0.4% death unrelated to CVA) p = 0.002). The average duration of follow-up was 11.9 months. The probability of a primary outcome over time significantly differed between the two treatment groups (p = 0.009), with a one-year rate of 20.0% primary outcome in the PTAS group, and 12.2% in the AMT group [8].

The patients in the AMT group only had a 5.8% CVA or death rate at 30 days, which is substantially lower than 10.7% at 30 days in the WASID assay (using the same inclusion criteria as SAMMPRIS) [46].

Other antiplaque agents like cilostazol, a phosphodiesterase inhibitor, in dual therapy (aspirin 100 mg/day + cilostazol 200 mg/day) have been tested in the TOSS (Trial of cilostazol in Symptomatic intracranial arterial Stenosis) study [47]. No data on the superiority or equivalence of other antiplaque regimes such as monotherapy with clopidogrel, cilostazol or extended release dipyridamole, or the combination of dipyridamole and aspirin has been published for the prevention of CVA in patients with S-ICAD.

Endovascular treatment

Reports in 1999 and 2002, which involve a small number of patients with ICAD that were treated with coronary angioplasty catheters or balloon-expandable stents showed promising results [48,49]. Nevertheless, the safety of these procedures could have been compromised by these factors: 1) flexibility limitations of the coronary balloons or the placement systems of balloon-mounted stents; 2) high inflation precision required to deploy stainless steel stents in fragile intracranial vessels; 3) risk of shearing the stent from the balloon while navigating to the target lesion; and 4) difficulty to precisely dimension the balloons and endoprostheses according to the diameter of the vessel (50). Figure 3.

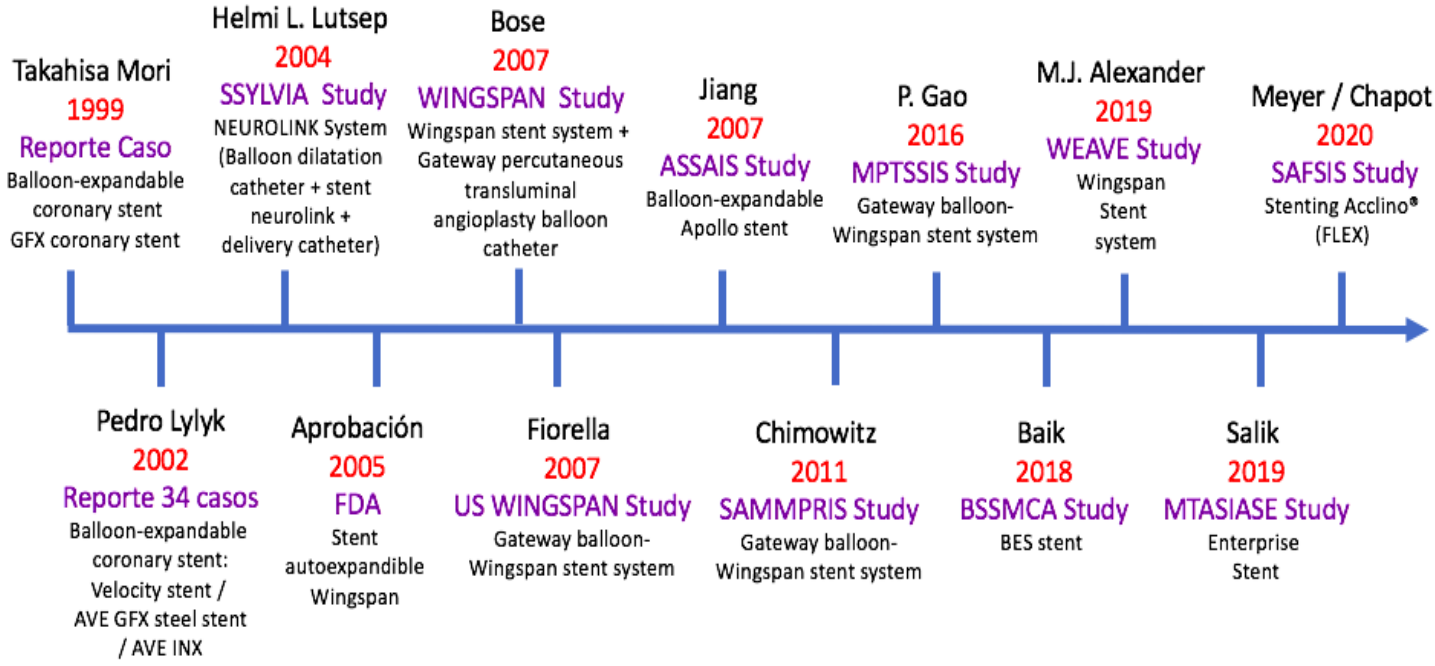

Figure 3: *Endovascular treatment timeline in patients with S-ICAD.*

In 2004, the SSYLVIA Study Investigators, published the a prospective, multicentric and non-randomized study: "Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) Study Results", which evaluated the NEUROLINK system (Boston Scientific, Natick, Mass), comprising a balloon dilatation catheter and a stainless steel stent. They included patients between 18 and 80 years, with symptoms attributable to target lesions with ≥ 50% stenosis. They recruited 61 patients, with 95%success rate of the procedure. During the first 30 days, four patients (6.6%) suffered a CVA and no deaths occurred. At six months, a > 50% stenosis occurred in 32.4%, and from these patients, the recurrent stenosis was symptomatic in 39% of them. In conclusion, the NEUROLINK system is associated with a high rate of successful deployment in the endoprosthesis. CVA occurred in 6.6% of patients within 30 days, and 7.3% between day 30 and one year. Even though stenoses occurred in 35% of patients, 61% were asymptomatic [51].

In 2005, the FDA approved the Wingspan (Stryker Neurovascular, Freemont, CA, EE. UU.) self-expanding stent for use under the exception of the humanitarian device in medically-refractory patients with TIA or CVA secondary to 50-99% stenosis of a major intracranial artery [52].

In 2007, Bose et al published "A Novel, Self-Expanding, Nitinol Stent in Medically Refractory Intracranial Atherosclerotic Stenoses the WINGSPAN Study", which was a prospective, multicentric study with just one arm. They evaluated the safety and performance of the Wingspan stent system and the slow-inflation nominal pressure undersized balloon catheter PTA - Gateway in the treatment of high-grade S-ICAD in patient who had not responded to medical treatment. The inclusion criteria were: refractory patients to AMT, modified Rankin score ≤ 3, and recurrent symptoms attributable to intracranial stenosis seen angiographically ≥ 50% in a 2.5 to 4.5 mm diameter vessel. They included 45 patients, the stenosis grade was reduced from an initial value of 74.9 ± 9.8% to 31.9 ± 13.6% after the placement of the stent and to 28 ± 23.2% at the six-month

follow-up. The combined death/ipsilateral CVA at 30 days was 4.5%, and during the six-month follow-up, the CVA/ ipsilateral death rate 7.0%, the rate for all CVA was 9.7%, and mortality due to all causes was 2.3%. To summarize, in medically refractory patients with high-grade S-ICAD, a new treatment paradigm that involves pre-dilation with an undersized balloon catheter for PTA Gateway followed by the deployment of the self-expanding Wingspan stent endoprosthesis to remodel the target vessel even further and maintain the permeability without the need for post-dilation seems to be safe, may facilitate the remodeling, and may contribute to favorable angiographic results [50].

Subsequently, the results of two multicentric studies in the USA were recorded. Based on the reports of the WASID study that showed that patients with high-grade S-ICAD (70% - 99%) have a particularly high risk of ipsilateral CVA even with AMT: 18% per year. Thus, the following two multicentric studies to evaluate the effectiveness and safety of endovascular treatment are shown.

In 2007, Fiorella et al publish "US Multicenter Experience With the Wingspan Stent System for the Treatment of Intracranial Atheromatous Disease Periprocedural Result", a study that informed the initial periprocedural experience with Wingspan (Boston Scientific / Target), the first self-expanding stent system designed for ICAD treatment. All petients underwent angioplasty and stent placement using the Gateway balloon–Wingspan stent system. During a period of nine months, the treatment with the stent system was performed on 78 patients (average age: 63 years) with 82 atheromatous intracranial lesions, from which 54 had ≥ 70% stenosis. The success rate for this procedure was 98.8% during the first treatment session. In one case, the stent could not be placed through the lesion. Average stenosis pre-treatment was 74.6 ± 13.9%, improving to 43.5 ±18.1% after balloon angioplasty, and to 27.2 ± 16.7% after the placement of the endoprosthesis. Out of the 82 treated lesions, there were five (6.1%) important neurological complications during the procedure, from which four finally led to the death of the patient within 30 days of treatment. In conclusion, angioplasty and endoprosthesis placement for S-ICAD could be carried out with the Gateway balloon–Wingspan stent system with a high rate of technical success and an acceptable periprocedural morbidity. This procedure is considered a viable treatment option for these patients [53].

In 2007, Jiang et al published "Apollo Stent for Symptomatic Atherosclerotic Intracranial Stenosis: Study Results", a prospective study that evaluated the viability and results of a new intracranial balloon-expandable Apollo stent (MicroPort Medical [Shanghai], Shanghai, China) that comprises a semi-compliant balloon, a stent, and a delivery catheter. They recruited 46 patients with ≥ 50% stenosis. The viability of the procedure was assessed through the success of the stent (residual stenosis ≤ 30%) and procedure length. The primary final outcome was CVA in the territory of the target lesion artery, including any CVA and death within 30 days. In total, 91.7% were successful with the stent with an average procedure time of 50.6 minutes. Three patients (6.5%) suffered minor CVA within 30 days. All patients were available for follow-up with a mean of 23.9 months. After 30 days, one patient (2.2%) developed a mild CVA in the territory of the target lesion in the artery after 6.7 months. The primary outcome rate was 4.3 per 100 patients-year. Angiographic follow-up was done for 25 patients. They detected seven restenosis (28%), one of which was symptomatic. Concluding, an angioplasty with the Apollo stent for S-ICAD is feasible. Severe tortuosity is an independent predictor of stent failure. Our clinical results seem to be favorably comparable to the results of aspirin therapy [54].

In 2008, Zaidat et al published "The NIH registry on use of the Wingspan stent for symptomatic 70–99% intracranial arterial stenosis", a multicentric study where 16 centers participated. They recruited a total of 129 patients with severe S-ICAD (70 - 99%). The technical success rate was 96.7%. The average stenosis pre- and post-stent were 82% and 20%, respectively. The frequency of any CVA, intracerebral hemorrhage (ICH) or death within 30 days or ipsilateral CVA after 30 days was 14.0% at six months. The frequency of restenosis ≥ 50% in the follow-up angiography was 25%. To conclude, the use of a Wingspan stent in patients with severe S-ICAD (70-90%) is relatively safe with a high technical success rate and a moderately high rate of restenosis. The comparison of event rates in high-risk patients in symptomatic warfarin and aspirin intracranial disease (WASID) against this registry, does not discard that the stent placement could be associated with a substantial reduction of the relative risk (e.g, 50%) or that it does not have any advantage compared to medical therapy. A randomized assay that compares stent placement and medical therapy is required [55].

As stated previously, the SAMMPRIS assay that started enrollment in 2008, had opposite results in relation to the researchers hypothesis, evidencing that AMT was superior to PTAS in high-risk S-ICAD patients [8]. An analysis in 2012 was done by Fiorella et al, who found that the risk factors that were significantly associated with periprocedural ischemic events in the SAMMPRIS study were: not smoking (possibly because smoking increases the clopidogrel conversion into its active metabolite), basilar artery stenosis, diabetes, and advanced age, while risk factors associated with peroprocedural ICH included high percentage of stenosis and clopidogrel load associated with a coagulation time above the target range [56].

The explanations for the highest periprocedural events in SAMMPRIS compared to previous Wingspan reports are: more severity of the necessary stenosis for the enrollment in SAMMPRIS, and previous treatment in SAMMPRIS (within the 30 days after the qualifying event), which could have increased the risk of PTAS. Besides, it had a more rigorous adjudication procedure.

In 2016, P. GAO et Al published "Multicenter Prospective Trial of Stent Placement in Patients with Symptomatic High-Grade Intracranial Stenosis", a prospective multicentric assay in only one arm aiming at evaluating if the modifications in the selection of the patients for stenting could lead to lower rates of CVA or periprocedural death. They included patients with recent TIA or CVA (excluding performing vessel CVA) related to high grade stenosis (70 -99%) of a main intracranial artery. They were treated by angioplasty and self-extending stents three weeks after the index ischemic event. The endovascular technique used the Gateway angioplasty balloon (Stryker Neurovascular). After the angioplasty, the Gateway angioplasty balloon catheter, self-expanding nitinol Wingspan stent delivery system. They recorded 100 patients, target lesions were located more frequently in the M1 segment of the MCA (38. 3%), intracranial ICA (17.17%), intradural vertebral artery (18.18%), and basilar artery (27.27%). The technical success rate of the deployment of the endoprosthesis with < 50% residual stenosis was 100%. The global rate of CVA and/or death at one month was 2%. Two CVA occurred in the pons region (distribution of performing vessels) in patients after angioplasty a stent placement by stenosis of the basilar artery. Concluding, they evidenced that the modifications in patient selection and the aspects of the procedure could greatly reduce the rate of CVA and/or death a month after the placement of the intracranial stent [42].

In 2018, Baik et al published "Balloon-expandable stents for treatment of symptomatic middle cerebral artery stenosis: Clinical outcomes during long-term follow-up", where they retrospectively reviewed the clinical results during long-term follow-up after the insertion of expandable balloon stents in patients with MCA S-ICAD. They analyzed 34 patients, with an average age of 67 years with MCA S-ICAD. They used the BES stent (Flexmater; Abbott, Abbott Park, MI, USA) that was sized to approximate the diameter of the normal patent vessel. During the follow-up period after the placement, which varied between 61 and 108 months (median of 67.5 months), TIA occurred in five patients, from which one

experienced complete reocclusion of the MCA stent and three had symptomatic restenosis. The remaining 29 patients did not experience more ischemic events or restenosis during the follow-up period. In conclusion, treatment with expandable balloon stents in patients with MCA S-ICAD resulted in low recurrence rates, both for ischemic events and restenosis during long-term follow-up [7].

In 2019, Michael J. Alexander et al from WEAVE Trial Investigators published "WEAVE (Wingspan Stent System Post Market Surveillance) Trial Final Results in 152 On-Label Patients", where they analyzed 152 patients who complied with the criteria for use indicated in the FDA label (22-80 years of age, severe S-ICAD (70-99% stenosis), base modified Rankin score ≤3, ≥2 CVA in the vascular territory of the stenotic lesion with at least one CVA during medical treatment and stent placement in the lesion ≥8 days after the last CVA, in 24 hospitals. They underwent an angiography and stent placement using a Wingspan stent (Stryker, Kalamazoo, MI). The assay stopped before completion after the intermediate analysis of 152 consecutive patients evidenced CVA, ICH, and death rates during the procedure lower than expected (2.6%) (4/152 patients). This was lower than the 4% safety reference of primary outcome established for the intermediate analysis in the study. A total of 97.4% (148/152) of the patients were event-free at 72 hours, 1.3% (2/152) non-fatal CVA, and 1.3% (2/152) patients died. In conclusion, experienced interventionists and an adequate selection of the patients following the FDS label indications, the use of the Wingspan stent for S-ICAD showed a low rate of periprocedural complications and an excellent safety profile. This is the biggest multicentric prospective study on the Wingspan stent system label up-to-date with the lowest reported complication rate [57].

In 2019, Salik et al published "Medium-term results of undersized angioplasty and stenting for symptomatic high-grade intracranial atherosclerotic stenosis with Enterprise", a study which assessed the medium-term results of the undersized balloon angioplasty and stenting for high grade S-ICAD (70-99%) of a main intracranial artery with an Enterprise stent (Codman Neurovascular, Raynham, Massachusetts, USA), which was originally designed for neck remodeling in the treatment of intracranial aneurysms. In total, 68 patients with S-ICAD under AMT with high grade stenosis (70-99%) of a major intracranial artery that were treated endovascularly with undersized balloon angioplasty and Enterprise stent deployment. The primary outcome was CVA or death within 30 days of the procedure. Secondary outcomes were technical success rates, CVA, and restenosis during the follow-up period. The success rate for the procedure was 99%. The garde of stenosis prior to the procedure was 92 ± 6%, and it decreased to 12 ± 10% after the deployment of the stent. No patients suffered CVA or death during the periprocedural period. ICH was observed in one (1.5%) patient. In 60 (88%) patients with available imaging follow-up, they observed restenosis in the stent in two patients. The average follow-up period was 22 ± 17 months (range 6-72), and none of the patients experienced recurrent TIA or CVA during follow-up. Concluding, undersized balloon angioplasty and deployment of a self-expanding stent with a relatively low radial strength was safe and efficient for endovascular treatment of high grade S-ICAD with high technical success rates, low periprocedural complication rates, and favorable results at medium-term [9].

In 2020, Meyer - Chapot et al published "Stenting with Acclino® (flex) for symptomatic intracranial stenosis as secondary stroke prevention", reporting their experience with elective intracranial stenting (EICS). They retrospectively reviewed the data from three high-volume CVA centers, and they analyzed patients treated with EICS due to S-ICAD using the acclino® stent (FLEX), and Neurospeed® balloon catheter (Acandis GmbH, Pforzheim, Germany). Evaluation criteria were periprocedural CVA rates independent of the territory or death at the time of discharge and during follow-up after EICS. The safety evaluation included asymptomatic and symptomatic ICH, adverse events related to the intervention and evaluation of the permeability of the stent during follow-up. The average age of patients who complied with the inclusion criteria was 69 years. The target vessels were located in anterior circulation in 55.3% of patients. Periprocedural CVA rates were 6.5% (fatal CVA 2.6%; non-fatal CVA 3.9%) increasing after EICS, and asymptomatic ICH in 5.2% of them. Follow-up by DSA revealed intra-stent restenosis in 25%, and a new percutaneous transluminal angioplasty was performed aagin in 11.6% of patients. Summarizing, stent placement for S-ICAD using the acclino® (flex)/neurospeed balloon® catheter system appeared to be safe and it strengthens EICS as an endovascular therapeutic option for secondary prevention of CVA. Future studies are required to confirm these findings and to research antithrombotic strategies and restenosis in the stent to minimize periprocedural complications and guarantee permeability of the stent in the long-term [58].

Restenosis was evaluated in a recently published meta-analysis in 2020: "Incidence and Risk Factors of In-Stent Restenosis for Symptomatic Intracranial Atherosclerotic Stenosis: A Systematic Review and Meta-Analysis", where they analyzed all the literature that reported intra-stent stenosis in S-ICAD in PubMed, Ovid EMBASE, and Ovid MEDLINE databases. In total, they included 51 studies with 5043 patients. The combined incidence rate of intra-stent restenosis was 14.8%. Among the lesions with intra-stent restenosis, 28.8% were asymptomatic. The series in the USA had a higher intra-stent restenosis rate (27.0%) compared to Asia (13.6%). The multi regression analysis showed that the age of the youngest patients was related to high rates of stenosis in the stent (p=0.019), and the location of the vertebrobasilar junction (p = 0.010), and low residual stenosis (p = 0.018) were two independent risk factors for intra-stent restenosis sintomática [56].

Conclusion

In summary, substantial progress in the treatment of patients with ICAS has been achieved in the past decade, which has led to better prognosis for patients with this high-risk disease. Multidisciplinary medical treatment that incorporates short-term dual antiplaque treatment (for 90 days), followed by monotherapy with aspirin, together with intensive treatment of vascular risk factors, is the preferred treatment for CVA prevention in these patients. In spite of this aggressive medical treatment, a large subgroup of patients still have a high risk of recurrent CVA. For them, the advancement of endovascular therapy devices are offering better effectiveness and safety rates, which explains the frequent reporting of successful treatment studies with stenting.

Conflicts of interest:

None

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