BALLOON AND STENT FOR ISCHEMIC AND HEMORRHAGIC STROKE: A NEW TREND FOR STROKE PREVENTION AND MANAGEMENT

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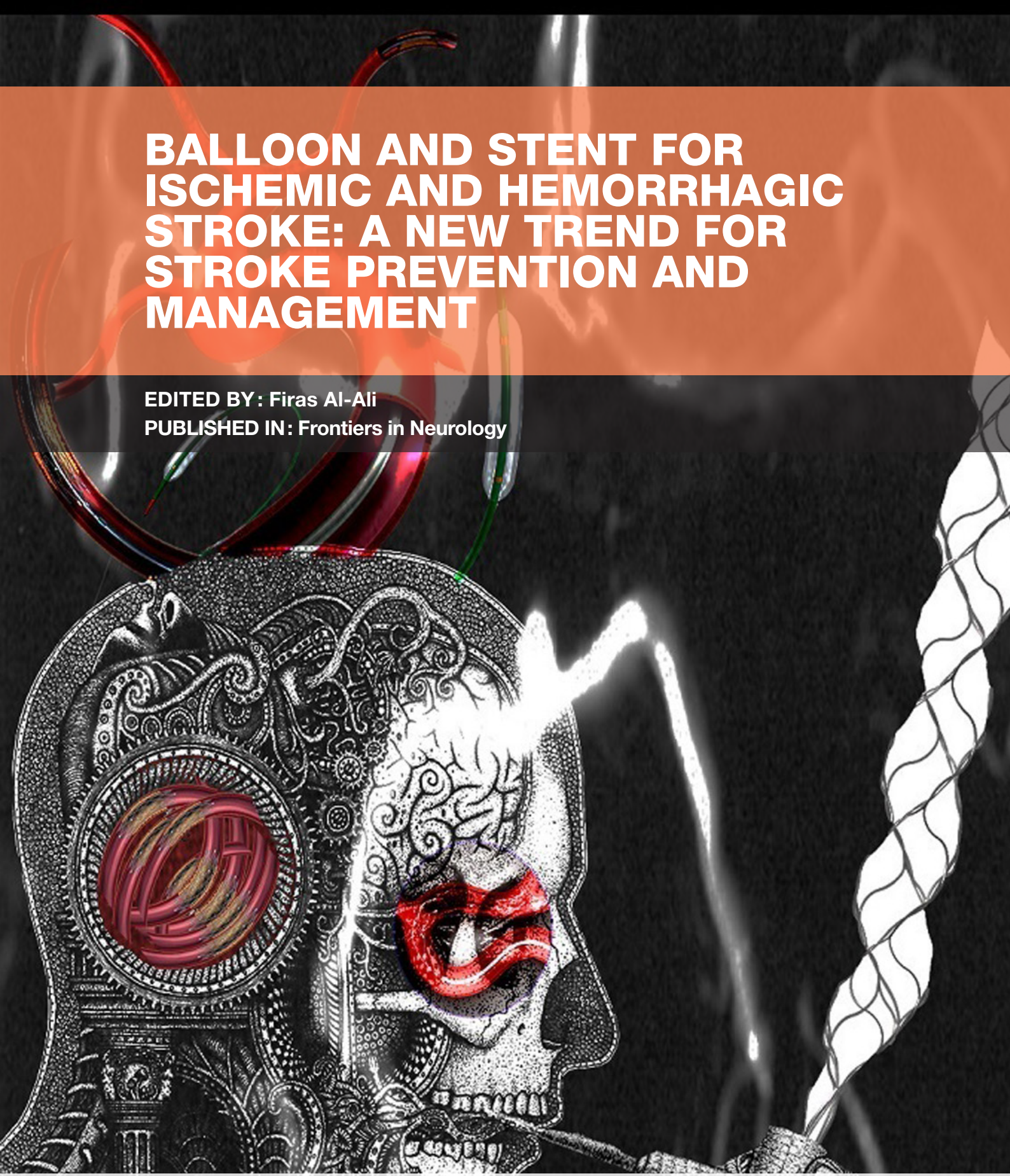

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BALLOON AND STENT FOR ISCHEMIC AND HEMORRHAGIC STROKE: A NEW TREND FOR STROKE PREVENTION AND MANAGEMENT

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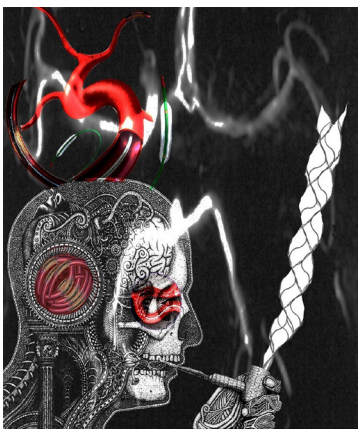

Balloon and Stent for Ischemic and Hemorrhagic Stroke. Balloon and stent images were adapted and reproduced with permission from Stryker®. Copyright © 2015 Stryker. Cover designed by Noor Alali.

In recent years, intracranial endovascular use of Balloon and Stent has grown significantly. This issue will focus primarily on recent advances in the use of these methods today. This discussion will also highlight our improvements in understanding the disease process, and not only relying on devices to treat a patient.

Wide-necked intracranial aneurysms (IA) were originally thought to be either untreatable or, at the very least, significantly challenging to treat by endovascular means due to the risk of coil protrusion and possibly parent vessel occlusion. However, this view now outdated, today and we will discuss the significant advancment in different flow diverters. The treatment of post-sub arachnoid hemorrhage vasospasm is mature now, as this issue will highlight.

In addition, Intracranial atherosclerosis is still a prominent cause of stroke in various populations worldwide. This issue will summarize the challenges of risk factor modification and secondary stroke prevention by defining optimal methods. We will try to outline a new approach for intracranial angioplasty and stenting for stroke prevention.

Finally, despite recent impressive increase recanalization rates in acute ischemic stroke treatment, the clinical improvement rate has remained relatively stable. This article will discuss a new means of improving patient selections using the capillary index score (CIS).

The future of our specialty relies heavily on better devices, and on a deeper understanding of the disease process. The future is bright and we have already taken the first successful steps.

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EDITORIAL
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Editorial: Balloon and stent for ischemic and hemorrhagic stroke: a new trend for stroke prevention and management

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Keywords: acute ischemic stroke, brain anuerysm, intracranial angioplasty, intracranial stenting, atherosclerosis, capillary index score

It was the helium-filled balloons floating in the air during the 1959 International Workers' Day in Moscow that first inspired Dr. Serbinenko to navigate from the common carotid artery to the intracranial circulation (1). He achieved that on February 8, 1964, by performing the first selective extracranial carotid injection with the assistance of temporary balloon for internal carotid artery occlusion. This was followed by the selective catheterization of the intracranial circulation using a flow-directed balloon catheter. Shortly after, he successfully treated a carotid-cavernous fistula (December 15, 1969) using a detachable balloon (1), marking the birth of our specialty: Neurointerventional Surgery.

Balloon catheters are no longer needed to achieve selective intracranial catheterization, but their therapeutic role has expanded significantly. Building upon the success of balloon angioplasty and balloon-mounted stents in the cardiology literature, Neurointerventionalists began using them intracranially, first for atherosclerotic stenosis (2), and then as an adjunct to coiling (3). Over the last 20 years, the applications and successes of these various balloons and stents have significantly expanded. We aim in this research topic to highlight the different trends being practiced today, some of which have the potential to become an integral part of our practice, while others may fade away.

The advent of aneurysm coiling (stand-alone coiling) has permanently changed the treatment of intracranial aneurysms, despite its limitations. The balloon remodeling technique (BRT) was first introduced in 1997 (3) and was followed by the stent-assisted coiling technique (SACT). Each has dramatically expanded the impact of aneurysm coiling, by allowing us to treat wide-neck aneurysms. Relying on their extensive experience, Dr. Piotin et al. detailed both BRT and SACT (4). They presented us with their mature technique and strategy concerning the use of each modality and device.

The different coiling techniques, however, suffer from two main shortcomings: aneurysm recurrence and an inability to treat giant aneurysms. Flow-diverters (FD) were recently invented to address these issues, for which Dr. Zanaty et al. gave a detailed introduction (5). Stemming from their title "Flow-Diversion Panacea or Poison?" it is apparent that there are still many questions about this technique, which they admirably try to address.

Another source of doubt and controversy in the care of subarachnoid hemorrhage patients is vasospasm prevention and treatment. Although it was first angiographically described in 1950 (6, 7), it is still a significant source of delayed morbidity and mortality. Dr. Bauer et al. detailed, in this research topic, the different methods of prevention and treatment as well as the controversy, but thankfully left us with clear and practical recommendations for day-to-day practice (8).

On another note, our knowledge of intracranial atherosclerotic disease (ICAD) is very limited, despite its prevalence, as Pu et al. highlighted in their review article. They emphasize, and rightly so, the stroke risk difference between symptomatic (approximately 10% per year) and asymptomatic

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ICAD (on the order of 3%) and the dynamic nature of the disease (9). Significant research on this subject is still needed.

Unfortunately, and despite its health burden worldwide, we still do not have a suitable treatment for ICAD. The EC-IC Bypass and SAMMPRIS trials failed to prove the benefits of surgical or endovascular treatments. We believe, however, that progress is still possible, especially in the pharmacology and endovascular realms. The authors of this research topic have already published some of the largest studies to date, relying on their extensive clinical experience. Concurrent with our distinguished panel, we believe that the reasons the endovascular treatment arm of the SAMMPRIS trial failed to show benefits are multifactorial, most of which can be corrected. First, the technique used was not meticulous enough as Connors et al. discuss in their paper here. They emphasize the importance of their previously described method (*Slow Inflation Undersized Balloon Technique*) in reducing technical complication rates (10). Second, only one device was allowed in the SAMMRIS trial (The Wingspan™, Stryker, Kalamazoo, MI, USA). McTaggart et al. argue in their paper in this research topic for intracranial "*angioplasty alone*" technique, mainly due to its safety profile in most cases (11), especially when coupled with Connors' technique (10). Third, Miao presents, in his paper here, yet another critique to improve the SAMMPRIS trial results, where all lesions were treated identically (12). He successfully argues that each lesion is unique and should be treated differently, mainly based on lesion morphologies (*different lesion, different device*). For example, a concentric and short lesion could be treated by angioplasty alone, while other lesions need a more complex device. His *"Complex Strategy"* is very intriguing indeed.

Farooq et al. present a synthesis about the overall strategy of endovascular treatment regarding ICAD (13). They try to incorporate all authors' recommendations, while placing an emphasis on the guiding catheter position *"the closer to the lesion, the better."* They conclude with the assessment that a new trial, incorporating all these critiques and recommendations, is needed.

The final chapter of this research topic addresses acute ischemic stroke treatment. Al-Ali et al. argue that the presence or absence of collaterals (Circle of Willis and pial collaterals) determines the clinical outcome more than time from ictus to revascularization (14, 15): *"collaterals, not time, is brain."* They argue for the use of the capillary index score (CIS) rather than an arbitrary time window to select patients for endovascular treatment. The CIS presumably reflects the percentage of viable tissue in the ischemic area, while its absence indicates non-viable tissue. The possibility that genetic factors play a determining role in the extent of collaterals, as emphasized by Dr. Faber (14), is a very exciting hypothesis and if proven will significantly impact the way we understand and treat ischemic strokes.

While in this research topic, we aim to present a synthesis of certain techniques practiced today; our true aim is to challenge our esteemed colleagues worldwide by raising more questions. We believe in their abilities and in the future of our promising specialty.

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Hemorragic Stroke

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Balloons and stents in the endovascular treatment of cerebral aneurysms: vascular anatomy remodeled

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Wide-neck intracranial aneurysms were originally thought to be either untreatable or very challenging to treat by endovascular means because of the risk of coil protrusion into the parent vessel. The introduction of the balloon remodeling technique (BRT) and later stents specifically designed for intracranial use has progressively allowed these lesions to be endovascularly treated. BRT and stent-assisted coiling technique (SACT) were first designed to treat sidewall aneurysms but, with gained experience and further technical refinement, bifurcation complex-shaped wide-neck aneurysms have been treated by coiling enhanced by BRT and SACT. In this article, we will review and describe the inherent benefits and drawbacks of BRT as well as SACT.

Keywords: aneurysm, coiling, balloon remodeling, stent-assisted coil embolization, complications, strategies, angiography, vascular diseases

INTRODUCTION

Wide-neck (when the neck is $\geq$4 mm, or when the dome/neck ratio $<$1.5–2) intracranial aneurysms were originally thought to be either untreatable or very challenging to treat by endovascular means because of the risk of coil protrusion into the parent vessel. The introduction of the balloon remodeling technique (BRT) and later stents specifically designed for intracranial use has progressively allowed these lesions to be endovascularly treated. BRT and stent-assisted coiling technique (SACT) were first designed to treat sidewall aneurysms but, with gained experience and further technical refinement, bifurcation complex-shaped wide-neck aneurysms have been treated by coiling enhanced by BRT and SACT. In this article, we will review and describe the inherent benefits and drawbacks of BRT as well as SACT. The specific role of flow diverter stents in the endovascular treatment of cerebral aneurysms will not be addressed in this article.

BALLOON REMODELING TECHNIQUE

VARIOUS TECHNIQUES OF BALLOON REMODELING

The standard coil embolization (stand-alone coiling) technique is limited by its inability to occlude wide-neck aneurysms. The BRT consists in the temporary inflation of a non-detachable balloon across the aneurysm neck during each coil placement to avoid inadvertent coil protrusion into the parent artery as initially described by Moret et al. nearly two decades ago (1). At the end of the procedure, the balloon is removed and no device is left in place in the parent vessel (unless stent placement is subsequently performed). Some balloon catheters allow the placement of a stent at the end of the procedure by inserting the stent into the lumen of the balloon microcatheter after withdrawal of the wire (2). The "classic" BRT, using a single low-compliance balloon, was initially limited to sidewall aneurysms, and was often inadequate for protection of both the neck and arterial branches of complex bifurcation aneurysms. Nowadays, the most popular remodeling balloon microcatheters are the HyperGlide™ (compatible with 0.010″ microguidewire), the Transform™, and the Septer™ (both compatible with 0.014″ microguidewires). Balloons compatible with 0.014″ microwire seem more stable than balloon operating on 0.010″ platforms but induce more deformation of the cerebral arteries during navigation. The Septer™ has two independent lumens, giving to the operator the opportunity to navigate coils or some microstents while the balloon is still inflated. For bifurcated lesions, the use of more compliant balloon (compliance is a mechanical property defined by the propensity of the balloon to change its cylindrical shape to the anatomy of the vessel in which it is inflated) allows the treatment of complex, wide-neck bifurcation aneurysms for which the standard embolization technique would not have permitted safe (regarding the patency of bifurcation arterial branches) endovascular occlusion. In these situations, it is necessary to completely protect the neck to avoid coil protrusion. Several options are available. First, a more compliant balloon can be used to mold the neck and the origin of bifurcation branches (3). The most popular compliant balloons microcatheters are the HyperForm™ (compatible with 0″ microguidewire), the Transform™ C and SC (C and SC for compliant and super compliant, respectively) and the Septer C and SC™ (both compatible with 0.014 microguidewires). An alternative to the use of a super compliant balloon consists in the placement of two balloons instead of one (one balloon in each of the bifurcated arterial branches) (4). The third option consists in the navigation of the balloon through the circle of Willis to cross and protect the aneurysm neck (e.g., to navigate from the internal carotid, the posterior communicating arteries and the P1 segment of both posterior cerebral arteries to protect the neck of a basilar tip aneurysm) (5). Another technique consists in the navigation of a dual-lumen balloon in front of the neck to allow coil deposition through the second lumen of the balloon microcatheter (6). Nowadays, BRT can be used in all aneurysm locations.

COMPLICATIONS AND CLINICAL OUTCOME OF BRT

The two most frequent and feared complications of the endovascular treatment of intracranial aneurysms are thromboembolic events and aneurysm perforation. The use of an adjunctive balloon for aneurysm coiling has raised some concerns about potential added morbidity over the standard coiling procedure. In a recent large prospective multicenter study, a consecutive series of patients with ruptured aneurysms (the CLARITY study) who underwent endovascular treatment with either conventional coil embolization or BRT showed that both techniques had similar safety in terms of perioperative complications and clinical outcome (7). The overall rate of treatment-related complications, with or without clinical manifestations, was 17.4% with coil embolization and 16.9% with BRT. The difference in the rates of thromboembolic events, intraoperative rupture, and early rebleeding between the two treatment groups was not statistically significant. The cumulative morbidity and mortality rate related to the treatment in the remodeling group (3.8%) was similar to that in the stand-alone coil embolization group (5.1%). Likewise, the global cumulative morbidity and mortality rates related to both the treatment and the initial hemorrhage did not differ significantly between groups (16.2% with BRT and 19.6% with coil embolization). In the ATENA study (unruptured aneurysms) (8), the overall complication rate, regardless of whether the adverse events led to clinical consequences, was 10.8% for standard coiling of unruptured aneurysms and 11.7% for BRT of unruptured aneurysms. The morbidity and mortality rates did not differ significantly between groups: 3.1% in the standard treatment group and 3.7% in the BRT group, respectively (8). In the Shapiro et al. review article (9), in ruptured aneurysms, the clinical outcome was a symptomatic event or death in 2.7% in the stand-alone coiling group and 1.7% in the BRT group. In unruptured aneurysms, clinical outcome was a symptomatic event or death in 0.6% in the stand-alone coiling group and 0.9% in the BRT group. **Table 1** provides with an overview of the rates of complications with BAT.

ANEURYSM PERFORATION

In the Shapiro et al. review article (9), the rate of intraoperative rupture was 3.4% in ruptured aneurysms treated with standard coiling, 1.7% in ruptured aneurysms treated with the remodeling technique, 1.4% in unruptured aneurysms treated with standard coiling, and 1.8% in unruptured aneurysms treated with the remodeling technique. In the ATENA study (unruptured aneurysms) (8), the rate of intraoperative rupture was 3.2% in the remodeling group and 2.2% in the coiling group. In the Sluzewski et al. personal series (10), the rate of intraoperative rupture was higher in the remodeling (4.0%) compared with the coiling group (0.8%). In the CLARITY study (ruptured aneurysms), the rates of intraoperative rupture were similar in both BRT and stand-alone coiling groups (7).

Table 1 | Balloon remodeling technique and complications with clinical significance.

	Morbi-mortality	
	Stand-alone coiling (%)	BRT (%)
CLARITY, ruptured aneurysms (7)	5.1	3.8
ATENA, unruptured aneurysms (8)	3.1	3.7
Shapiro et al. review, ruptured aneurysms (9)	2.7	1.7
Shapiro et al. review, unruptured aneurysms (9)	0.6	0.9

THROMBOEMBOLIC COMPLICATIONS

In the Shapiro et al. review (9), the rate of thromboembolic events was similar in patients treated with coiling (8.1%) and remodeling (8.0%). Symptomatic thromboembolic events were encountered in 4.6% of patients treated with coiling and 4.4% of patients treated with remodeling. Death related to thromboembolic events was reported as 1.2% for patients treated with coiling and 0.4% for patients treated with remodeling. In the Layton et al. series (11), the rate of thrombus formation was not significantly different in patients treated with standard coiling compared with the remodeling technique (9 and 14%, respectively). Symptomatic thromboembolic events were also observed in a similar percentage of cases (5% in standard coiling and 7% in remodeling). Similarly, Brooks et al. reported that diffusion-weighted-imaging abnormalities were detected in 32% in the coiling group and 24% in the BRT (12). Conversely, Sluzewski et al. reported that the rate of thromboembolic events was higher in the remodeling group (9.8%) compared with the coiling group (2.2%) (10). In the ATENA study, thromboembolic events occurred in 6.2% in the stand-alone coiling group versus 5.4% in the BRT group (8).

ROLE OF BALLOON INFLATION TIME FOR BRT REGARDING ISCHEMIC COMPLICATIONS

Critical questions regarding the maximum permissible balloon occlusion time, the minimum effective reperfusion time between inflations, and whether total balloon inflation time or the number of inflations is a higher risk factor of BRT than stand-alone coiling for ischemic complications has been assessed using diffusion-weighted MR imaging (13, 14). For Albayram et al., the only variables found to influence this risk during or after BRT coil placement were microcatheter repositioning, coil removal and repositioning, and size of the aneurysmal neck (13). More recently, Spiotta et al. found that asymptomatic ischemic event rate in this population for BRT embolization was 24.7%, a rate equal to stand-alone coiling of patients treated in the same time period without BRT (14). Both silent and symptomatic ischemic rates were similar in the internal control group. It is possible that the higher rate of antiplatelet therapy in the BRT group is masking a higher ischemic rate. The baseline patient risk factors for ischemic complications identified included older age and diabetes. One possible explanation for this finding is that all patients have intraprocedural showering of emboli, but older and diabetic patients are more likely to have irreversible ischemia attributable to preexisting microvascular disease. Embolic infarcts were more common than watershed infarcts. The total number of inflations times, the maximum occlusion time, minimum reperfusion time between two consecutive inflations, and mean reperfusion time did not appear to be risk factors for thromboemboli. However, higher maximum inflation time was significantly correlated to watershed pattern infarcts.

ANATOMIC RESULTS OF THE BRT

The Shapiro et al. literature review does not confirm the Sluzewski et al. findings (9, 10). Both initial and follow-up aneurysm occlusion rates were higher in BRT cases. The initial total occlusion rate was 73% in patients in the BRT group and 49% of patients in the standard coiling group, subtotal occlusion in 22% in the BRT group and 39% in the coiling group, and incomplete occlusion in 5% in the BRT group and 13% in the coiling group. At follow-up, there were similar results: total occlusion in 72% of patients in the BRT group and 54% of patients in the standard coiling group, subtotal occlusion in 17% in the BRT group and 34% in the coiling group, and incomplete occlusion in 10% of the BRT group and 11% of the coiling group. According to the ATENA and CLARITY studies, results are possibly different in unruptured and ruptured aneurysms. In ATENA (unruptured aneurysms), immediate anatomic results reported were similar in both stand-alone coiling and BRT groups (complete occlusion in 59.8% of aneurysms in the stand-alone coiling group and 59.8% of aneurysms in the BRT group) (8). In CLARITY (ruptured aneurysms) (7), immediate anatomic results were different, the rate of adequate angiographic aneurysm occlusion being significantly higher in the BRT group (94.9%) than in the stand-alone coil embolization group (88.7%). A recent meta-analysis from Shapiro et al. demonstrated that although balloon use was associated with superior initial and follow-up angiographic occlusion rates (9).

STENT-ASSISTED COILING OF INTRACRANIAL ANEURYSMS

RATIONALE FOR THE STENTING OF INTRACRANIAL ANEURYSMS

The widespread acceptance of coiling has been hindered by the potential for aneurysm to recur over time after coiling (15). This issue is even more relevant for large aneurysms for which angiographic recurrence is more likely than smaller lesions (16). However, fusiform and some wide-neck aneurysms remained unaddressed by both reconstructive surgical and endovascular techniques until the introduction of dedicated intracranial self-expandable stent. Stent deployment across the aneurysm neck, followed by coil packing of the aneurysm, has progressively been more widely adopted, particularly for wide-neck complex aneurysms, in order to stabilize the coil mass inside the aneurysmal sac and to avoid coil herniation into the parent artery (17, 18). Some authors have also advocated using the stent (or several stents deposited in a telescopic fashion to augment mesh density) as a stand-alone procedure to treat fusiform aneurysms, obtaining progressive aneurysm thrombosis without the adjunct of coils within the aneurysm sac (19–23). With gained experience, SACT has been employed to treat a larger range of aneurysms (not only wide-neck and complex aneurysms) with the idea of the likelihood of diminished risk of aneurysm recurrence (24–26). The major current concern is the small size of the parent vessel relative to the diameter of the smallest available stent with inherent potential suboptimal stent deployment. Nevertheless, some stents can be adequately deployed even in vessel smaller than 2 mm (27). Conversely, the use of SACT has brought with it other important considerations, including the necessity of antiplatelet therapy that carries inherent risks of intracranial bleeding (28, 29). Moreover, antiplatelet therapy is limited in the setting of subarachnoid hemorrhage for the majority of the operators (30). The other drawback, even if limited, of SACT is the potential for delayed stent-related issues such as the development of in-stent stenosis and parent vessel occlusion (31–33).

CLOSE- AND OPEN-CELL DESIGNS FOR SELF-EXPANDABLE STENT

There are two major different, close- and open-cell designs for the construction of self-expanding stents dedicated to the intracranial use. The close-cell design makes the stent to work as a whole body (e.g., Enterprise™); thus, a force used at one end will be transmitted to the other end immediately. For a stent with open-cell design (e.g., Neuroform™), each independent segment can serve as a separate fixing device, to enhance apposition of the stent to the arterial wall, and a force used at one end will not be transmitted to the other end so easily. Open-cell design stents better cover the aneurysm neck when compared to close-cell stents, and induce less straightening of the vessel. The open-cell stents have, however, less struts apposing well to the vessel wall compared to close-cell stents (34). Open-cell stents conforms better to vascular tortuosities. However, open-cell stents may show increased opening of cells and outward prolapse of struts into an aneurysm neck when situated at the convexity of the curvature, whereas at the concavity, struts, or stent segments may protrude inward.

When a closed-cell stent is bent, it has less flexibility to conform to a curved or irregular anatomy. The close-cell unsegmented design does not allow the stent to lengthen at the outer curve or to shorten at the inner curve. This limitation in adapting to a vessel curvature will cause flattening of the stent or kinking (35) resulting in incomplete stent apposition. Incomplete stent apposition has recently been found to be a critical factor associated with higher thromboembolic complication rates in SACT embolization of intracranial aneurysms (36). The major advantage of a close-cell stent is ability to be deployed in the vessel lumen and resheated in its delivery microcatheter, allowing the operator to optimize the position of the stent regarding the aneurysm neck. Conversely, an open-cell stent, once partially delivered, cannot be resheated and repositioned owing to its design consisting in independent stent segments soldered by connectors.

There are two different types of close-cell stents: laser-cut (as the Enterprise™) or woven (as the LVIS™ and the LEO™). Nowadays, the last two stents offer the lowest profile to be delivered in a 0.017″ inner lumen microcatheter.

STENTING TECHNIQUES

Four options may be proposed. Firstly, the coil delivery microcatheter can be placed first within the aneurysm lumen to allow coil delivery and then the stent is positioned and immediately delivered across the aneurysm neck (jailed-catheter technique). Secondly, the stent can be first delivered across the aneurysm neck and then the coiling microcatheter is placed within the sac through the stent struts (trans-cell technique) (**Figure 1**) (37). Finally, the aneurysm can be coiled with or without the balloon remodeling technique and then the stent is delivered across the aneurysm neck at the end of the procedure, aiming at decreasing the recanalization rate by diminishing intra-aneurismal flow by diversion and also by creating a mesh at the level of the neck to be colonized and covered by endothelial cells (25). On the other hand, delivering the stent prior to aneurysm coiling has some drawbacks. Firstly,

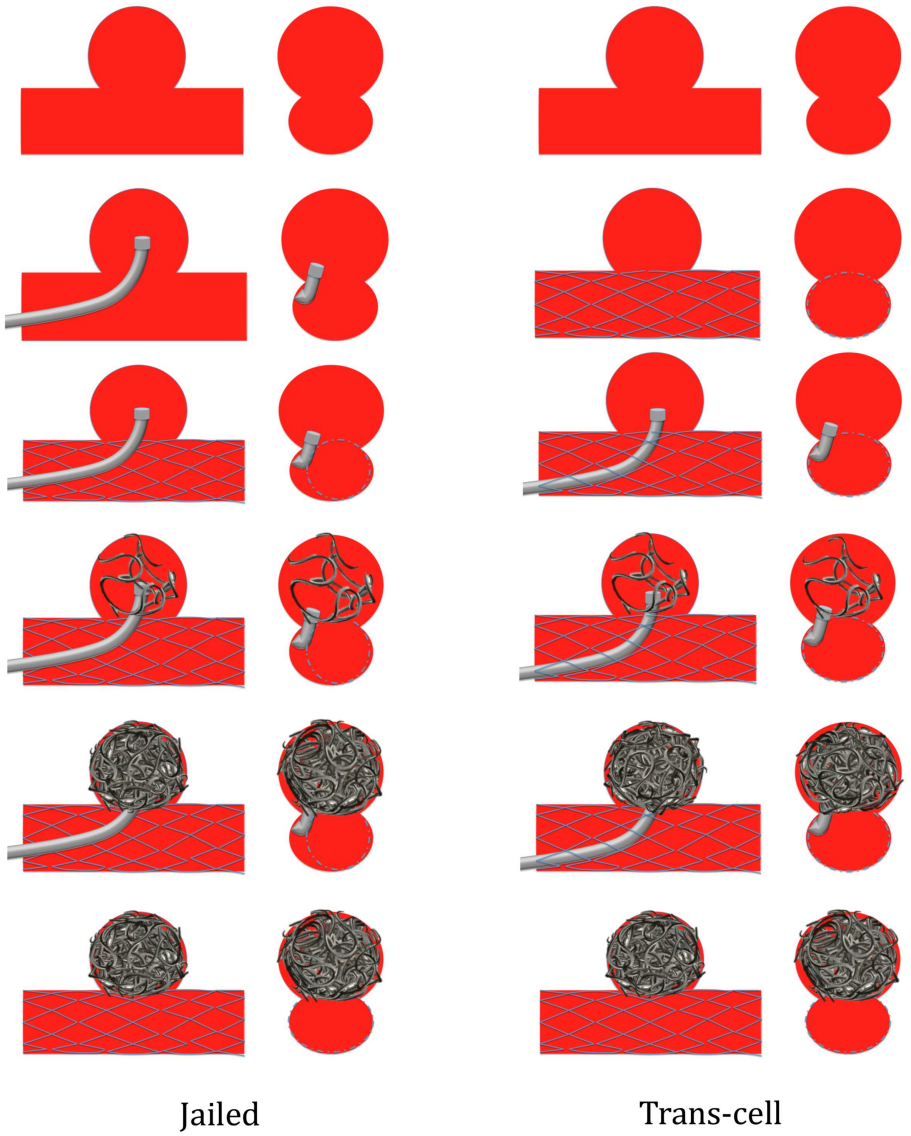

FIGURE 1 | Jailed-catheter and trans-cell techniques.

the jailed-catheter technique does not offer the possibility to modify the microcatheter position within the aneurysm sac, resulting in many instances in the diminution of aneurysm packing with coils. Secondly, when the stent is deployed prior to the coil delivery microcatheter placement, the operator should be very cautious while catheterizing the aneurysm through the stent strut in keeping with the potential hazard of stent displacement and stent cell impingement (38). A fourth SACT, the stent-jack technique, has been more recently described. It consists in positioning the coil delivery microcatheter first into the aneurysm sac, then navigating a self-expandable stent into the parent vessel without delivering the stent before the first coil is deposited in the sac (39). The first coil is placed into the sac (no matter if a coil loop was slightly protruding into the arterial lumen) with coil deployment aiming at forming the most homogenous framing of the aneurysm sac. As a next step, before coil detachment, the stent is carefully deployed across the neck. Once the stent is delivered, the first coil is detached. If necessary, additional coils are introduced into the aneurysm to obtain circulatory exclusion of the lesion.

STENTING OF BIFURCATION ANEURYSMS

Stents have been designed originally to treat sidewall aneurysms. Single-stent SACT is suitable for many bifurcation aneurysms, as a stand-alone technique or in conjunction with BRT (the balloon to be placed in one of the bifurcated branch, the stent being delivered in the other branch). More recently, double stenting in a Y or X configuration may be used to treat a subset of wide-necked aneurysms not amenable to reconstruction with a single-stent due to anatomical conformation (40, 41). Y- and X-stent reconstructions enable the endovascular management of otherwise complex, wide-neck

cerebral aneurysms and can be performed as safely as single-stent technique in experienced hands with satisfactory results.

Y-stent and waffle-cone technique

The Y-stent technique has been developed first to treat wide-neck basilar tip aneurysms (42). It includes the crossing-Y and kissing-Y techniques (43). The crossing Y-stent technique is based on the strategy that a second stent is advanced through the first stent interstices and into the contralateral branch vessel. By contrast the kissing technique, two stents are deployed in a parallel fashion from both daughter arterial branches down to the main arterial trunk, forming a kissing-Y configuration. The first bifurcation vessel to be stented is determined according to the angle between the proximal parent vessel and the arterial branches just distal to the aneurysm; the branch with a sharper angle to be stented before the one with wider angle. In 2004, Horowitz et al. described a single-stent technique to treat broad-neck bifurcation aneurysm consisting in a single-stent to be placed partially into the aneurysm and into the afferent artery, the portion of the stent protruding into the aneurysm fundus providing neck support for the subsequent successful coiling (44).

X-stent technique

Anterior communicating artery (AcoA) aneurysms may present with complex anatomic features, often associated with a wide-neck and variety of anomalies. X-configured stent-assisted coiling for treatment of wide-neck and complex AcoA aneurysms, for which otherwise there would be no endovascular treatment alternative (40, 45). Of course, X-stent placement is to be reserved for patients having good-sized A1 segments, bilaterally. The side of the first stent is determined according to the angle between the A1–AcoA complex and the contralateral A2; the A2 with a sharper angle to be stented before the one with wider angle. On the basis of this decision, the first stent is placed across the aneurysm neck, extending from the contralateral A2 to the ipsilateral A1 segment, crossing through the AcoA. Then after, the second stent is crossed from the other side. Both strut crossing and kissing stenting technique have been reported (40, 45–47).

EFFECT OF SACT ON IMMEDIATE ANGIOGRAPHIC OUTCOME AND AT FOLLOW-UP

Immediate angiographic complete occlusions are obtained less frequently in stented than in the not stented aneurysms. This is because larger aneurysms are more likely to be stented than small aneurysms, and that dual antiplatelet therapy impacts on the immediate intra-aneurysmal thrombosis. Moreover, the use of dual antiplatelet therapy during the procedure in addition to heparin does not favor immediate per procedural sac thrombosis (25). Tight coiling is more difficult to obtain when the stent is implanted prior to coiling, giving less maneuverability to the coiling microcatheter thus resulting in looser aneurysm packing.

Conversely, at follow-up, complete occlusions increased to 73.4% in the stent-assisted group, while it diminished to 54.0% in the no-stent group. For stent-assisted coiling, numerous articles have reported a broad range (13.2–94.4%) of immediate complete occlusion (48–54). However, most mid-to-long-term follow-up series have reported augmented rates of angiographic complete occlusion at follow-up (range 54–81%) (24–26, 49–62). An absence of stent has been identified as one of the most relevant factors for angiographic recurrence (25). This durability can be explained by the combination of biological, geometrical, and hemodynamic mechanisms (63–68). Hemodynamic effects of the stents in the endovascular treatment of aneurysms include disruption of intra-aneurysmal flow pattern, resulting in turbulence, and production of blood stasis within the aneurysm, resulting in aneurysmal thrombosis. This hemodynamic effect seems even more preeminent in case of Y-stenting (65).

COMPLICATIONS OF SACT

There are more procedure-related complications than in the stand-alone coiling. The main cause of morbidity and mortality is thromboembolism. The necessity of dual antiplatelet therapy in SACT is also known to increase the risk of hemorrhagic complications (69). Thromboembolic complications are also more frequent in the stented patients (70). Antiplatelet activity assessment prior to stent delivery allows diminishing the occurrence of such complications by identifying the patients not responding to antiplatelet drugs (71, 72). In a recent review article, Shapiro et al. reported an overall complication incidence of 19%, with an overall death incidence of 2.1%. Thromboembolic issues were most prevalent at close to 10%, leading to death in 0.6% of overall cases. Hemorrhagic complications occurred in 2.2% of cases but carried a higher association with mortality, accounting for 0.9% of overall deaths. Coil-related technical issues were infrequent (2%) and almost always asymptomatic. Complication rates decrease overtime while the operator practice of stenting increased showing also the effect of a learning curve (26). More recently, Nishido et al. have reported 7.0% of ischemic and 2.3% of hemorrhagic complications with an overall rate of procedure-induced mortality of 2.7% with SACT (73). Geyik et al., in a series of 500 consecutive SACT aneurysms, reported 5.6% of thromboembolic and 0.8% of hemorrhagic complications, with a procedure-related mortality of 0.8% (74). **Table 2** provides with an overview of the rates of complications with SACT.

SACT IN THE ACUTE SETTING OF SAH

The use of SACT in the acute setting of subarachnoid hemorrhage remains controversial despite positive results reported in limited series (75, 76). It appears that the risks of intracranial hemorrhage are augmented in this particular condition. In their review article, Bodily et al. reported that SACT in ruptured aneurysms

Table 2 | Stent-assisted coiling technique complications with clinical significance.

	Morbi-mortality	
	Stand-alone coiling and BRT	**SACT**
Nishido et al. (73) unruptured and ruptured aneurysms	5.6%	9.4%
Shapiro et al. (10) review, unruptured and ruptured aneurysms	NA	12.2%

could be performed with high degrees of technical success, but adverse events appeared more common and clinical outcomes were likely worse than those achieved without stent assistance (30). The optimal antiplatelet medication during acute-phase treatment has yet to be determined, and a longer follow-up series is needed to evaluate the long-term efficacy and safety of stent-assisted coil embolization during acute SAH. In a series of 36 patients, Golshani et al. found that SACT was an option for treatment of ruptured wide-neck ruptured aneurysms and for salvage treatment during unassisted embolization of ruptured aneurysms but complication rates appeared to be higher than for routine clipping or coiling of cerebral aneurysms (28). This applies even more dramatically to the patients requiring ventriculostomy (77).

WHEN TO USE BAT

In our center, BAT is used in slightly over 60% of the cases for both ruptured and unruptured aneurysms. BAT provides the ability to avoid coil protrusion and to protect from the deleterious effect of a massive subarachnoid hemorrhage in case of aneurysm perforation. The balloon can be immediately inflated in case of dome (re)rupture during intervention. The main drawback of the technique is the need for dual femoral approach, augmenting the potential for access site complications. Alternatively some operators advocate the use of a single guiding catheter (with a minimal inner lumen diameter of 0.070″), allowing the navigation of both the balloon and the coil delivery microcatheters. The main drawback of this single guiding catheter technique is the potential inadvertent forward and backward movements of one of the two microcatheters while manipulating the second one.

WHEN TO USE SACT

The need for dual antiplatelet therapy makes the SACT to be avoided in acutely ruptured aneurysms. In this setting, SACT should be reserved as a bail-out procedure to avoid parent vessel closure when inadvertent coil protrusion is threatening. We rather prefer to perform a partial coiling to protect the fundus of the aneurysm to avoid early rebleed and to carry back the patient to the angiographic suite a few weeks later to optimize the aneurysm occlusion with the adjunct of a stent if required.

ANTIPLATELET THERAPY MANAGEMENT FOR ELECTIVE SACT

Our standard dual antiplatelet regimen is based on the oral administration of clopidogrel and aspirin. Instead of using a loading dose of clopidogrel we initiate dual antiplatelet therapy (clopidogrel and oral aspirin) 10–15 days prior to the procedure. For antiplatelet activity assessment we use the VerifyNow (Accumetrics, San Diego,

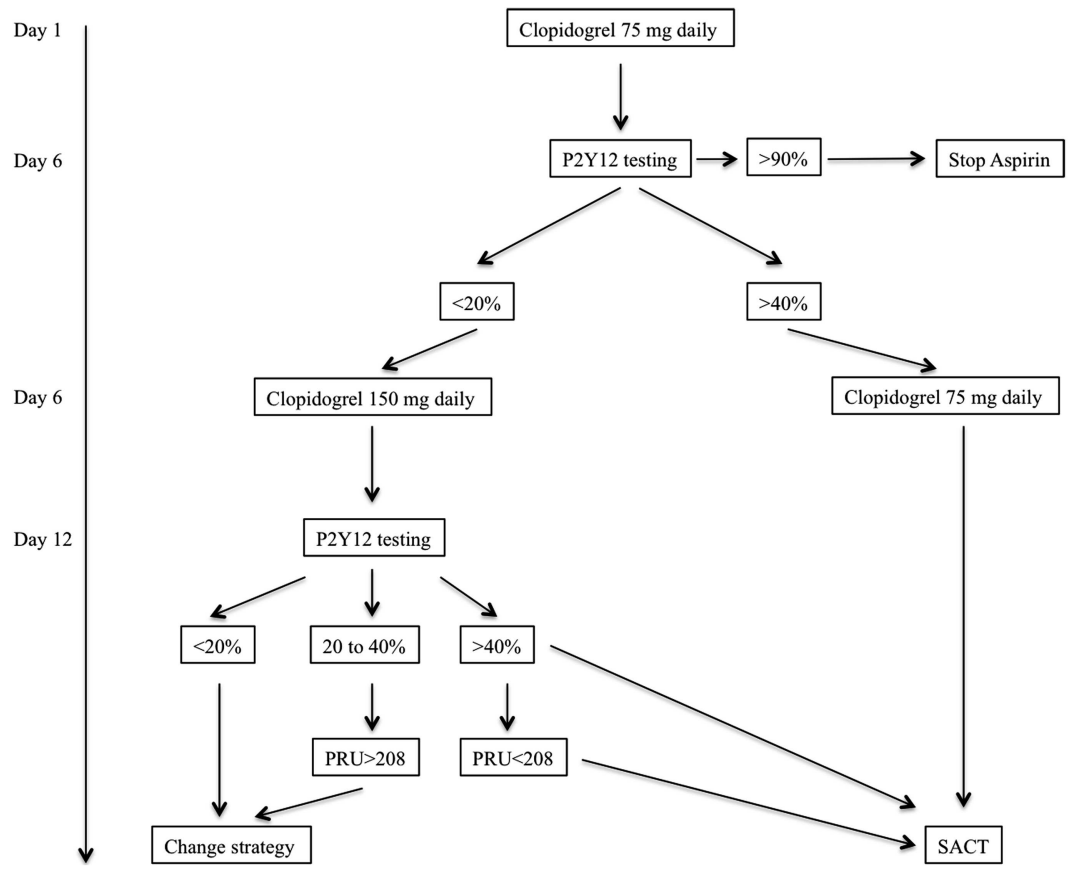

FIGURE 2 | Flow chart of our antiplatelet therapy assessment prior to elective stent-assisted coiling procedures. The patient is given clopidogrel and aspirin (250 mg daily) at Day 1. Because clopidogrel is a prodrug treatment should be initiated 5–6 days before efficacy assessment. PRU, platelet reaction unit; SACT, stent-assisted coiling technique.

CA, USA) system which a bedside system that is requiring minimal manipulation. This measurement is based on the principles of optical aggregometry. Because low responder patients may not be recognized with loading dose we rather prefer to initiate the treatment with a standard dose of Clopidogrel (75–150 mg daily). Our protocol has been standardized and applied to all patients for whom elective aneurysm treatment with SACT is scheduled (**Figure 2**).

CONCLUSION

Despite the fact that aneurysms treated by the remodeling technique are different from aneurysms treated with standard coiling, the safety of both techniques is similar with a higher anatomic efficacy of the remodeling technique. Accordingly, wide use of the remodeling technique can be proposed. SACT is associated with a higher mortality compared with coiling with or without remodeling and remains more hazardous than stand-alone or BRT coiling in keeping with augmented risks of both ischemic and hemorrhagic insults. However, SACT reduce significantly angiographic recurrence, a factor that alters the results of endovascular treatment over surgical clipping. In the setting of subarachnoid hemorrhage, SACT should be reserved to the otherwise untreatable aneurysm, even if BRT is used, in order to protect the patient from early rebleeding. The optimal antiplatelet regimen in the acute setting has not been determined yet.

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Flow-diversion panacea or poison?

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Endovascular therapy is now the treatment of choice for intracranial aneurysms (IAs) for its efficacy and safety profile. The use of flow diversion (FD) has recently expanded to cover many types of IAs in various locations. Some institutions even attempt FD as first line treatment for unruptured IAs. The most widely used devices are the pipeline embolization device (PED), the SILK flow diverter (SFD), the flow redirection endoluminal device (FRED), and Surpass. Many questions were raised regarding the long-term complications, the optimal regimen of dual antiplatelet therapy, and the durability of treatment effect. We reviewed the literature to address these questions as well as other concerns on FD when treating IAs.

Keywords: flow diversion, pipeline, intracranial aneurysm, FRED, Surpass, PED

INTRODUCTION

Endovascular therapy is now the treatment of choice for intracranial aneurysms (IAs) for its efficacy and safety profile. Still, many aneurysms such as large, giant, wide-necked, and fusiform aneurysms are considered more challenging and less amenable to traditional endovascular coiling (1). Stent-assisted coiling (SAC) and balloon-assisted coiling (BAC) were alternative techniques developed to deal with such complex aneurysms, but studies have shown their less than expected efficacy given their high rate of recanalization (2–5). The flow-diversion (FD) technique has brought a feasible and effective solution. In addition, the use of FD has recently expanded to cover many types of IAs in various locations. Some institutions even attempt FD as first line treatment for unruptured IAs. The most widely used devices are the pipeline embolization device (PED), the SILK flow diverter (SFD), the flow redirection endoluminal device (FRED), and Surpass. Many questions were raised regarding the long-term complications (i.e., delayed bleeding and device migration), the optimal regimen of dual antiplatelet therapy (APT), and the durability of treatment effect. We reviewed the literature to address these questions as well as other concerns on FD when treating IAs.

FLOW-DIVERSION METHOD

The FD technique relies on a concept of endoluminal reconstruction of the parent artery and the aneurysm neck by excluding the aneurysm from the circulation. The stasis of blood flow in the aneurysm leads to an inflammatory response followed by thrombosis and "healing" of the aneurysm while the stent acts as a scaffold for neointimal proliferation and remodeling of the parent vessel. Therefore, the FD approach is considered physiologic as it restores the normal homeostasis. A recent study showed that flow-diverter device (FDD) reduces the velocity in the aneurysm sac significantly more than multiple "non-flow diverter" stents, even though both dramatically reduce the aneurysmal fluid movement (6). To break the communication between the parent artery and the aneurysm while maintaining a patency of sidewall branches, the device must fulfill two requirements: a low porosity (metal-free to metal-covered area) and a high pore density (number of pores per square millimeters for a given porosity) (7, 8). However, sidewall branch occlusions do not always lead to ischemia since collaterals may maintain flow to the dependent area. Even more, when collaterals are not present, the increased demand for tissue perfusion may, in some cases, generate a pressure gradient sufficient to maintain an anterograde flow through the device (7).

The technique involves navigating an FDD through the arterial system and deploying it across the aneurysm neck. Proper deployment is essential as inadequate wall apposition may decrease the flow with consequent thrombus formation at the interface followed by thromboembolic events (8). Proper deployment and adequate wall apposition can be achieved by balloon (Boston angioplasty (9), though not always needed. More so, the increased turbulence along with the lytic enzymes released from platelet aggregation predisposes to a possible lysis of the aneurysmal wall that can usually occur in the following days post-op (10). This may lead to rupture and SAH if the aneurysm is not completely thrombosed. After stent deployment, there are no data-driven guidelines on optimal APT. Most of the time, the patient is maintained on dual APT for 3–6 months followed by lifelong monotherapy. In practice, the indication varies depending on the aneurysm location (anterior vs. posterior), and parent artery/side vessels stenosis (1, 8). The blood-thinning component makes FDD of limited use in ruptured aneurysm, at least not before the aneurysm is entirely secured. The heterogeneity of the response to APT, especially with clopidogrel, could explain the in-stent thrombosis on

one hand, and the hemorrhagic events on the other. One study led by Lee et al. showed that all cases of intraprocedural thrombosis occurred in patients with poor response to antiplatelet treatment (11). Delgado et al. found that pre-procedure P2Y12 reaction unit (PRU) value of <60 (over-inhibition) was an independent predictor of perioperative hemorrhagic events and a PRU value of >240 (under-inhibition) was an independent predictor of perioperative ischemic events (12). Both a technically difficult procedure and labile hypertension are independent risk factors of thromboembolic and hemorrhagic complications. In practice, some authors recommend loading the patient 10 days prior to the procedure with 75 mg/day of clopidogrel (or another thienopyridine) and 81 mg/day of aspirin until 30–90% $P2Y_{12}$ inhibition is achieved (9). In our institution, Clopidogrel assays are checked at baseline before the administration of Clopidogrel and then again just before the procedure. The percentage of inhibition is calculated and the dosage is adjusted to achieve a platelet inhibition between 30 and 90% before the procedure. Patients with resistance to Clopidogrel are switched to Prasugrel. Dual APT is envisioned for at least 6 months, followed by lifelong monotherapy of aspirin (81 mg).

Table 1 | Indications and concerns regarding flow diversion treatment.

Indications for flow diversion	Concerns
Diameter >10 mm	Bifurcation aneurysm
Neck width >4 mm	Small saccular aneurysm with low recurrence risk after coiling
Complex morphology: fusiform, dissecting	
Recurrence after coiling	

The FDDs offer the advantage of avoiding IA manipulation that increases the rupture risk as well as avoiding any coil insertion that may worsen the preexisting mass effect. The findings of Lylyk et al. (13) and Szikora et al. (14) were consistent with this advantage as they reported that improvement of mass effect symptoms occurred after FD treatment. On the contrary, the inflammatory changes inside the aneurysm may cause a transient worsening of the mass effect that can be seen initially after the procedure, by increasing the aneurysm size or perhaps by direct spread of the inflammation to the surrounding parenchyma (15). A well-known yet poorly understood complication is the rupture of previously silent IAs. One reason could be the hemodynamic alteration of flow after PED or SFD placement (16). Delayed hemorrhage is another unfavorable outcome whose risk factors are not fully elucidated. Evidence shows that large size, complex geometry, and high aspect ratio (>1.6) predispose to delayed hemorrhage (17). More so, Kuzmik et al. highlighted the unpredictability of FD by showing that even when the morphology and the location are similar, the treatment outcomes may differ enormously (18). One final major area of ambiguity is the delayed remote intracerebral hemorrhage (ICH), explained by some as shower emboli with hemorrhagic conversion and by others as a damping effect after FD that increases the pulsatility of distal vasculature and leads to small arteriolar rupture (15). As for the indications of FD (**Table 1**), it was used traditionally for large and giant aneurysms (diameter >10 mm), wide-neck aneurysms (neck width >4 mm), and aneurysms with a morphology unsuitable for coiling (fusiform and dissecting). In theory, FD can be used for any type of aneurysm but concerns remains about its use in bifurcation-aneurysms and whether it is worth using in small saccular aneurysms with low recurrence rate after coiling (15) (for illustrative pictures of aneurysm treated with PED, check **Figures 1–6**).

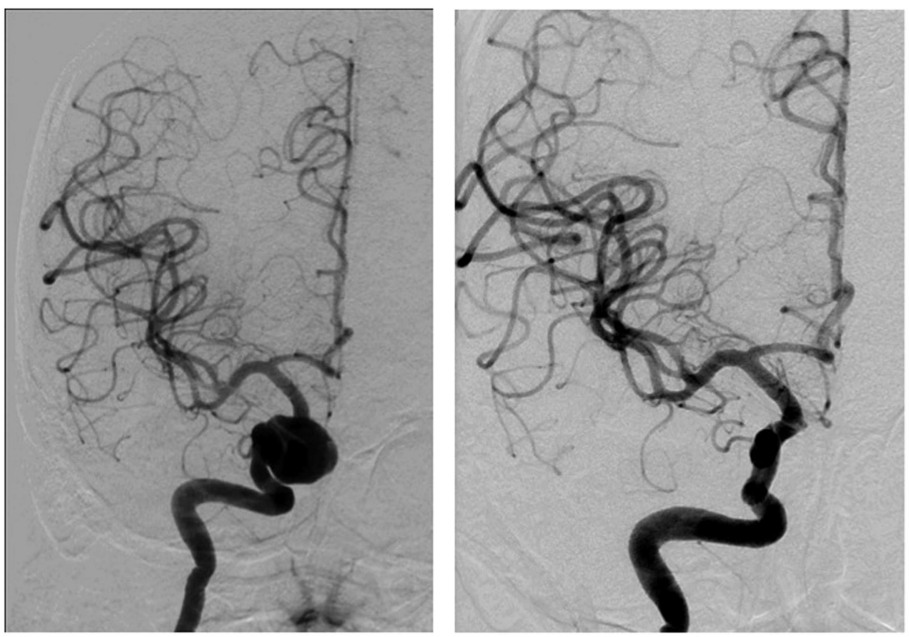

FIGURE 1 | Case 1.

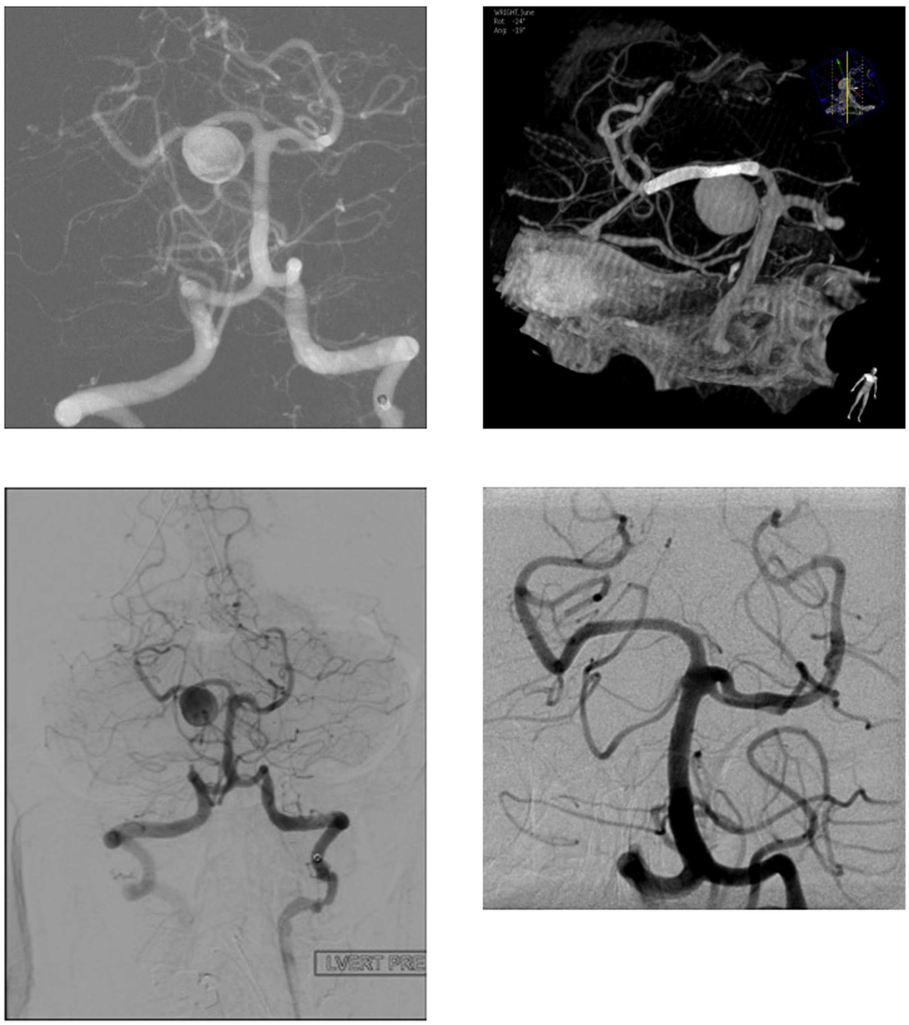

FIGURE 2 | Case 2.

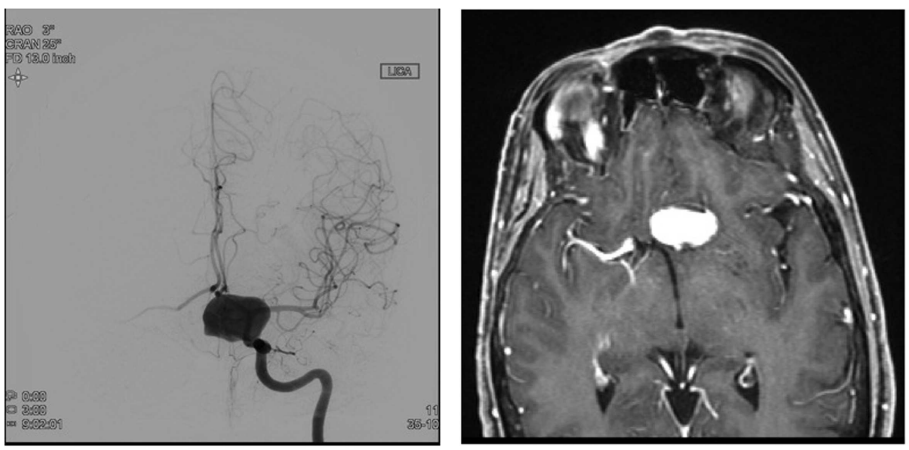

FIGURE 3 | Case 3.

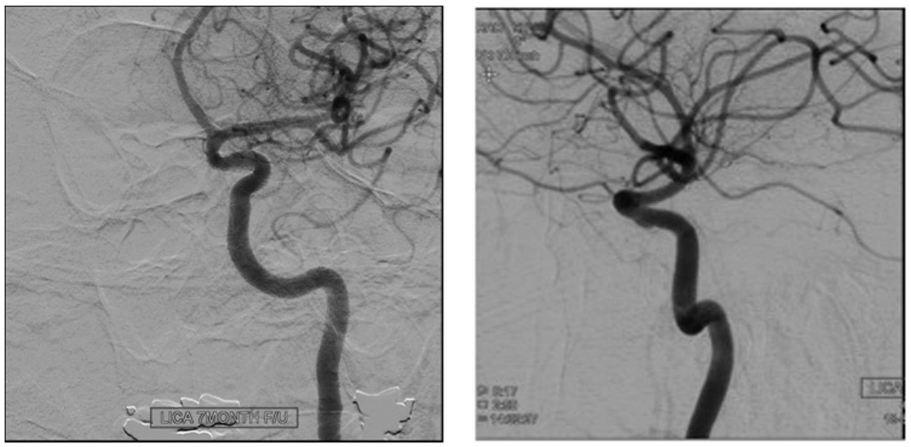

FIGURE 4 | Case 4.

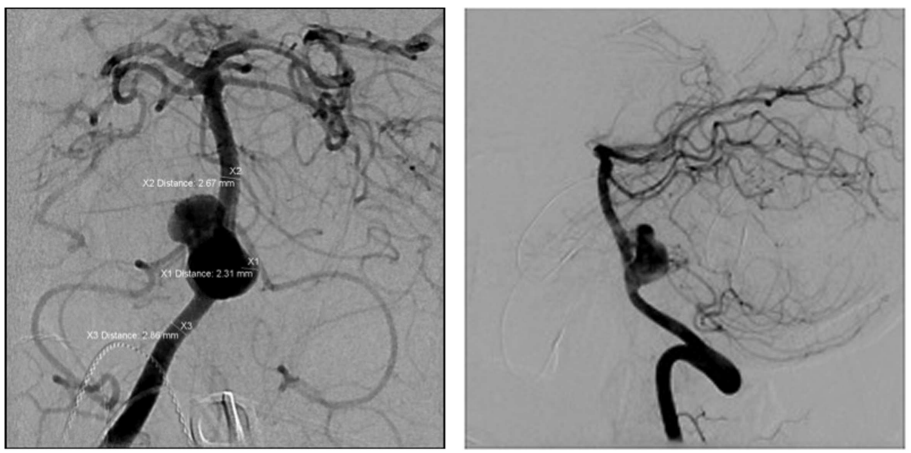

FIGURE 5 | Case 5.

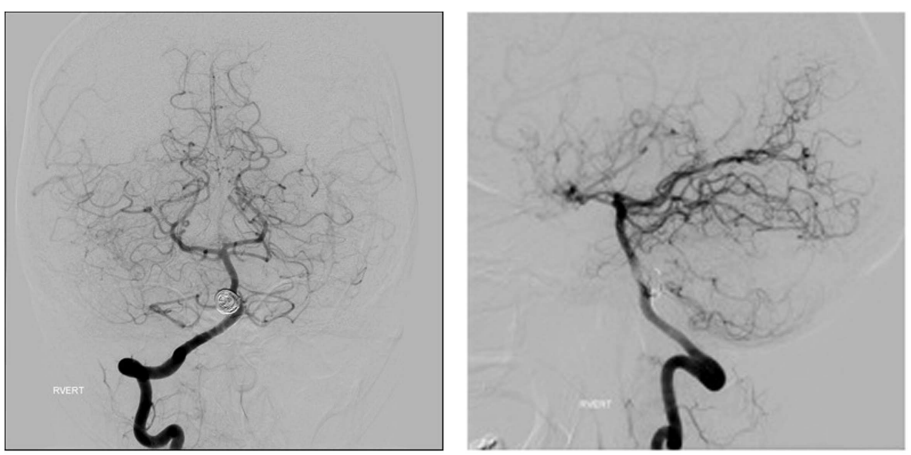

FIGURE 6 | Case 6.

PIPELINE EMBOLIZATION DEVICE

The PED (ev3, Irvine, CA, USA) is a microcatheter-delivered, self-expanding, cylindrical stent composed of a mesh of 48 individual cobalt chromium and platinum strands. It has a low porosity, high metal coverage, and is specifically designed for FD. It is available in lengths up to 35 mm with diameters of 2.5–5 mm in 0.25 mm increments.

This device once initially used for large and giant aneurysm has been increasingly used for smaller and less complex ones. Recently, PED has been shown in the treatment of large (>10 mm) saccular unruptured aneurysms (UAs) to achieve higher occlusion rate, fewer recanalization rate, and similar morbidity and mortality than with traditional coiling (9). Another benefit of PED when compared to coiling is the fewer cost when the aneurysm is $>0.9\,cm^3$ and only one device is used (19). It is of highly importance to estimate the number of PED required as it affects the cost, the safety, and the efficacy of the procedure (20).

In a systemic review of the literature involving 10 studies, Leung et al. managed to pull out data on 414 patients with 448 IAs treated with PED (1) (**Table 2**). The mean number of PED used was 2 devices per IAs. The procedure-related complications were IAs rupture, ischemic strokes, non-IA-related intracranial hemorrhages, worsening of mass effect, and femoral/retroperitoneal hematomas. The overall symptomatic complication rate was 10.3% (46/447), of which 6.3% were exclusively intracranial vascular events (ischemic or hemorrhagic). The procedure-related mortality was 2.2% (9/413), mostly due to rebleeding. The morbidity and mortality rate following treatment of UAs was much lower than those following the treatment of ruptured ones (6.1 vs. 18.8%, 0.8 vs. 12.5%, respectively), but no statistical test was applied in their study. The limited number of ruptured IAs in the studies makes the difference in morbidity and mortality rates less valid. Still, the authors advised against the use of PED in context of ruptured IAs given the lack of evidence on its efficacy and safety in the literature. The authors found that IAs that have been previously stented posed a challenge to PED deployment, had a higher rate of vascular complications and a lower rate of complete obliteration. Thus, the previous findings should be taken into consideration while planning PED treatment for previously stented aneurysm. Complete obliteration was achieved in 82.8% (293/354) at 6-month follow-up, which compares favorably with SAC (21) and balloon-assisted embolization (22). However, a more scientific comparison is needed before concluding. Fargen et al. (16), in their review of reported complications associated with the PED, found similar morbidity (5.3%) and mortality (1.3%) rates.

In another study, PED was used to treat complex, simple, wide-necked, giant, small, fusiform, dissecting, and saccular aneurysms (23). Technical deployment was successful in all cases. On average, the number of PED device used was 1.91 per aneurysm (23). Reported symptomatic complications constituted 13.9% and included thromboemboli, ICH, dissection, and death. Multiple stents were used to ensure proper coverage and care was taken not to cover the perforator with more than one stent.

Piano et al. managed to treat successfully 47 aneurysms with Silk and 57 with PED without any technical failure (24). The morbidity and mortality rate, including delayed complications were both 3%. Follow-up after 6 months showed complete occlusion in 85% of the cases. At 1-year follow-up, no recanalization was observed.

On the other hand, some authors reported remarkably lower rates of mortality and morbidity. Saatci et al. treated 251 aneurysms in 191 patients using PED with a morbidity rate of 1% and a mortality rate of 0.5%. Similarly, Pistocchi et al. in a series of 30 aneurysms beyond the circle of Willis reported no mortality and a morbidity rate of 3.7% (25). Finally, Brinjikji et al. in their meta-analysis of 29 studies, examined 1452 patients with 1654 IAs and found that the procedure-related morbidity and mortality with FDDs (both PED and SFD) were 5% (95% CI; 4–7%) and 4% (95% CI; 3–6%), respectively, and the complete occlusion rate to be 76% (95% CI; 70–81%) (26) (**Table 2**). They also noted that treatment of posterior circulation aneurysm is more prone to ischemic events, particularly perforator infarction when multiple devices are used. Overall, the perforator occlusion risk was 3%.

Another major concern with PED stent is the higher risk of spontaneous migration, which could be early or delayed, and results in aneurysm rupture or ischemic events (27). It is best managed by placing additional stents to achieve once again complete coverage or even more precociously, by taking preventive measures in the first place, such as using longer PEDs, achieving complete expansion, avoiding dragging and stretching of the PED that distorts and shortens the device, and finally using adjunctive coiling to prevent any prolapse of the PED into the aneurysm (27).

SILK FLOW-DIVERTER

SILK stent (Balt Extrusion, Montmorency, France) is a self-expanding flexible stent constructed of woven nitinol strands

Table 2 | Morbidity, mortality, and occlusion rates for FDDs as reported from case series, systemic reviews, and meta-analysis.

	FDD used	Morbidity rate (%)	Mortality rate (%)	Complete occlusion at follow-up (%)
Leung et al. (systemic review)	PED (1–3.2/patient)	Ruptured and unruptured aneurysms: 6.3 Ruptured only: 18.8 Unruptured only: 6.1	Ruptured and unruptured aneurysms: 2.2 Ruptured only: 12.5 Unruptured only: 0.8	82.8
Saatci et al.	PED (1.3/patient)	1	0.5	91.2
Brinjikji et al. (meta-analysis)	PED and SFD	5	4	76
Pistocchi et al.	PED and SFD	3.7	0	78.9
Briganti et al. (meta-analysis)	PED and SFD	3.7	5.9	85

and platinum microfilament with low porosity and high metal coverage of 35% (28). It is available in 2–5 mm diameters and in 15–40 mm lengths.

Treatment with Silk has been shown to be efficacious, safe, with reasonable morbidity and mortality. Silk was found in some studies to achieve similar occlusion rates to PED, but with the cost of higher early complications (25, 29). Mortality rates for the device reported from case series ranged from 0 to 8% and morbidity rates from 3.9 to 15% (29–33). Complete aneurysm occlusion rates were 50–69% at 6-months follow-up, and one study of 26 aneurysms reported an occlusion rate of 86% at 1 year (29). However, the number of studies does not allow a fair head-to-head comparison with PED.

A multicenter study enrolling 25 Italian centers evaluated 273 patients with 295 IAs that were treated with Silk or PED (10). The trial included fusiform, large, giant, and wide-necked aneurysms. Also, small aneurysms deemed untreatable by conventional coiling were included in the study. The morbidity and mortality rate in the anterior location were 2.3 and 3.5%, respectively. In the posterior location, the reported morbidity and mortality rate were 5.4 and 19%, respectively. The overall mortality rate was 5.9% and the morbidity rate was 3.7%. Hemorrhagic events occurred in 5.5% of patients, of which 50% were device-related complications: seven patients had delayed aneurysm rupture (two with SFD, five with PED), and one patient had middle cerebral artery (MCA) perforation during PED retrieval after distal migration of the device. The remaining seven had hemorrhagic events that were deemed procedure-related such as iatrogenic vessel perforation and ICH on APT.

Thromboembolic events occurred in 4.8% of patients and included: side-branch occlusions (one with Silk, two with PED), in-stent thrombosis (three with Silk, three with PED), and procedure-related ischemia. The authors also noted a higher mortality in the subgroup of intracavernous aneurysms (4%) treated by FDD and in the small subgroup of patients with giant complex aneurysm treated by coiling (35.7%; 5/14) (10). Thus, it is recommended that extradural aneurysm be treated only if symptomatic and in expert hands (10). Finally, failure of device deployment, device mispositioning, in-stent aggregation, and other technical complications occurred in 21.5% of the procedures without clinical manifestations. This high rate may be related to the recent introduction of the devices (10). At 3-month follow-up, complete occlusion was achieved in 85% of patients. The remaining 15% were exclusively aneurysms of the anterior circulation. Finally, the authors conducted a meta-analysis of six studies, including their own (13, 14, 30, 33, 34) that showed an overall morbidity rate of 6.2% (CI 95% 2.0–6.7%) and a mortality rate of 3.4% (CI 95% 2.4–4.7%). The safety and efficacy of FD use in bifurcation aneurysms remain unknown. So far, FD has been reserved for bifurcation aneurysms that are not amenable to surgery and when other means of endovascular treatment are deemed risky (35). A study was recently published on PED treatment of 25 aneurysms located at MCA bifurcation or M2 in case one of the bifurcating branches or a distal branch originated directly from the aneurysm sac (35). Follow-up (3–30 months) showed a complete occlusion rate of 84%. They had no mortality and an SAH as the only procedural complication. Even with the limited number of cases and the lack of long-term follow-up, the results are somewhat encouraging.

SURPASS FLOW-DIVERTER

The Surpass flow diverter (Surpass; Stryker Neurovascular, Fremont, CA, USA) is a new device that comes in various diameters and length so that most of the time, one single stent is sufficient for aneurysm occlusion (8). The essential features of the device are a low porosity, and a uniformly distributed high pore density that remains constant regardless of the diameter. The advantage of a single device use is the maintenance of a constant porosity by alleviating the need of random telescoping of two implants. This offers additional protection for side branches by allowing a better control of porosity and pore density (8). In a study of 37 patients, harboring 49 UAs, a single device was used to treat each patient except in one case, where telescoping of two devices had to be done to cover the whole diseased segment of a giant fusiform basilar aneurysm (8). The study included: large, giant, wide-necked, dissecting/fusiform, and blister-type aneurysms. Recurrent or recanalized saccular aneurysms that have been previously coiled and small aneurysms that were judged to have a high risk of rupture were also included. In this study, 38 devices were used to treat 49 aneurysms, which means an average of 0.8 devices per aneurysm. There was no failure of device delivery. Complete occlusion was achieved in all 35-non-bifurcation aneurysms. The higher occlusion rate in the study could be due to the maintenance of pore density with the change in diameter of the device, in contrast to PED and Silk (8). As experimental studies have showed, a constant pore density over the length of the aneurysm neck leads to a more efficient FD and durable aneurysm occlusion (7). Still, this conclusion would be premature given the absence of control group in the study. Even more, the high proportion of small aneurysms included in this study could have influenced the higher occlusion rate and the lower complication rate (8). In comparison, none of the 14 bifurcation-aneurysm received complete neck coverage, and only 50% were occluded on follow-up after 6 months. As for the complications, a clot formed in one case over the Surpass stent and was successfully treated by intra-arterial abciximab. Other complications were: small asymptomatic MCA perforation, 2 internal carotid artery traumatic dissections by the microwire (one of which was noticed during the operation and successfully treated by Surpass). There was no major intraoperative vasospasm or migration of the implant, and no periprocedural mortality or significant morbidity. During follow-up, four patients (10.4%) experienced transient ischemic events and one patient (3%) developed a minor stroke 1 month after stopping clopidogrel with persistent neurological deficit. Therefore, the morbidity rate was comparable to coiling and SAC as well as to other FD devices such as PED and Silk (36, 37) (**Table 3**). The majority showed improvement or resolution of their symptoms while the remaining remained stable. The authors concluded that Surpass flow diverter is safe, reliable, and very effective given the right indications. The main limitations of this single trial are the small number of patients and the high proportion of small aneurysms (37).

Table 3 | Mortality, morbidity, and complete occlusion rate as reported from case series.

Device	Mortality rate (%)	Morbidity rate (%)	Complete occlusion (%)
PED	0–6	0–9	76–91.2
SILK	0–8	3.9–15	69

FLOW REDIRECTION ENDOLUMINAL DEVICE SYSTEM

The FRED system (MicroVention, Tustin, CA, USA) is a new generation of FDDs used in the treatment of IAs. Diaz et al. reported the first use of FRED in the western world, in their small trial of 13 patients with 14 IAs (38). They had no immediate complications or technical difficulties. However, the trial lacked follow-up on long-term complications and angiographic results. The authors viewed the ability of the device to maintain its internal shape when navigating in tortuous and kinky cerebral vessels as an improvement over the older generations of FDDs (38). The authors were encouraged by the outcomes of the study.

NOVEL USE OF FLOW-DIVERSION DEVICES

Newly, PED was used for arterial deconstruction instead of reconstruction by inducing a progressive thrombosis of the parent artery that fed the aneurysm (39). In this case report, a patient with a giant distal MCA aneurysm who refused open surgery did not tolerate superselective balloon-occlusion test and catheterization of the aneurysm for PED treatment was unattainable. PED was used for a compromise between branch occlusion and FD. The patient eventually tolerated the progressive thrombosis promoted by PED. It was postulated that chronic ischemia favored the expression of vascular endothelial growth factor, thereby inducing the development of a collateral network by angiogenesis, and restoring the blood flow (39, 40). Nyberg et al. took advantage of the unique property adherent to PED in order to salvage the MCA after surgical clipping of the internal carotid artery aneurysm that left the flow compromised in the MCA (41). The final configuration of PED as well as the final radial forces are related to the material properties of PED and, unlike other FDD, are operator dependent such as the more foreshortened the device is, the greater its radial force (41). The diamond-like configuration of the strands provides PED with high resistance to crushing; more pressure is required to crush the device to its pre-deployment configuration then to deploy it (41). PED was used to expand the MCA against the clip, with the help eventually of balloon angioplasty.

Flow-diversion is also being used for intracranial dissecting aneurysms. In the acute phase, FD can be problematic. First, navigation of the device through tortuous vessel is challenging. More so, the patients have to be put under aggressive antiaggregation, which could be problematic in case of rerupture and rebleeding when the aneurysm is not completely secured. This risk of hemorrhage should be weighed against the risk of ischemic events. On the other hand, FD offers the advantages of avoiding aneurysm catheterization. In addition, the densely packed woven mesh slow or avert the progression of the dissecting aneurysm by holding the flap up against the wall and vessel remodeling (42). Therefore, FDDs are being used effectively and with caution in the treatment of acute dissecting aneurysms. Still, parent artery occlusion, when feasible, remains the preferred and safest treatment option (42, 43).

CONCLUSION

Treatment of UAs with FDDs is safe and effective with high complete occlusion rates. The procedure-related morbidity and mortality varied in the literature, yet remained encouraging. Posterior circulation aneurysms, previously stented aneurysm, bifurcation-aneurysm, and multiple stent use may result in poorer outcomes. These factors must be thought of when determining the type of treatment. Careful manipulation of the device, proper device deployment, and complete coverage of the neck help reduce the procedure-related complications. The use of FD in recently ruptured IAs has not been solidly proven safe. More trials are needed to clarify the management of aneurysms that failed treatment and the management of clinical adverse outcomes as well as their prevention. Finally, the remarkable efficacy that led recently to PED use in smaller and less complex aneurysm should be challenged in randomized controlled trials with traditional endovascular coiling.

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Treatment of intracranial vasospasm following subarachnoid hemorrhage

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Vasospasm has been a long known source of delayed morbidity and mortality in aneurysmal subarachnoid hemorrhage patients. Delayed ischemic neurologic deficits associated with vasospasm may account for as high as 50% of the deaths in patients who survive the initial period after aneurysm rupture and its treatment. The diagnosis and treatment of vasospasm has still been met with some controversy. It is clear that subarachnoid hemorrhage is best cared for in tertiary care centers with modern resources and access to cerebral angiography. Ultimately, a high degree of suspicion for vasospasm must be kept during ICU care, and any signs or symptoms must be investigated and treated immediately to avoid permanent stroke and neurologic deficit. Treatment for vasospasm can occur through both ICU intervention and endovascular administration of intra-arterial vasodilators and balloon angioplasty. The best outcomes are often attained when these methods are used in conjunction. The following article reviews the literature on cerebral vasospasm and its treatment and provides the authors' approach to treatment of these patients.

Keywords: cerebral vasospasm, balloon angioplasty, subarachnoid hemorrhage, cerebral aneurysm, delayed ischemic neurologic deficit

INTRODUCTION

Cerebral aneurysmal rupture leading to subarachnoid hemorrhage is reported to occur at a rate of 5–8 per 100,000 annually, with a peak in incidence in the fifth decade of life (1). The first peak in morbidity and mortality comes with the aneurysmal rupture and ensuing brain damage and hydrocephalus. Treatment with urgent surgery if there is intraparenchymal clot, or external ventricular drain placement to treat hydrocephalus and elevated ICP has significantly lowered morbidity and mortality in this initial period. Early treatment of the ruptured aneurysm by either surgical or endovascular methods to avoid further morbidity and mortality from re-rupture is also indicated (2, 3).

After the initial subarachnoid hemorrhage, patients are still at risk of developing further morbidity and mortality or delayed ischemic neurologic deficit (DIND; also referred to here as clinically significant/symptomatic vasospasm). Symptomatic vasospasm develops in 20–40% of subarachnoid hemorrhage patients and is one of the least understood components in their care (4). Strokes from vasospasm account for nearly half of the early deaths in patients who survive the initial subarachnoid hemorrhage and aneurysm treatment (5). Angiographic vasospasm following aneurysmal subarachnoid hemorrhage was first described in 1950 in the work of Reid and Johnson (6) and published the following year (7). The recognition that development of vasospasm may play a large role in surgical outcomes was recognized early (8) and substantiated in 1976 with a large series suggesting that patients fare better if surgically treated within the first 48 h (9). The benefits of avoiding surgery during peak risk times for vasospasm were further characterized in the 1990s with the International Cooperative Study on the Timing of Aneurysm Surgery (10) showing that surgery during the time of peak vasospasm leads to the worst outcomes. The development of endovascular techniques has favorably impacted this concept as endovascular interventions can be coupled with treatment of vasospasm and do not seem to carry a worse prognosis when performed within the high-risk period.

While the ultimate underlying mechanisms that cause vasospasm are poorly understood, it has been established that the risk of DIND is closely related to the size of the subarachnoid clot. In 1980, Fisher published the landmark paper establishing a classification system for subarachnoid hemorrhage patients that was able to predict their risk of developing DIND (11). Although still widely used in clinical practice, the Fisher classification was based on computed tomography performed in its infancy, but the added risk related to increasing amounts of subarachnoid or intraventricular blood has been verified by other studies (12). Other factors such as young age, smoking, drug abuse, and pre-existing hypertension have been thought to be risk factors for vasospasm, but these have not helped much in prediction models for vasospasm (5). It is possible that these antecedent factors may play a role in the severity of spasm and the response to treatment.

Given that DIND is one of the leading causes of morbidity and mortality after aneurysmal subarachnoid hemorrhage, it is not surprising that many strategies have been proposed to effectively deal with it. Thus far, some of these have proven fruitful, while others have not. This has culminated in the publication of The Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage in 2009 (2). While aneurysm treatment has continued to improve, treatment of vasospasm continues to be the clinical event that often frustrates neurosurgeons and neurocritical care physicians and can easily ruin a technically brilliant "save" in this patient population. The remainder of this chapter

will summarize some of the strategies that have been proposed to combat this challenging clinical entity.

DIAGNOSIS

To adequately diagnose vasospasm, one must first be careful to differentiate between clinical and radiographic spasm. The gold standard radiographic test for diagnosis is cerebral angiography, however, this is an invasive and expensive test and it is not practical for daily surveillance in all cases. Up to 70% of patients with aneurysmal SAH show constriction of the cerebral arteries on angiography after post-bleed day 3, but only about 50% of these patients have a neurologic deficit attributable to this arterial distribution, and 20% of them will go on to develop infarction (2). This brings some controversy into the algorithm that should be used for vasospasm treatment or prophylaxis as many of the treatments carry some degree of morbidity themselves. In our practice, subarachnoid hemorrhage patients between day 3 and 14 who develop a new neurologic deficit not explained by rebleeding or hydrocephalus are taken for emergent angiography. High-grade patients with limited neurologic exam are more difficult and the index of suspicion must be kept higher.

Transcranial Doppler technology was developed in the 1980s for indirect measurement of vessel caliber by way of blood flow velocity. Given that it is an indirect measure of vessel diameter, its use is somewhat controversial and benefits are not entirely clear. In addition, the utility can be limited by patients with extremely thick temporal bone that limit ultrasound windows, systemic therapies such as HHH (discussed below), which alter hemodynamics, and inter-observer and institutional variability, which make it difficult to standardize across the general population. TCDs have been shown to be reliable in the MCA with sensitivity of 67%, specificity of 99%, positive predictive value of 97%, and negative predictive value of 78% (13). These values fall off significantly when looking at other brain vessels, again making TCDs less reliable in areas such as the posterior circulation. In 2004, the American Academy of Neurology conducted a systematic review of the literature and concluded that TCDs can be used reliably to screen for the presence of vasospasm in the MCA, but not other vessels (14). They also suggested the following criteria for the diagnosis or exclusion of vasospasm: flow velocity >200 or <120 cm/s, respectively, significant increase in the flow velocities from day to day (>50 cm/s), and Lindegaard ratio (MCA velocity/ICA velocity) >6. In our practice, we routinely obtain daily or every-other-day transcranial Doppler studies in these patients from the day of the bleed to post-bleed day 14 and use the values mainly to follow trends and as a warning sign.

CT angiography has also been used in some centers for the detection of cerebral vasospasm. Several small prospective cohorts have shown good correlation between CTA and DSA in predicting vasospasm and that many unnecessary angiograms could be avoided by using CTA as a screening test (15–17). A more recent meta-analysis found a sensitivity and specificity for CTA of 80 and 93%, respectively (18). It has been thought that adding CT perfusion, or another dynamic imaging modality to CTA would significantly increase its use as a screening study for cerebral vasospasm, but this has not necessarily been the case. One of the difficulties has been in which parameter of CTP to follow. Overall, meta-analysis has found a sensitivity of 74% and specificity of 93% of CTP in the detection of cerebral vasospasm (18). In our practice, we do not use CTA or CTP routinely in diagnosis of vasospasm but reserve its use for sporadic complex cases. We find it more efficient to move the patients with new deficits or large TCD changes directly to angiography as this is the most accurate diagnostic tool and also gives the option of treatment. This also serves to limit the amount of radiation and contrast the patient is exposed to.

PREVENTION OF DIND

The first step in the reduction of morbidity and mortality from vasospasm is prevention of DIND. Several preventive strategies have been proposed and studied and all are used with variable degrees of frequency in the care of subarachnoid hemorrhage patients today. Several excellent reviews are available detailing the trials that have been conducted (2, 19).

Treatment with oral Nimodipine, a calcium channel blocker, has become essentially standard of care in the United States for all patients with subarachnoid hemorrhage. This is based on the 1983 trial by Allen et al. (20) in which 13% of patients in the placebo group suffered a severe neurologic deficit related to vasospasm vs. 1.7% in the Nimodipine group ($p < 0.03$). A larger randomized trial was conducted in 1989 and showed reductions of 34% in ischemic stroke and 40% in poor outcome in patients treated with Nimodipine compared to placebo (21). It is thought, however that these results may be in some way related to cerebral protection since there has been no demonstration of reduction of angiographic spasm in patients on Nimodipine (2, 22). Ongoing trials using different preparations of Nimodipine are ongoing. Other agents such as nicardipine have not shown the same benefits when given intravenously (23). One promising new use for calcium channel blockers is through intrathecal administration. No large-scale studies have been conducted but the intrathecal administration of nicardipine has been shown in smaller studies to reduce TCD velocities within 8 h of administration (24). Nicardipine pellets have also been developed that can prevent local vasospasm after aneurysm clipping (25, 26). Clinical benefits of these therapies have not yet been firmly established.

There has been much interest in the potential of statins to reduce the morbidity and mortality of vasospasm. Statins are thought to improve cerebral vascular reactivity through cholesterol-dependent mechanisms. Much of this literature has stemmed from cardiology. Several clinical trials have been conducted using statins in SAH. Tseng et al. (27) found that SAH patients randomized to pravastatin had a 32% reduction in TCD-diagnosed vasospasm, as well as 83% reduction in vasospasm-related DIND and 75% reduction in mortality. A meta-analysis including this trial and the other RCTs of statin use in 158 SAH patients showed statistically significant reduction in vasospasm (RR = 0.73), DIND (RR = 0.38), and mortality (RR = 0.22) (28). More recent trials have failed to show such a robust benefit (29, 30).

The idea that DIND is caused by clotting in the spastic small cerebral vessels has led to some investigation of the merits of fibrinolytic agents in the treatment of SAH patients. A meta-analysis including five prospective trials and three retrospective series with historical controls found significant absolute risk reduction of 14.4% for DIND, 9.5% for poor GOS score, and 4.5% for death

(31). The benefits to functional outcome, morbidity, and mortality have been offset by the high number of complications with this therapy and it has not gained widespread acceptance in clinical practice (32). This same line of thinking has led to trials with aspirin (33), enoxaparin (34, 35), and tirilizad (36, 37), but these therapies have not been shown to be effective in reducing vasospasm-related morbidity and mortality in subarachnoid hemorrhage.

Magnesium has also been studied as an agent to inhibit voltage-gated calcium channel contraction of vascular smooth muscle. The magnesium in aneurysmal subarachnoid hemorrhage (MASH) trial (38) randomized 283 patients to continuous IV magnesium infusion vs. placebo. This showed a trend toward lower delayed cerebral infarction (RR = 0.66) and poor clinical outcome at 3 months (RR = 0.77), but these findings failed to reach statistical significance. This finding was confirmed in a second trial, MASH-2, which also included a meta-analysis of 2047 patients, which also showed that magnesium was not superior to placebo for reduction of poor outcome after subarachnoid hemorrhage (39). It is our general practice in the ICU, however, to monitor magnesium and supplement to normal levels.

Perhaps the most promising of the new medical therapies for vasospasm are the endothelin receptor antagonists. Endothelin I, when bound to its receptor, is a potent activator of vascular smooth muscle cells resulting in vasoconstriction. Several trials have been conducted using Clazosentan (AXV-034343) (40) and TAK-044 (41) and all have shown significant decreases in angiographic vasospasm. Perhaps the most interesting study of clazosentan randomized 32 patients to continuous IV infusion of clazosentan vs. placebo and monitored for symptomatic, angiographically proven vasospasm (42). Patients in the placebo arm who developed vasospasm were allowed to cross over into the study group. There was 48% relative risk reduction in symptomatic vasospasm in the groups as designed, and 50% of the patients who crossed over had resolution of their vasospasm when treated with the study drug. In the intention-to-treat analysis, there was a trend toward decreased delayed cerebral infarction with clazosentan (15 vs. 44%, $p = 0.13$), but it failed to achieve statistical significance. It is promising; however, that the endothelin receptor antagonists may be a target not only for prevention of vasospasm, but also potentially a treatment once it has already developed. While there has been a clear trend toward decreased angiographic vasospasm in these studies, they have failed to show a clear benefit in outcomes and there has been a relatively high rate of pulmonary complications, hypotension, and anemia (19).

Ultimately, the only medical strategies for prevention of vasospasm with enough evidence to be included in the guidelines for SAH patients were maintenance of normal circulating blood volume (discussed below), and oral Nimodipine. Hopefully this will change in the future as further randomized trials are conducted using newer preventive therapies.

TREATMENT OF VASOSPASM

The ultimate goal in the treatment of cerebral vasospasm after subarachnoid hemorrhage is to avoid DIND by reducing ICP, optimizing the rate of cerebral oxygen demand, and improving cerebral blood flow. Given these goals, early aneurysm treatment and ventriculostomy placement for patients with elevated intracranial pressure is a necessity. Early aneurysm treatment allows the treatment team to be more aggressive with further vasospasm treatment over the course of care.

HHH-therapy (hypertension, hypervolemia, and hemodilution) has been a mainstay in the treatment of SAH patients for many years. The idea that avoiding hypovolemia and hemoconcentration as a mechanism to improve outcome is not novel, and seems intuitive; nonetheless, taking an active roll in driving these parameters has been a little more controversial. This is especially true since the detrimental effects of this therapy include pulmonary edema, respiratory failure, cardiac failure, renal dysfunction, and exacerbation of cerebral edema. It is useful to break this therapy into its components for further analysis.

One of the heralding signs of vasospasm is often elevated blood pressure, with whatever is left of cerebral autoregulation attempting to increase cerebral blood flow by increasing systemic pressure. Whether induced hypertension is useful in preventing arterial vasospasm is another question altogether. One study showed that induced hypertension was able to achieve higher flow in ischemic, but not infarcted territories, despite no change in global CBF (43). No study of induced hypertension in isolation, though, has shown a decrease in the development of angiographic vasospasm. Thus, it is likely that hypertension may be useful in reversing neurologic deficits that develop from vasospasm, but not as a preventive mechanism by itself (44). In our practice, we allow the patient to auto-regulate the blood pressure to levels up to 180 or sometimes 200 systolic once the aneurysm is secured. If the patient develops symptomatic vasospasm with a systolic blood pressure lower than 180, then we usually augment the blood pressure with vasoactive medications.

Hypervolemia is perhaps the most controversial of the HHH components. Many centers continue to use hypervolemia, often dictated by the use of central venous and pulmonary artery catheters, despite the lack of evidence that it is beneficial. One study (45) randomized 82 patients to either hypervolemic or euvolemic status, which was maintained to day 14 after aneurysmal rupture. The central venous pressures were higher in the hypervolemic group, but here was no difference in cerebral blood flow or cerebral blood volume and the incidence of vasospasm was 20% in both groups. Another study found no difference in the incidence of vasospasm or in clinical outcome, but the hospital costs and complication rate were much higher in the patients treated with hypervolemia (46). There is little doubt to the fact that hypovolemia is detrimental to these patients, but hypervolemia may be detrimental as well (2). In our practice, we prefer euvolemia and make every effort to monitor the fluid status and patient weight closely.

Relatively little attention is given to hemodilution as a component of HHH-therapy. Many SAH patients become hemodiluted as a result of operative blood loss and aggressive fluid resuscitation. While hemodilution can increase local CBF by decreasing blood viscosity, it does so at the expense of severe decreases in oxygen delivery capacity (47). Other studies have shown that blood transfusion is an independent risk factor for poor outcome (48), however this finding may be the result of whatever insult caused the need for blood transfusion. The guideline authors did not find

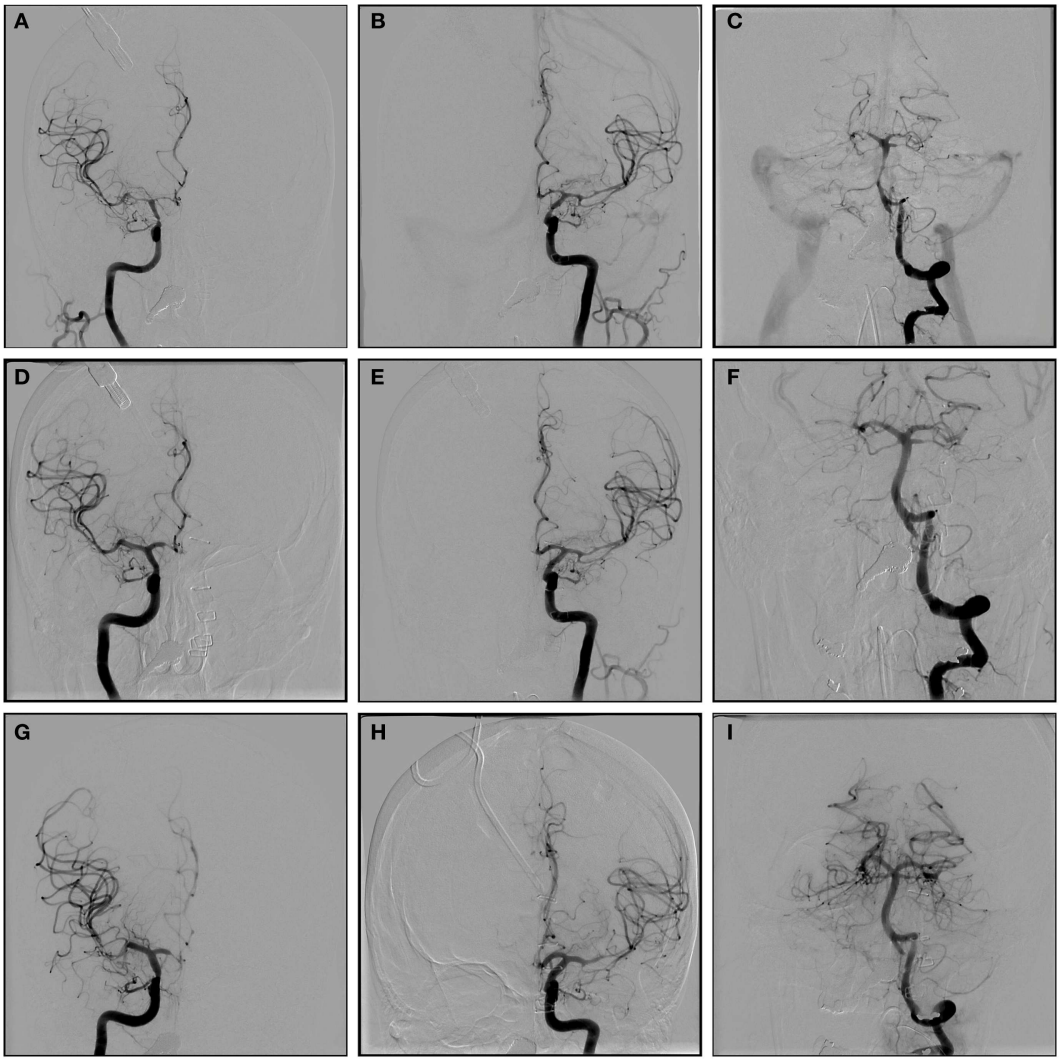

FIGURE 1 | A-P angiographic images of a 58-year old woman with Hunt and Hess grade V subarachnoid hemorrhage from ruptured dissecting right vertebral aneurysm. Concern for vasospasm was generated from routine transcranial Doppler testing. The patient was already maximally medically managed so was taken for angiography. A-P images of RICA **(A)**, LICA **(B)**, and basilar artery **(C)** showing very severe vasospasm. A-P images of RICA **(D)**, LICA **(E)**, and basilar artery **(F)** immediately after balloon angioplasty and administration of intra-arterial verapamil showing resolution of the spasm in the ICA, M1, A1, and basilar artery, as well as improvement in the more distal spasm. A-P images of the RICA **(G)**, LICA **(H)**, and basilar artery **(I)**, 6 days after original treatment showing durability of the angioplasty treatment in the ICA, A1, M1, and basilar artery, but recurrence of spasm in the more distal vessels. This was treated with administration of verapamil.

sufficient evidence to make a recommendation either way (2). In our practice, we generally keep the hematocrit around 30%, and use clinical indicators such as tachycardia or signs of decreased oxygen delivery as indications for transfusion.

ENDOVASCULAR MANAGEMENT OF VASOSPASM

Endovascular balloon angioplasty techniques for treatment of cerebral vasospasm were first described in 1984 (49). The further development of these techniques in the treatment of vasospasm is attractive as it may improve outcomes and ameliorate the detrimental effects of aforementioned HHH-therapy. There is still much controversy today, however, regarding which techniques are best, which patients should be candidates, and the best time to intervene. Overall, the quality of evidence for intra-arterial therapies is low, but it has gained nearly universal acceptance in the algorithm for SAH treatment in centers that have quality endovascular services.

Some controversy exists as to the specific timing of endovascular therapy. One randomized trial (50) has been conducted on the use of balloon angioplasty as a prophylactic measure. Patients treated with prophylactic balloon angioplasty had a significant decrease in the need for urgent rescue therapy for symptomatic vasospasm (12 vs. 26%, $p = 0.03$) but had no statistical difference in the rate of cerebral infarction (23.5 vs. 31.8%, $p > 0.05$) or poor outcome at 3 months (relative risk reduction 29.4%, $p > 0.05$). Several studies have shown that patients had better neurologic

improvement if the intervention (angioplasty or intra-arterial vasodilator administration) is performed as urgently as possible after the neurologic decline with vasospasm (51, 52). The risk of complications must be taken into account when determining the timing of intervention. In the prophylactic intervention study, 4/85 (4.7%) patients had vessel perforations leading to death in three (50).

The choice of therapy is largely dictated by the presumed pathology. If there is little angiographic spasm in the carotid siphon or M1 segment, then intra-arterial administration of vasodilators is the best therapy. Studies have been conducted using many different drugs, but many are small and retrospective. In 1993, Kassell et al. (53) described the intra-arterial administration of papaverine for the treatment of vasospasm and showed marked angiographic improvement in 66% and clinical improvement in 33%. These findings have been replicated in other studies (54). Papaverine was reported to be neurotoxic and resulted in neurologic decline in one study (55) and is very rarely used today in favor of calcium channel blockers. Verapamil (56, 57) and nicardipine (58, 59) have also been used successfully by intra-arterial administration in the treatment of vasospasm. The exact protocol for the dosing and delivery of these agents is not clear. Some prefer a long, slow administration time, while others give the medication as a bolus. Interestingly, it has also been described to administer intra-arterial verapamil via an indwelling microcatheter in the treatment of refractory vasospasm (60). This method could easily be complicated by thromboembolic events, however. All of these agents are vasodilators and administration should result in increased CBF and CBV, therefore, it is recommended that ICP be monitored during treatment (2). It is also important to monitor for systemic hypotension, as this may be more detrimental than the vasospasm itself. In our practice, we use verapamil and nicardipine in 10 mg aliquots in each vessel. At times, if there is no systemic hypotension it is reasonable to increase to 20 or 30 mg in divided doses if the spasm is severe. We have also seen better and somewhat more durable results when the 10 mg dose is infused slowly on a pump over 10–20 min, although this method may not be possible depending on the stability of the patient.

In the larger cerebral vessels (ICA, M1, and basilar), balloon angioplasty has been shown to be very effective and may be more durable. Angioplasty is not generally considered to be safe beyond the carotid or M1 segments (50), although this thought may change with the introduction of newer balloon catheters that are safer in more distal segments. We use angioplasty sparingly in the A1 segment. Overall, the current literature regarding balloon angioplasty for vasospasm is somewhat sparse in terms of quality data. One study compared the effectiveness of balloon angioplasty to intra-arterial Nimodipine and found both therapies to be effective in radiographic resolution of vasospasm, but no difference in clinical outcomes (61). The only high-quality data regarding angioplasty for vasospasm comes from the prophylactic balloon angioplasty trial mentioned above (50). This trial showed a significant decrease in DIND as well as need for therapeutic angioplasty, suggesting the durability of this treatment. A few other smaller trials have shown similar trends, but are significantly limited by small sample size (62). Further clinical trials in this area are necessary to fully investigate the benefits of balloon angioplasty for cerebral vasospasm. In our institution, we favor balloon angioplasty when moderate to severe vasospasm is seen in the large vessels (ICA or M1), but we always use this in conjunction with intra-arterial vasodilator therapy (**Figure 1**), to adequately treat spasm in the more distal vessels.

CONCLUSION

Cerebral vasospasm is an important source of morbidity and mortality in subarachnoid hemorrhage patients. Aggressive ICU care and compulsive management style are necessary to adequately manage these patients. The body of literature on cerebral vasospasm is relatively well developed, but still subject to the relative heterogeneity and complexity of this group of patients. The only Class I evidence regarding cerebral vasospasm used in the publication of the AHA subarachnoid hemorrhage guidelines (2) was that in favor of oral Nimodipine. Early aneurysm treatment, HHH-therapy, cerebral angioplasty, and selective intra-arterial vasodilator therapy was recommended based on Class II evidence. Many other pharmacologic and interventional strategies are currently being investigated. There is little doubt that reduction of DIND will go a long way in reducing the overall morbidity and mortality of subarachnoid hemorrhage patients, and significantly improve our ability to care for them in the future.

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Natural history of intracranial atherosclerotic disease

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Intracranial atherosclerotic disease was very common among stroke patients of Asians, Blacks, and Hispanics ancestry. Furthermore, stroke patients with intracranial atherosclerosis (ICAS) have higher recurrence rate of cerebral ischemia and death than those without ICAS. However, the natural history of intracranial atherosclerotic disease is still in controversy. Most of the studies were retrospective and randomized controlled trial of drugs. This review summarized the prognosis of symptomatic and asymptomatic intracranial atherosclerotic disease in order to guide clinical decision-making and further clinical research.

Keywords: natural history, intracranial atherosclerosis, stenosis, prognosis, outcome

INTRODUCTION

The natural history of disease refers to a description of the uninterrupted progression of a disease in an individual from the moment of exposure to causal agents until recovery or death. Knowledge of the natural history of disease ranks alongside causal understanding in importance for disease prevention and control. It includes four stages: biologic onset, subclinical stage, clinical stage, and outcome. In this review, natural history refers to the clinical outcome under current treatment (including death, recurrent cerebrovascular, or other vascular events, etc.) and regression of intracranial atherosclerotic lesions.

Many studies had confirmed that extracranial carotid atherosclerotic stenosis was the most common vascular lesion found in stroke patients in Caucasians, otherwise intracranial atherosclerotic disease was found commonly among stroke patients of Asians, Blacks, and Hispanics ancestry (1–3). Stroke patients with intracranial atherosclerosis (ICAS) have higher recurrence rate of cerebral infarct event and death. Owing to heterogeneity in vascular anatomy and physiology, atherosclerosis in different vessels may represent diseases with fundamentally distinct courses. Therefore, it is important to distinguish vascular territories when studying the natural history of this condition (4).

PROGRESSION OF CEREBRAL ATHEROSCLEROTIC LESIONS

Atherosclerosis is a progressive disease that starts early in life and is manifested clinically as coronary heart disease (CHD), cerebrovascular disorders, or peripheral arterial disease (5). This disease can be hidden in the human body for many years and ultimately lead to vascular remodeling. Glagov and co-workers (6) put forward the concept of vascular remodeling early in the 80s of the last century. They held that it leads to expansion of the vascular wall at first and does not influence diameter of lumen and supply of blood in the early atherosclerosis, and then to late, it leads to stenosis of blood vessel diameter, thus it causes changes in hemodynamics and even occlusion. Early in 1994, Schwarze et al. (7) had found that intracranial arterial stenoses are dynamic lesions, and that they can evolve and cause further reductions of the arterial diameters after relatively short periods of time. They observed a group of patients with a mean follow-up of 21 months. Ten (35%) arteries with lesions had TCD evidence of progression.

Wong and his colleagues (8) observed 143 patients with symptomatic middle cerebral artery (MCA) stenosis or occlusion. They repeated TCD examinations 6 months after the initial examinations and recorded any stroke or coronary events during this period. The changes of MCA flow velocities were categorized as normalized artery, stable artery, and progressed artery, which were determined according to the changes of MCA velocities at 6 months. By analyzing both the initial and repeated TCD findings, there were 42 patients (29%) in the normalized group, 88 patients (62%) in the stable group, and 13 patients (9%) in the progressed group. For the clinical events during the 6-month period, 18(12.6%) of the patients had further documented vascular events, including 10 recurrent strokes (9 ischemic strokes and 1 hemorrhagic stroke), 5 TIAs, and 3 acute coronary syndromes. Progression of MCA occlusive diseases is associated with an increased risk of vascular events. Jeon et al. (9) studied 103 patients with MCA stenosis (include symptomatic and asymptomatic). To understand its progress situation, patients need to take the TCD reexamination at 6 months after the initial examination. After 6 months, 13 (12.6%) patients showed worsening, whereas 90 were stationary or showed regression upon TCD examination. In this study, the definition of the progression of MCA stenosis as determined TCD examination was not the same as Wong's.

So, intracranial artery stenosis is a process of dynamic changes. The speed of progress is different from each other. Through the prospective study, it is found that lesions may progress, improve, or no change over a period of time. The proportion of progression is about 9–12% for 6 months. The possibility of the progression depends on the time, and it may be greater as time goes on. The progression of stenosis may lead to increased risk of vascular events. However, there is a lack of large sample studies in this area, and the risk factors leading to advances in intracranial artery

stenosis still remain to be determined. Most of the present studies are based on TCD. This examination method needs to a higher requirement for operators and exists to some limitations. In the future, it is urgent to develop the studies based on MRA, CTA, or DSA.

THE CLINICAL OUTCOME OF INTRACRANIAL ARTERY STENOSIS

Major trials investigating prognosis of asymptomatic and symptomatic intracranial large artery stenosis or occlusion disease was shown in **Table 1**.

ASYMPTOMATIC INTRACRANIAL ARTERY STENOSIS

Kremer and co-workers (16) follow-up 50 white patients with asymptomatic atherosclerotic middle cerebral artery stenosis (MCAS) as determined TCD examination for [mean (SD)] 815(351) days. The results showed that no patient suffered an ischemic event in the MCAS territory; one had a transient ischemic attack (TIA) in the contralateral hemisphere; three patients died (one from a subdural hematoma in the contralateral hemisphere, and two from non-stroke-related causes) during the follow-up period. So they came to the conclusions that asymptomatic MCAS of atherosclerotic origin appears to have a benign long-term prognosis with a low risk of ipsilateral stroke in medically treated white patients. Kern et al. (10) took the comparison of the symptomatic and asymptomatic MCA stenosis in patients with recurrent stroke risk and came to a similar conclusion. The authors observed 102 consecutive patients with significant MCA stenosis or occlusion as demonstrated by transcranial Doppler and transcranial color-coded duplex ultrasonography. Patients with symptomatic MCA

Table 1 | Major trials investigating prognosis of asymptomatic and symptomatic intracranial large artery stenosis or occlusion disease.

Reference	Design	No. of patients	Mean follow-up (Month)	Degree of stenosis (%), diagnosis method	Outcome Assessment	Prognosis
Kern et al. (10) (For asymptomatic MCA)	Prospective, observational	102	30.7	TCD and TCCD	Cerebrovascular events, including TIA and stroke	Overall stroke risk was 12.5% per year (ipsilateral: 9.1%) for patients with symptomatic MCA disease the annual; that of asymptomatic MCA disease was only 2.8% (ipsilateral: 1.4%).
Wong and Li (11)	Prospective, observational	705	42	>50%, by TCD	Further vascular events (including TIA, stroke, or acute coronary syndrome) or death	Annual risk of death: 11.2%. Annual risk of cerebrovascular event: 17.1% (For patients only have intracranial stenosis or occlusion)
Chimowitz et al. (12)	Randomized, double-blinded, multicenter trial	569	21.6	50~99%, by DSA	The primary end point: ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke	The primary end point occurred in 22.1% of the patients in the aspirin group and 21.8% of those in the warfarin group.
Mazighi et al. (13)	Prospective, multicenter, non-randomized	102	23.4	50~99%, by DSA or ultrasonography and confirmed by MRA, angiography, or CT	Cerebrovascular event: ischemic stroke and TIA, or vascular death.	The overall vascular death rate was 8.8%. The rate of patients had a cerebrovascular event was 38.2%.
Chimowitz et al. (14)	Investigator-initiated, randomized, clinical trial	451	11.9	50~99%, by angiography	The primary end point: stroke or death within 30 days or stroke in the territory of the qualifying artery beyond 30 days.	1-year rates of the primary end point was 20.0% in the PTAS group and 12.2% in the medical-management group.
Miao et al. (15)	prospective, randomized, controlled, single-center	70	12	Symptomatic MCA stenosis ≥70%, by DSA	The end point events: any kind of ipsilateral stroke or transient ischemic attack, or death from any origin	30-day rate of end point events was 8.3% for PTAS group and 5.9% for medical group. One-year rate of end point events was 19.4 and 17.6%.

TIA, transient ischemic attack; TCD, transcranial Doppler; TCCD, transcranial color-coded duplex ultrasonography; PSV, peak systolic flow velocity; DSA, digital subtraction angiography; MCA, middle cerebral artery; PTAS, percutaneous transluminal angioplasty and stenting; MRA, magnetic resonance angiography; CT, computer tomography; WASID: warfarin–aspirin symptomatic intracranial disease; GESICA: Groupe d'Etude des stenoses intra-craniennes atheromateuses symptomatiques; SAMMPRIS, stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis.

disease had an overall stroke risk of 12.5% per year (ipsilateral: 9.1%), whereas the annual incidence in primarily asymptomatic MCA disease was only 2.8% (ipsilateral: 1.4%; $p < 0.01$). It was significantly lower than that of symptomatic MCA stenosis. Symptomatic MCA disease was an independent predictor for overall [hazard ratio (HR)] 7.91, 95% CI 2.03–30.79; $p < 0.01$) and ipsilateral (HR 9.66, 95% CI 1.5–62.25; $p = 0.02$) cerebrovascular events. Borozan et al. (17) made a retrospective study for patients with intracranial ICA stenosis with mean follow-up of 25.5 months, 93 patients were included, and 24% were symptomatic. Patients were considered for inclusion in this study if a carotid siphon stenosis of 20% or greater was documented arteriographically, and they were identified from a review of 885 consecutive cerebral arteriograms. In this study, overall annual rate of stroke per year was 5.1%, annual incidence of ipsilateral stroke was 5.0%, and overall mortality was 10.6%. Obviously, subgroup analyses revealed that for patients with symptomatic stenosis, annual incidence of ipsilateral stroke per year was 6.4%, whereas that of patients with asymptomatic stenosis was 3.5%.

SYMPTOMATIC INTRACRANIAL ARTERY STENOSIS

Many studies have confirmed that there is a higher risk of death and vascular events in patients with ICAS. Wong et al. (11) included 705 patients with acute ischemic stroke and followed up for 42 months. The annual recurrent stroke rates during the first year were 10.9% for patients without vascular lesion, 17.1% for ICAS only, and 24.3% for both intracranial and extracranial atherosclerosis; for the second year, the rates were 7.5, 8.6, and 7.7%, respectively. More occurrence of death (log rank, 5.19; $p = 0.02$) or cerebrovascular event (log rank, 9.68; $p = 0.002$) was found among patients with than those without vascular lesions. Patients with both intracranial and extracranial arterial lesions were at highest risk of death (log rank, 9.64; $p = 0.008$) and cerebrovascular event (log rank, 11.56; $p = 0.003$). They came to the conclusions that patients with ICAS, especially co-existing extracranial carotid disease, are at higher risk of suffering death or further vascular event.

The GESICA study (13) was another prospective, multicenter, non-randomized study from France. The objective was to evaluate the natural history of ICAS and, in those patients refractory to medical treatment, the outcomes associated with intracranial angioplasty. Patients aged 18–80 were enrolled with symptoms attributed to a single ICAS of greater than or equal to 50%. Optimal medical therapy of vascular risk factors and preventive antithrombotic therapy were at the discretion of the local investigator. Intracranial stenosis (50–99%) had to be demonstrated by either DSA or ultrasonography and confirmed by one of the following methods: MRA, angiography, or CT. During a mean follow-up of 23.4 months, 38.2% of the patients had a cerebrovascular event: ischemic stroke in 13.7%, and TIA in 24.5%. Cardiovascular events occurred in 18.6% of patients. The overall vascular death rate was 8.8%. At the same time, the study also held that clinically significant hemodynamic stenoses were associated with stroke recurrence and may help identify a high-risk subset of patients.

Specific medicine was still not found for ICAS patients. Antithrombotic therapy for intracranial arterial stenosis was evaluated in the Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) trial (18). They reported the risk of stroke in the territory of the stenotic artery was highest with severe stenosis $\geq$70% (HR 2.03; 95% CI 1.29–3.22; $p < 0.0025$). In the NIH registry on use of the Wingspan stent for symptomatic 70–99% intracranial arterial stenosis (19), comparison of the event rates in high-risk patients in WASID do not rule out either that stenting could be associated with a substantial relative risk reduction (e.g., 50%) or has no advantage compared with medical therapy. The frequency of any stroke, intracerebral hemorrhage, or death within 30 days or ipsilateral stroke beyond 30 days was 14.0% at 6 months (95% CI = 8.7–22.1%). The frequency of $\geq$50% restenosis on follow-up angiography was 13/52 (25%). The SAMMPRIS (14) study compared percutaneous transluminal angioplasty and stenting (PTAS) with medical management to prevent recurrent stroke. One-year rates of the primary end point (stroke or death within 30 days after enrollment or after a revascularization procedure) were 20.0% in the PTAS group and 12.2% in the medical-management group.

In the Chinese IntraCranial AtheroSclerosis (CICAS) study (20), we evaluated 2864 consecutive patients who experienced an acute cerebral ischemia within 7 days of symptom onset. The prevalence of ICAS was 46.6% (1,335 patients, including 261 patients with co-existing extracranial carotid stenosis). Patients with ICAS had more severe stroke at admission and stayed longer in hospitals than those without intracranial stenosis (median NIHSS 3 vs. 5; median length of stay 14 vs. 16 days, respectively, both $p < 0.0001$). After 12 months, recurrent stroke occurred in 3.34% of patients with no stenosis, 3.82% for 50–69% stenosis, 5.16% for 70–99% stenosis, and 7.40% for total occlusion.

CLINICAL OUTCOMES OF ICAS BY DIFFERENT VESSELS

The clinical outcomes of ICAS may depend on the situation of vessels (21). A multicenter prospective study from German showed the prognosis of basilar artery occlusion was worse than carotid artery and MCA occlusion (22). The location of lesions may affect prognosis and treatment. It is necessary to take a review to natural history based on distribution of ICAS.

Intracranial internal carotid artery

In 1982, Craig et al. (23) published their first retrospective study and explored the natural history of intracranial internal carotid artery (ICA) atherosclerosis. The diagnosis was confirmed by DSA to demonstrate that stenosis rate >30%. The results suggested that overall annual incidence of stroke was 11.6%; annual incidence of ipsilateral stroke events was 7.6%; symptomatic patients is higher than that in patients with asymptomatic stenosis in annual recurrence rate of cerebral ischemia events (45 vs. 36%); but there was no differences between the two groups in overall mortality (42 vs. 45%). In the same year, Marzewki et al. (24) published a similar retrospective case series study on intracranial ICA stenosis. The diagnosis was confirmed by angiography that stenosis rate >50%. Overall annual recurrence rate of stroke per year was 3.9%; incidence of ipsilateral stroke was 3.1%. Bogousslavsky (25) observed 22 patients with stenosis rate greater than 30% documented by angiography. During a mean follow-up of 40.4 months, seven patients died (32%), and among them, six patients died of

heart disease and one died of stroke. In this study, annual incidence of ipsilateral stroke per year was 8.1% and the annual mortality was 9.5%.

Middle cerebral artery

Although most of previous studies were miniature retrospective studies, recently, more and more countries and regions successively carried out a number of large-size prospective studies. These studies reported that average annual mortality and annual incidence of ipsilateral stroke were 2.7–7.1%. Furthermore, these studies also suggested that progression of plaque and appearance of Microembolic signals (MES) often foreshowed stroke recurrence. So these methods were helpful to screen high-risk patients. For studies on MCA, they also began from a series of small-sample retrospective case studies, which was similar to the related studies on intracranial ICA and vertebrobasilar artery (VB). The first paper published in 1979. Hinton et al. (26) analyzed 16 consecutive patients with symptomatic MCA stenosis. Follow-up was from 1 month to 6 years, and finally 2 of the 16 (12.5%) developed severe stroke events, which were located in the territory of stenotic MCA, no deaths. Corston et al. (27) reviewed 21 patients with symptomatic intracranial artery stenosis confirmed by angiography, and among them, 90% had M1 segment of MCA lesions. During the mean follow-up period of 6.5 years, 5 patients (24%) suffered stroke events (4 of them were fatal stroke), 10 patients (48%) died due to various reasons. Annual incidence of stroke was 3.7%, overall annual mortality was 7.1%, and annual incidence of fatal stroke was 2.9%.

The first prospective study about MCA stenosis was from a subgroup analysis of intracranial and extracranial bypass (28). This study was about the efficacy of drug therapy and extracranial–intracranial bypass operation for ICAS. In the group of drug therapy, 138 patients with symptomatic MCA stenosis or occlusion were recruited. During the mean follow-up period of 55.8 months, 23% of patients suffered stroke events in the territory of arbitrary vessels and overall annual incidence of stroke was 5.0%. This study did not report location and mortality of stroke. Arenillas et al. (29) conducted a prospective study in view of symptomatic MCA stenosis. They screened from consecutive TIA or stroke patients and 40 of them entered this study, which confirmed by TCD and cerebral angiography as MCA stenosis. During the mean follow-up period of 26.5 months, eight patients (20%) occurred cerebral ischemic event in the territory of stenotic MCA (six TIAs and two stokes), annual incidence of ipsilateral TIA was 6.8%; annual incidence of ipsilateral stroke was 2.3%. Progression of stenosis was independent predictors of stroke recurrence. The results of this study suggested that periodic review of transcranial Doppler ultrasound was helpful to screen patients with high-risk. Gao et al. (30) provided another method to identify high-risk population for us. This prospective study observed 114 consecutive patients with acute ischemic stroke. These patients were confirmed by TCD as MCA stenosis. Each patient received TCD examination for three consecutive days during acute period, 30 min for each time, which detected the existence of MES. During the mean follow-up period of 13.6 months, 10 patients recurred stroke in the territory of stenotic MCA and 9 patients died. Annual recurrence rate of ipsilateral stroke was 7.8%; overall annual mortality was 7.0%. TCD found that MES was independent predictors of stroke recurrence. This study not only indicated mechanism of embolization in stroke recurrence, but also showed a new method to confirm patients at high-risk – MES detection. Recently, Miao et al. (15) performed a prospective, randomized, controlled, and single-center clinical trial to compare PTAS with medical treatment for symptomatic MCA stenosis ($\geq$70%). The PTAS group received stenting or balloon angioplasty, whereas the medical treatment group received standard medical treatment (aspirin 100 mg plus clopidogrel 75 mg/day), and all the patients were under strict control of the risk factors. The end point events were any kind of ipsilateral stroke or TIA, or death from any origin during 1-year follow-up. The 1-year rate of end point events was 19.4 vs. 17.6% ($p = 0.85$) for PTAS and medical group, respectively.

Vertebrobasilar artery

Researchers in WASID carried on a investigation, which prompted that in the case of intracranial artery stenosis, the involved vertebral basilar artery was 35–40% (12). There were also many limitations in studies of outcomes of posterior circulation atherosclerosis. There exist obvious variation in the average annual stroke recurrence rate in territory of stenosis artery, overall annual incidence of stroke, overall annual mortality in these studies, and range of which was 0–8.7%, 3.0–14.3%, and 2.9–42.8%.

The subgroup analysis from warfarin–aspirin symptomatic intracranial disease (WAISD) (31) study group showed that 22% of patients had an ischemic stroke (arbitrary territory of artery), 15% of patients suffered stroke in the territory of the stenotic artery, and 10.3% of patients died (5.9% of them died of stroke). These results suggested that annual mortality was 6.2%, overall incidence of stroke was 13.1% and incidence of stroke in the territory of vertebral basilar artery was 8.7%. According to the location of specific plaque, they assessed the recurrence rate of stroke. For patients with vertebral artery stenosis, annual incidence of stroke in the territory of the stenotic artery was 7.8%, whereas for patients with basilar artery stenosis, incidence of stroke was 10.7%. For posterior cerebral artery and posterior inferior cerebellar artery, the incidence of stroke was 6.0%.

Qureshi et al. (32) published a retrospective multicenter study. A total of 102 patients were included, which accepted the mean follow-up period of 15 months. Fourteen patients experienced recurrent stroke (arbitrary territory of artery). Eight patients experienced stroke in the territory of vertebral basilar artery. Twenty-one patients died during follow-up, and among them, 16 patients died of fatal stroke. These results suggested that overall incidence of stroke was 11%, annual incidence of stroke in the territory of vertebral basilar artery was 6.3%, and overall annual mortality was 6.3%. Kaplan–Meier analysis revealed that stroke-free survival of patients was 76% at 12 months and 48% at 5 years. This suggested that most of patients with symptomatic intracranial VB stenosis, in the 5 years after the initial onset, would suffer recurrent stroke or death. In this analysis, elderly and lack of antiplatelet or anticoagulant therapy are independent predictors of poor prognosis.

A series of reports from New England Medical Center Posterior Circulation registry made us better understanding the stroke in posterior Circulation. The overall 30-day mortality was 3.6%. Embolic mechanism, distal territory location, and basilar artery-occlusive disease carried the poorest prognosis. The best outcome was in patients who had multiple arterial occlusive sites; they had position-sensitive TIAs during months to years (33). For patients with moderate to severe BA occlusive disease, the mortality rate was 2.3%, and 62 patients (almost 75%) had minor or no deficits at follow-up (34). For patients with bilateral ICVA (intracranial vertebral artery) occlusive disease, the short- and long-term (mean length of follow-up was 31.4 months) outcomes were usually favorable, but patients with bilateral ICVA and basilar artery-occlusive lesions often have poor outcomes (35). The patients with distal territory infarcts due to emboli from the ICVA had the worst outcome (36).

SUMMARY AND EXPECTATION

Overall, intracranial arterial stenoses are dynamic lesions, and that they can evolve and cause further reductions of the arterial diameters or further vascular events as time goes on. However, it is still uncertain that how to recognize high-risk population and what methods can prevent further vascular event efficiently. On the other hand, the natural history of symptomatic and asymptomatic disease is different. The annual incidence of ipsilateral stroke per year for patients with asymptomatic stenosis was much lower than that of patients with symptomatic stenosis. Asymptomatic and symptomatic lesions can transform for each other. But, we do not yet know how this conversion is made. Furthermore, location of the diseased vessel may affect prognosis and treatment. There still lack of large sample, prospective, and observational study to identify the natural history of intracranial large artery disease by different vessels.

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The technique of endovascular intracranial revascularization

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Intracranial atherosclerosis was traditionally believed to carry a risk of stroke of 8% to 22% per annum. The annualized stroke rate in the recent stenting and aggressive medical management for preventing stroke in intracranial stenosis (SAMMPRIS) trial medical management arm was 12.2%. This trial was halted due to excessive periprocedural events in the stent arm. This stroke rate is still unacceptably, high and a treatment strategy is still needed. SAMMPRIS has no bearing on angioplasty alone. Angioplasty alone has always been our primary intervention for intracranial atherosclerosis and remains so to this day due to its relative simplicity, low complication rate, and efficacy. We have, however, made adjustments to our patient management regimen based on the results of SAMMPRIS. This paper outlines our current patient selection, procedural technique, and post-procedure management. The complications we have encountered while developing our technique are described along with how to avoid them and how to manage them. Our most recent results (since previous publications) are also discussed.

Keywords: intracranial stenosis, stroke, angioplasty, stenting, technique

INTRODUCTION

The results from the completed warfarin versus aspirin for symptomatic intracranial disease study (WASID) demonstrated that the rate of subsequent stroke was 18% in the first year for patients with symptomatic [transient ischemic attack (TIA) or stroke] stenoses of ≥70% on "best medical therapy" (1, 2). The annualized stroke rate in the medical arm of the recently published stenting and aggressive medical management for preventing stroke in intracranial stenosis (SAMMPRIS) was 12.2% (3, 4). This improvement from WASID was achieved by utilizing aggressive medical management that included dual antiplatelet therapy with intensive management of vascular risk factors combined with aggressive lifestyle modification (3, 5). Even so, the subsequent 12.2% stroke risk is still unacceptably high. Therefore, a treatment strategy is still needed.

The SAMMPRIS trial was prematurely stopped due to excessive periprocedural events in the stent arm. These results, however, have no bearing on the procedure of angioplasty alone and the associated risks and benefits, nor does SAMMPRIS have implications concerning the much simpler procedure utilizing balloon-mounted stents. The failed stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYLVIA) trial examined balloon expandable stents; all 30-day complications were in locations not recommended by the authors (6). The Vitesse intracranial stent study for ischemic therapy (VISSIT) trial also did not incorporate the patient selection described here but final results are not known; the trial was stopped prematurely (7).

Angioplasty has always been our primary intervention for intracranial atherosclerosis and remains such to this day due to its simplicity, low complication rate, and proven efficacy. Following SAMMPRIS, however, we adjusted our overall patient management regimen, as we will highlight below.

METHODS: CURRENT PRACTICE

PATIENT SELECTION

All patients presenting with transient ischemic attack or stroke undergo cross sectional imaging [computed tomography (CT) or magnetic resonance imaging (MRI)], with vascular studies [CT angiography (CTA), MR angiography (MRA)]. Patients with intracranial lesions thought to be the cause of the presenting event (>70% stenosis by North American symptomatic carotid endarterectomy trial (NASCET) criteria or <1 mm residual lumen in the artery supplying the affected territory) are placed on maximal medical therapy as utilized in SAMMPRIS (3, 5). This is managed by the neurologist (and cardiologist if the patient is under the care of one) and is adjusted as needed to address each patient's specific condition and risk factors. Only patients who continue to have symptoms on maximal medical therapy are considered for endovascular therapy. Patients with incidentally discovered asymptomatic lesions are considered for endovascular therapy only if they have a high-grade stenosis (>70% and/or <1 mm residual lumen) and require major surgery such as coronary artery bypass grafting.

RATIONALE FOR TECHNIQUE

Our technique and its rationale evolved over the first decade of our experience (~1990–1999) and have been described (8). A primary goal in the development of any procedure is to minimize periprocedural complications. In this instance, this was further driven by the belief that complications could outweigh any minor benefit for

stroke prevention, later confirmed by SAMMPRIS (4). Observations led to certain conclusions: (a) procedural simplicity fosters procedural success, (b) excessive or rapid stretching of the vessel leads to intimal damage (8), (c) selecting a balloon approaching the size of the vessel more frequently leads to dissection, (d) intimal damage can lead to acute or subacute thrombosis, occlusion and/or stroke (8–10), and (e) intimal dissection leads to recurrent stenosis (10). It was, and is, our belief that the diseased vessel lacks flexibility and is more fragile and brittle. This fact led us to the analogy that this diseased vessel is like old leather: tough and easily cracked. Very slow stretching seemed to reduce cracking.

Past attempts to achieve a nearly normal vascular channel resulted in complications. While excellent post-angioplasty images might be obtained, important perforators have been sheared off even without visible dissection. This problem has been observed not where plaque is located (where the wall is thick and tough) but rather in normal areas of the wall opposite the plaque (where the wall is thin). This result could possibly be due to various layers of the vessel wall (intima, media, etc.) stretching at differing rates or in different directions, thus, leading to occlusion of the trans-wall microvascular channels. "Snowplowing" of plaque into (or onto) a perforator is a serious consideration but is rare in our observations.

PRE-PROCEDURAL MANAGEMENT

Diagnostic cerebral angiography is generally performed as a separate procedure in order to assess collateral flow and hemodynamics as well as to plan the intervention. It also allows a more accurate estimation and discussion of the risks and benefits of the procedure for that specific patient. Treatment options and timing are discussed with the patient and family. The potential use of "off-label" devices is explained. In general, patients continue to receive all medications until endovascular treatment except when contraindicated; the exception to this would be for the isolated posterior (vertebrobasilar) circulation. Stenoses in an isolated posterior circulation can cause secondary systemic hypertension in an effort to perfuse the brainstem. When normal perfusion is restored, the blood pressure can drop precipitously. We hold the blood pressure medications on the day of the procedure for patients undergoing treatment in an isolated posterior circulation. Reperfusion hypertension can lead to hemorrhage, however, and continuous close observation is required after reperfusion in case the blood pressure needs to be acutely lowered.

PROCEDURE

General

All procedures are performed under general anesthesia. It is difficult or impossible to perform the entire procedure with the necessary finesse while having even minor patient motion; eventually there will be a problem. The majority of procedures are performed via a common femoral artery approach. Distal vertebral and/or basilar artery angioplasties/stents are occasionally performed via an ipsilateral brachial artery approach if there is access difficulty from a femoral approach.

Guide catheter

The position and stability of the neurointerventional guide catheter is critical. Every effort should be made to place the tip as close as possible to the lesion in the intracranial portion of the internal carotid artery (ICA) (typically petrous), or the level of C1 or C2 in the vertebral artery. Lack of safe, stable, and adequately distal position can "make or break" the procedure. A distal position of the guide catheter will help ensure a stable platform for delivery of the microcatheter/balloon and facilitate navigating the lesion with the necessary finesse. Once the working catheter and microguidewire are outside the guide catheter, they will take the outside track in all curves, thus, displacing the vital vectors of force. Once vectors are displaced, all friction exponentially increases and the "memory" in the shaft of the microguidewire can produce stored energy while torquing or steering. Distal microguidewire and catheter manipulation no longer have finesse and are more unpredictable. This distal guide catheter position will also simplify delivery of a stent if needed.

Modern guide catheters have significantly improved our ability to position the tip where necessary [e.g., Neuron (Penumbra, Inc., Alameda, CA, USA)]. Sometimes, however, a high position of the guide catheter is not enough to ensure its stability due to markedly tortuous proximal vessels. In these patients we advise the use of tri-axial system [e.g., a Shuttle sheath (Cook Inc., Bloomington, IN, USA)] through which a neurointerventional guide catheter is placed intracranially (e.g., Neuron). Indeed, a tri-axial system is now frequently employed (see Distal Tri-Axial Guide Catheter).

Telescoping distal access technique. If a carotid or vertebral artery is particularly tortuous and catheterization with a standard wire is difficult or dangerous, we recommend performing a telescoping access maneuver. Place the guide catheter proximal to the difficult access and load a microcatheter and microguidewire through a Y-connector. Select the vessel with a microguidewire and navigate the tortuous curves, following with the microcatheter. Once the microcatheter is well downstream, remove the microguidewire and replace with a stiff microwire, either regular length or exchange length. If the guide catheter itself is made coaxial by the use of an inner distal access catheter [DAC (Stryker Neurovascular/Concentric Medical, Mountain View, CA, USA)], the stiffer exchange-length microwire can provide sufficient stability to allow advancement of the distal access catheter followed by the guide catheter. In this way, there is progressive straightening of the vessel and never a large wire or blunt face of a guide catheter snowplowing on the vessel and potentially causing a dissection.

Proximal tri-axial stabilized guide catheter. If there is a congenitally small vertebral artery, a sheath (e.g., 8 Fr Shuttle) can be positioned in the subclavian artery proximal to the vertebral artery origin. First select the axillary artery and position an exchange wire [e.g., Connors exchange wire (Cook Inc.,)] with the tip distally in the axillary artery. Follow with the Shuttle sheath into the subclavian artery and then replace the exchange wire with a stiff exchange-length microwire [Hi-Torque Sparatcore (Abbott Vascular, Abbott Park, IL, USA)] and secure this wire. The sheath can then be withdrawn to a point just proximal to the vertebral artery without fear of the guide catheter buckling into the aorta.

Distal tri-axial guide catheter. Many times it is necessary to provide stiffer support for the guide catheter. This can be performed

by placing a long 8 Fr. sheath (e.g., Shuttle) into the carotid artery and then advancing the guide catheter through the sheath. For shorter patients, and depending upon where the tip of the guide catheter is to be placed, a 60–80 cm sheath [e.g., Raabe (Cook Inc.,)] is placed so that the guide catheter has adequate length distal to the sheath.

Intraprocedural and periprocedural medication

Oral dual antiplatelet medication is mandatory before all cases. With modern medications, this should never be an issue. Traditionally, aspirin (325 mg non-coated) and clopidogrel have been utilized, although newer antiplatelet agents are also utilized. Platelet inhibition is usually assayed when a patient fails medical therapy; it is increasingly assayed on a routine basis. When a patient is on a single antiplatelet agent prior to an elective procedure, the second agent is started and platelet inhibition is assayed prior to the procedure.

Intraprocedural anticoagulation (e.g., heparin, bivalirudin) is always administered. With the advent of modern antiplatelet medications, rarely is there a need for rescue with GP IIb/IIIa inhibitors such as abciximab. The exceptions to this rule include emergent procedures, such as angioplasty performed in the course of acute stroke therapy, where a GP IIb/IIIa inhibitor might be necessary for bridging until oral antiplatelets take effect. This is typically necessary for clopidogrel, but aspirin is effective within minutes when administered orally or rectally. Other newer antiplatelet agents (e.g., ticagrelor) are also more rapidly effective than clopidogrel.

When any GP IIb/IIIa inhibitor is used, a very dilute mixture is infused very slowly in order to bathe the thrombus over an extended period: minutes, not seconds. While a systemic dose can be infused rapidly (and thus recirculate to achieve benefit), a local intra-arterial dose is very effective without producing systemic effects when administered in this manner.

Any reperfused territory can be susceptible to reperfusion hemorrhage, but isolated vascular territories (those without circle of Willis collaterals) are particularly susceptible. For hypertensive emergencies, it is mandatory that intravenous (IV) labetalol bolus (not nicardipine drip) be immediately on-hand if needed. Labetalol (a mixed alpha/beta adrenergic blocker) is specifically intended for use in hypertensive crises (start with 10 mg IV bolus followed by 20 mg every 2–5 min up to 200 mg.). On the other hand, nicardipine (a calcium ion influx inhibitor/"slow channel" blocker or calcium channel blocker) is only intended for infusion and is safe but slow even as a bolus (effects take several minutes).

Choice of balloon

Angioplasty alone is almost always our intention. Occasionally we will choose primary stenting (see below). Secondary stenting is only performed in rare circumstances such as when the lesion does not respond to repeated angioplasty, there is unacceptable rebound stenosis (return to the pre-angioplasty degree of stenosis or worse), or there is a resultant large dissection.

Most balloons have coronary indications, as do the balloon expandable stents we primarily use. The shortest balloon that will comfortably cover the length of the stenotic segment is chosen, typically 9 or 10 mm. A longer balloon will typically straighten the vessel, thus, stretching the shorter length of the inner curvature and possibly causing a dissection. The balloon diameter is undersized relative to the vessel diameter by 0.25–0.5 mm as previously described (8–11). In most cases, an over-the-wire system is utilized due to superior tracking ability, more sensitive "push–pull," and appreciably more accurate control of the microguidewire when compared with a rapid exchange (monorail) system.

With modern tools and utilizing first-pass over-the-wire balloon technique, crossing a lesion is rarely a problem. Rapid exchange balloon systems perform far worse than over-the-wire systems for this challenge. Due to the fact that the wire is external to the shaft of the catheter, it will follow a different path from the catheter. This results in the development of excessive friction as well as stored energy. The wire will be forced to reenter the catheter and the combination of these factors will impede subtle and accurate microguidewire tip movement. We strongly believe that over-the-wire systems are more suitable for distal intracranial work. A monorail system can be utilized in the setting of proximal lesions (e.g., petrous or cavernous segment of the ICA or distal vertebral artery) and relatively straight vessels.

Choice of stent

Multistep self-expanding stents are rarely used unless necessary to tack down a large dissection (a rare occurrence with the defined technique). This is due to the fact they these are indeed "multistep" and require perfect technique every time. Two pairs of hands are required, both of which need to work in concert. In addition, it may be very difficult to safely re-cross self-expanding stents.

We now make occasional exceptions and perform primary stenting for specific locations. These would include the bare segments of the distal vertebral artery, the pre-ophthalmic carotid artery or, rarely, the proximal basilar artery. For instance, a stent might be chosen for a large eccentric plaque in a large vessel (proximal basilar artery) or for a larger artery in a segment known to have no perforators (distal vertebral artery proximal to the posterior inferior cerebellar artery). Stents are always the shortest available (8 mm if possible) and, of course, undersized. Even so, these stents are frequently hanging free in the vessel at one end of the plaque or the other with no clinical implications (free portions of stents are frequently present in vertebral origin or carotid stenting).

Procedural technique

Immaculate preparation of the balloon is mandatory if you wish to actually see the balloon. When inflating a balloon, the first thing that actually enters the balloon will be air and this must be essentially 0. A fully inflated 2 mm $\times$ 10 mm balloon will hold $<$0.06 ml of fluid. If any appreciable amount of air is present, the procedural damage might be done before you even see the balloon. Last second preparation with instant vacuum occasionally results in almost no contrast whatsoever (all air) in these micro-balloons. Therefore, we prepare these tiny balloons before the procedure with repeated vacuum syringes/stopcocks and replacing all air with contrast before advancing into the brain. A short microtube (30 cm) or luerlock can remain in place attached to the balloon port that can then be used to inflate the balloon after it has reached final position.

With the recommended technique, true inability to access the lesion is now rarely a cause of procedural failure (our technical

success rate over the past 7 years has been 100% in 121 patients). Utilizing modern devices, most cases are performed with a first intention direct approach with an over-the-wire balloon catheter and microguidewire [e.g., Transcend.014 EX Platinum (Stryker Neurovascular, Fremont, CA, USA)]. Accessing the lesion is a two-step process. The first step is simply getting the balloon to a point just proximal to the lesion. This is accomplished with task-specific roadmaps for aid in selecting the intracranial site just proximal to the stenosis. For instance, traversing the petrous and cavernous carotids requires different views and less magnification than those for the highly important part of actually traversing the middle cerebral artery stenosis for the first time. Once the proximal position has been reached, repositioning the image intensifiers will be necessary. One plane will be chosen with maximum magnification for the absolute best view of the stenosis itself (at right angles) with minimal bone overlap. The other plane is used for overall supervision of the procedure. The field of view must include a good view of the stenosis and an optimal view the targeted location for the distal tip of the microguidewire. Being able to see the distal tip of the microguidewire for the entire procedure is mandatory.

Certain lesions (carotid siphon, basilar artery) can be shelf-like and on the outer rim of a sharp turn. Simply traversing the stenotic region is *NOT* the goal. If the microguidewire crosses the stenosis *within the plaque*, balloon inflation will then displace the plaque into the vessel lumen and make the situation worse or critical. It is imperative to avoid dissection of the plaque when crossing it. Finesse, patience, a stable and distal guide catheter position and technical skill are all necessary to traverse particularly irregular or eccentric stenosis. For difficult lesion access, the use of a tight J-shaped curve may be helpful by keeping the microguidewire in the central lumen. The wire tip can safely choose its path better than the operator. If primary direct approach angioplasty is not possible safely, or if secondary stenting is to be performed, a low-profile microcatheter designed for intracranial use may be advanced across the stenosis over the microguidewire. The microguidewire is then replaced with a microexchange wire [e.g., X-Celerator (Covidien/ev3 Neurovascular, Irvine, CA, USA)] after placing a very tight (~2 mm) P-shaped curve at the tip of the exchange wire to more safely allow for the inevitable to-and-fro motion of the wire tip for the next 30 min (at least). The balloon or stent is advanced over this wire.

Experience has taught us that inflation needs to be extremely slow with a goal of about 1 min to reach 1 atm and 4 min for complete inflation. Self-control is very important; one way to accomplish this is to very slowly inflate the balloon to <1 atm and/or when the balloon can be *barely* seen, set the indeflator down, and walk away. Even when stenting is performed, minimizing underlying vessel wall damage is still the goal since intimal damage can cause secondary intimal hyperplasia with resultant restenosis (9, 10). Therefore, we still inflate very slowly but admittedly faster than with angioplasty.

Observation period

After angioplasty or stenting is performed, the balloon/delivery catheter is withdrawn proximal to the stenosis, *leaving the microguidewire (or microexchange wire if used) across the stenosis to preserve access*. Intraprocedural observation of the angioplastied/stented site is performed to observe for three possible sequelae: rebound stenosis, significant dissection, and/or acute/subacute thrombosis. With the use of pre-operative dual antiplatelets, the latter has been essentially non-existent as opposed to early experience when subacute appearance of clot was not infrequently observed. Follow-up angiography is performed twice within 20–30 min to ensure the absence any of the complications mentioned above; there is always delayed observation. If rebound stenosis is observed, prolonged repeat angioplasty with the same balloon (possibly to a higher pressure and longer interval) is initially performed. Be aware that this can then result in the very complication to be avoided: dissection. Be careful and judicious. Rarely, a larger balloon may be used or a stent might be tried, although it is best to avoid (a) catheter/balloon exchanges, and (b) use of a secondary stent (both thought to be primary causes of the periprocedural complications in SAMMPRIS). This is almost always possible. Even self-expanding stents are clumsy intravascular instruments in comparison to angioplasty alone. If a large dissection is observed with subsequent thrombus, abciximab may be used along with patient observation to avoid use of a stent. Even clearly visible severe dissections typically heal if adequate flow is maintained for an hour.

If occlusion or dissection progresses and rescue stenting becomes necessary, the necessity of maintaining distal microwire position is clear. If necessary, the working catheter/balloon can be advanced safely back through the lesion over the microguidewire and a microexchange wire can then be placed. The choice of a rescue stent (balloon mounted or self-expanding) depends greatly not only on the anatomy but also on personal skill and that of your team. Most of these problems occur in short vessel segments in curved arteries and necessitate a self-expanding stent but our recent experience indicates that the need for a stent or exchange technique is rare.

POST-PROCEDURE MANAGEMENT

A CT scan is obtained immediately after the procedure if there is angiographic concern, or any time that a change in neurological status raises suspicion of procedural complication.

The vascular territory downstream of the target lesion may not have seen systemic pulse pressure in quite some time. In order to prevent reperfusion/hyperperfusion hemorrhage strict attention is paid to blood pressure with the goal of keeping the systolic pressure within a specified low-normal range (110–140 mm Hg) utilizing IV labetolol or nicardipine drip. (A single reperfusion hemorrhage inspires a lifetime of caution). As previously discussed, in our experience the patients with the highest risk of reperfusion hemorrhage (or headache) are those who had very poor collaterals (pial or circle of Willis), resulting in an isolated territory. In this circumstance the vascular bed will be maximally dilated.

Patients are initially managed in the intensive care unit. Once stable, they are transferred to the stroke unit. Most patients are ready for hospital discharge (or transfer to rehabilitation in the case of patients presenting with an acute stroke) within 24 h of the procedure. Discharge medications are discussed with the attending neurologist who will be following the patient. All patients are discharged on dual antiplatelet therapy unless warfarin therapy is required for another condition such as atrial fibrillation in which case aspirin alone is added (81 mg/day).

FOLLOW-UP

All patients are followed clinically 1–2 weeks after discharge. All patients are evaluated with cerebral angiography 8 weeks after the procedure. If the follow-up appearance is satisfactory, imaging is repeated at 3 months, 6 months, 1 year, and then at yearly intervals using CT or MR angiography. Dual antiplatelet therapy is continued at least until stability is demonstrated on the 3-month images. Any decision regarding a change to single antiplatelet therapy is made in conjunction with the neurologist (and cardiologist if applicable).

If a *significant restenosis* (>70%) is demonstrated at the time of follow-up, the patient may undergo repeat angioplasty (or stenting if necessary) even without recurrent symptoms (as per local protocol) and is then followed as described above. The rationale for treating asymptomatic restenoses is twofold. WASID confirmed that a certain percentage of patients will not have recurrent symptoms manifested by TIA but rather by stroke or death (1, 2) and these patients have already failed a trial of maximal medical therapy for this lesion. We have also learned that repeat angioplasty is extremely low risk with an event rate approaching 0 (none in a decade). Asymptomatic restenoses of lesser severity are observed with repeat angiography and only treated if they became symptomatic.

Whenever a patient experiences symptoms possibly related to the treated stenosis, an MRI is obtained (or a CT if necessary) and an angiogram is performed. Repeat angioplasty is performed if indicated. Rarely, a lesion related to atherosclerotic plaque is encountered that continues to develop significant restenosis despite multiple interventions. In our early experience, some progressively stenotic lesions were observed that responded poorly to primary and repeated angioplasty as well as to stenting. Indeed, these behaved similarly to moyamoya disease but were not at the ICA terminus. These stenoses were typically in a single location and were usually found in the middle cerebral artery or supraclinoid ICA. They had smooth gradually tapering edges not typical of atheromatous plaque. These are currently thought to represent a form of inflammatory obliterative vasculopathy, similar to moyamoya disease. We now identify these lesions in advance and do not intervene but rather use maximum medical therapy, which for us includes cilostazol (12). No matter the treatment, these have a poor natural history. Encephaloduroarteriosynangiosis (EDAS) can be performed if indicated.

COMPLICATIONS, HOW TO AVOID THEM, AND THEIR MANAGEMENT

As discussed previously in the rationale for technique, we observed early in our experience that excessive or rapid stretching of the vessel and use of a balloon approaching the diameter of the vessel in size lead to intimal damage; intimal damage can lead to acute or subacute thrombosis, occlusion and/or stroke (8–10), and intimal dissection leads to recurrent stenosis (10). The resultant changes in technique have significantly reduced the incidence of complications. In current practice, if slightly excessive micro-dissection is seen, it is usually associated with "hurried" inflation.

The complications associated with the phases of development of our technique have been reported previously (8, 9). In current practice, periprocedural complications (within 24 h) are rare and minor. Specifically, the 30-day event rate over the past 7 years has been 2.5% (3/121 procedures), all minor. One patient presented with a symptomatic recurrent stenosis 27 days after angioplasty. Another patient had a very resistant eccentric stenosis in the cavernous ICA that required inflation of the balloon to 8 atm pressure and had a resultant dissection, which was treated conservatively and was healed on the first follow-up angiogram. The third patient had a transient neurological deficit of unclear etiology that resolved within 24 h; MRI obtained at the time did not reveal any acute findings.

GUIDE CATHETER PROBLEMS

All guide catheter problems should be avoidable; if there is doubt as to sufficient positioning with sufficient support, withdraw, and attempt another day. A final evaluation of the parent vessel and guide catheter location should always be performed at the end of the case. Thrombus forming around or in the guide catheter is related to procedural technique. Simply observing distal flow during injection does not indicate flow around the body of the guide catheter itself; that is confirmed by watching run-off, not the contrast injection. The most serious problem, in-catheter thrombus, is related to lack of constant adequate flush (*or slight back-bleeding*) with resultant stagnant blood in the guide catheter lumen. The final follow-up run will inject thrombus and reveal this situation.

PARENT VESSEL DAMAGE

Parent vessel damage is caused by poor guide catheter tip positioning, poor choice of guide catheter, initial manipulation, or intraprocedural movement. Stable position in the petrous (or more distal) ICA or C-2 vertebral artery level is recommended but admittedly might be difficult. It is imperative to choose the best guide catheter for the particular case in order to obtain a stable platform. The catheter tip will always be on an outer wall even if it looks like it is not. A suitable tip location with adequate support prevents the guide catheter for being forced to withdraw proximally, which could necessitate re-advancement into a high-tension system. The tip should not be positioned in a curved segment of the vessel where it will always be forcefully on an outer curvature and could cause dissection related to movement produced by the patient's heartbeat and/or respiration. If dissection is significant, stent placement may rarely be necessary. Dissections heal with the medical management the patient is already on. Unless emergent, we do not work through recently damaged intima associated with a stent but rather let it heal and return at another date.

If spasm of the parent vessel is detected, the guide catheter should be withdrawn to a more proximal (and comfortable) position in the vessel and simply observed. While injection of nitroglycerine might alleviate the vasospasm quickly (50 mcg/ml of normal saline up to 100–200 mcg.) this is at the cost of significant vasodilatation of the downstream capillary bed. Simply waiting usually suffices and is particularly true in the case of acute stroke.

VESSEL DAMAGE FROM THE DISTAL MICROWIRE TIP

It is important to use a suitable microguidewire designed for intracranial use with a soft and safe tip (e.g., Transcend.014 EX Platinum). Damage from the microguidewire tip typically occurs during initial wire manipulation or during active treatment of the lesion (balloon inflation). The single most hazardous event in

every case is inadvertent movement of the distal microguidewire (or microexchange wire) tip causing perforation. The distal tip of the microwire must remain within the fluoroscopic field of view at all times during the procedure in order to ensure that it does not veer into an unseen small side branch where it has no room to buckle, with resultant perforation. While small branch perforations can be tolerated occasionally, this might not be the case when a patient is on dual antiplatelets and full anticoagulation. If necessary, once the lesion is crossed with the balloon, the microguidewire can be withdrawn and a tight P-shaped curve placed at the tip before advancing it. If a microexchange wire is used, the same curve should be placed at the tip.

The microwire tip should be advanced well downstream from the tip of the balloon past the stenosis and carefully positioned in a relatively straight segment of a vessel. In the anterior circulation this might be the M-1 segment of the middle cerebral artery or the M-2 segment (the inferior angular branch). Never intentionally place the microwire tip in the anterior division of the middle cerebral artery. The "candelabra" branches of the anterior division make sharp 180° turns in a distance of millimeters from the M-1 bifurcation and the guidewire (no matter how soft) will easily perforate at the bend rather than make the 180° turn in 3 mm. It is mandatory to take the time to position the tip of the microwire correctly and in the location recommended. If necessary, you can withdraw the microwire and reshape the tip; another reason to use an over-the-wire system.

After angioplasty, it is very important to maintain distal microwire position and avoid recrossing the lesion, particularly after manipulation. No matter how adept the operator believes himself or herself to be, it is not possible to skillfully advance a microguidewire through the center of the lumen of a newly dilated vessel regardless of whether or not there is visible dissection. Trying to accomplish this can result in worsened vessel dissection, perforation, or occlusion. If distal microwire position is lost, it may be necessary to accept the angioplasty result and maximize efforts to prevent and treat thrombus rather than potentially worsen the situation. Prolonged observation is usually sufficient. Another attempt can be made several weeks later.

THROMBUS FORMATION AND DELAYED OCCLUSION AT THE SITE

In the early days of this procedure, delayed stroke (hours) was thought to possibly be the result of delayed vasospasm. We now understand that delayed stroke is due to delayed thrombus formation with or without progressive dissection leading to vessel occlusion. This was formerly the most common potential complication of this procedure. Delayed observation is therefore mandatory.

Exposed endothelial matrix is very thrombogenic. A small amount of intimal damage is inevitable when performing angioplasty or stenting, but visible thrombus is rarely seen in present practice. This is almost certainly due to the consistent use of preprocedure dual antiplatelet therapy. Visible subacute platelet clumping can be treated with GP IIb/IIIa inhibitors (e.g., abciximab). A very dilute and slow intra-arterial infusion will be vastly more concentrated than any serum level and will bathe the thrombus for a prolonged period with better clinical results. For abciximab, 5–10 mg in 30 ml injected over 5–10 min is usually sufficient and will not give an appreciable systemic effect.

DISSECTION AT THE SITE OF ANGIOPLASTY

A small amount of vessel damage might be unavoidable. However, the best solution for a true "macro" dissection (visible intimal flap) is *avoidance*. The techniques of *undersizing the balloon and extremely slow inflation* were developed to minimize this risk (9). The rate of significant dissection and subsequent restenosis has been very low (8).

If a hemodynamically significant dissection does occur, the lesion is accessible, and the microwire still has distal position, a stent can be placed as a last resort. With or without a stent, the current dual antiplatelet therapy and intraprocedural anticoagulation typically maintains patency in the vessel, allows the situation to stabilize, and usually is sufficient.

EMBOLI

There are three principal causes of downstream emboli, all rare. First, the guide catheter can produce thrombus (inside or out). Second, thrombus that forms at the angioplasty site can migrate downstream. Third, thrombus or plaque can be dislodged from the original lesion. The use of dual antiplatelet therapy has greatly reduced the incidence of emboli from this source. Thrombus at the site of the original lesion is usually encountered in the setting of a patient with recurrent or crescendo symptoms, presumably due to unstable plaque, and who fails medical therapy rapidly. If there appears to be thrombus present and it is necessary to continue with the procedure, it is better to treat thrombus *in situ* rather than downstream. Be patient and treat as described above.

Treatment of an embolus is dependent upon its composition. Acute thrombus is typically composed almost exclusively of platelets and responds well to GP IIb/IIIa inhibitors. The embolus will be relatively small and should migrate to a second- or third-order vessel; the time for rescue can be prolonged in this setting. If contrast reaches the thrombus, the therapeutic agent will also. Clinically significant emboli are rare in recent practice.

REBOUND STENOSIS

Rebound stenosis is the major drawback of angioplasty with an undersized balloon but this is not a complication. Purposely undersizing the balloon will prevent major intimal damage as completely as possible. This process will, however, cause some lesions to be inadequately dilated. A certain amount of damage may be necessary to produce sufficient dilation, but an inadequate result that must be retreated at a later date is preferable to a damaged vessel leading to intimal flap or occlusion. Recurrent stenosis secondary to intimal hyperplasia associated with healing of the angioplasty site is the reason for early evaluation at 8 weeks after angioplasty or stenting. In our experience, recurrent stenosis occurs very early in the post-procedure period.

Intrinsic elastic recoil does not appear to be as great a problem in intracranial lesions as in extracranial lesions such as the vertebral artery origin. Vessel geometry, however, can be a problem. The bend of a vessel (e.g., the curve of the distal vertebral artery at the skull base) is a poor location for effective angioplasty, and prone to kinking after angioplasty. Stent placement in these locations can also be problematic, but often produces a better result. This is a typical location for primary balloon-mounted stent use.

DISCUSSION

Clinical results have shown that modest angioplasty results produce satisfactory clinical results (8–11, 13, 14). A review of our experience over the last 7 years reveals that 121 procedures were performed. As noted above, there were three complications. Primary stenting was performed in 11 instances and secondary stenting in 3. There was 100% technical success. There has only been one patient who presented with a symptomatic recurrence, treated successfully. We attribute these results mainly to the decrease in significant dissection following angioplasty. Dissection has been shown prospectively to be a statistically significant predictor of not only stroke in the periprocedural period but also of restenosis at the follow-up angiogram (10). These facts confirmed our observational impression and affirm our mantra of "avoiding dissection at all costs."

The complication rate of angioplasty alone in these different papers consistently was <4.5% for major and minor complication combined at 1-year post intervention. This complication rate for intracranial angioplasty provides a reasonable treatment strategy for symptomatic intracranial atherosclerotic stenosis with its attendant risk of at least 12.2% stroke/death within the first year (1–4).

Concerning the issue of intracranial stenting in treatment of symptomatic intracranial atherosclerotic disease (ICAD), we believe that the available self-expanding stent technology has been proved to be difficult to place without complications. Conversely, we have found balloon-mounted stents to be simple to use, safe, and effective when used in the recommended locations. We believe that stenting, both self-expanding and balloon expandable, should be reserved for particular situations.

In summary, experience has taught us much about the safe and efficacious performance of intracranial revascularization. The key points of our current technique, as discussed above, are as follows:

1. Careful selection of the guide catheter combined with patient, skillful placement of the tip in the recommended distal location is extremely important both for technical success and avoidance of complications.
2. The shortest balloon possible should be chosen and the diameter should be downsized relative to the vessel diameter.
3. Impeccable attention to detail with wire manipulation and crossing of the stenosis is mandatory. Distal wire tip positioning is crucial. The distal tip of the microwire is the greatest cause of periprocedural complications.
4. Excruciatingly slow balloon inflation is second only to submaximal sizing in importance for preventing dissection.
5. Secondary stenting should be avoided if possible.

CONCLUSION

Although aggressive medical management has decreased the incidence of stroke associated with intracranial atherosclerotic stenosis, there is still a failure rate of >12% at 1 year. An important role for endovascular intervention remains. Angioplasty alone in carefully selected patients has repeatedly been shown to be technically feasible. Dissection should and can be avoided with the recommended technique. Studies have consistently demonstrated angioplasty alone to provide clinical benefit for intracranial atherostenosis better than stenting or medical management alone.

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The case for angioplasty in patients with symptomatic intracranial atherosclerosis

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Intracranial atherosclerotic disease (ICAD) is likely the most common cause of stroke worldwide and remains highly morbid even with highly monitored medical therapy. Recent results of the SAMMPRIS trial, which randomized patients to stenting plus aggressive medical management versus aggressive medical management alone have shown that additional treatment of intracranial atherosclerotic lesions with the Wingspan stent is inferior to aggressive medical management alone. In light of these results, there has been renewed interest in angioplasty alone to treat symptomatic ICAD. This article will briefly review the natural history of ICAD and discuss the possible future for endovascular treatment of ICAD with primary intracranial angioplasty in appropriately selected patients.

Keywords: angioplasty, stenosis, stents, intracranial stenosis, intracranial atherosclerosis

EPIDEMIOLOGY AND NATURAL HISTORY

Several important natural history and medical treatment studies have been published that allow us to appreciate the impact of ICAD (1–4). Approximately 5–10% of all strokes and TIA's are due to ICAD (5). A landmark, prospective multi-center study of 4157 patients admitted within 24 h of ischemic onset demonstrated symptomatic intracranial stenosis (>50%) in 6.5% of patients (6). The study showed proximal middle cerebral artery and basilar artery occlusions were seen in 3.7 and 1.2%, respectively (6). Mortality rates at 100 days were highest in the basilar artery occlusion group (44.7%) and were and 10.1 and 21.4% in the symptomatic intracranial atherosclerosis (>50%) and middle cerebral artery occlusion groups, respectively. The incidence of intracranial atherosclerosis does vary by race and is more prevalent in Chinese, Japanese, African-American, and Hispanic patients (7, 8), as compared with elevated extracranial atherosclerosis rates in white patients (9, 10).

The greatest concern for ICAD patients, particularly those with ≥70% stenosis, is the risk of subsequent stroke. While some medical subgroup data suggesting 7–8% stroke rates in untreated patients with symptomatic stenosis are available from the 1980s (11), the data are limited by selection bias and inadequate follow-up. Later studies aimed to address stroke risk (2, 12, 13). In a cohort of 705 Chinese patients who presented with acute ischemic stroke, Wong et al. reported 1-year stroke rate of 17.1% in patients with intracranial atherosclerosis only and 24.3% in patients in patients with both intracranial and cervical disease. Even more sobering data were derived in a study by Asil et al. (13) where 13 of 38 (38%) patients with >50% stenosis who completed 6-month follow-up had a stroke. Finally, in a study of patients with >50% stenosis, the GESICA (Groupe d'Etude des Stenoses Inta-Cranieenes Atheromateuses symptomatiques) study (2) patients had a 38.2% rate of a cerebrovascular event during approximately 2 years of follow-up, in spite of antiplatelet or anticoagulant therapy.

Our best natural history data for ICAD prior to the publication of the SAMMPRIS trial (4) came from the prospective, randomized Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial (1). This prospective, multi-center study randomized patients to ASA or warfarin. To be included, patients had to have symptomatic ICAD (>50% narrowing) and the 2-year primary endpoints were ischemic stroke, brain hemorrhage, and death from vascular causes. While WASID was criticized for its non-standard ASA regimen and high rate of dropout for both medications, warfarin offered no benefit over aspirin in preventing recurrent stroke, and the primary endpoints were reached in 21% in the aspirin group and 22% in the warfarin group. Notably, patients in the warfarin arm of the study had significantly higher rates of hemorrhage and for this reason and the lack of efficacy WASID was terminated prematurely.

SAMMPRIS targeted a group of high-risk, patients identified in subgroup analyses of WASID (14–16). This high-risk subgroup (14) demonstrated a 23% stroke risk at 12 months and was composed of patients with severe stenosis (>70%) enrolled earlier than 17 days after symptom onset. Another subgroup analyses (15, 16) germane to the construction of SAMMPRIS was the identification of elevated blood pressure and cholesterol levels as predictive of future stroke and other vascular events in symptomatic patients with intracranial stenosis and were the basis of the aggressive medical management used for both arms of SAMPRISS.

The SAMMPRIS trial (4) randomized patients with symptomatic intracranial stenosis (≥70%) to aggressive medical management versus endovascular therapy with aggressive medical

management. Enrollment in the trial was halted after 451 patients underwent randomization because the 30-day stroke and death rate in the group receiving endovascular therapy and medical management was 14.7% versus 5.8% in the group receiving medical management alone. In addition, the probability of experiencing the primary end point (any stroke or death within 30 days after enrollment or after any revascularization procedure of a qualifying lesion or a stroke in the territory of the symptomatic artery beyond 30 days) at 1-year was 12.2% in the medical management group.

It is important to recognize, as stated above, that the importance of aggressive medical management was derived from the WASID data (15, 16) and ultimately tested in SAMMPRIS. Aggressive medical management (available to both arms of the SAMMPRIS trial) consisted of two anti-platelet agents, a statin (goal LDL < 70), and one medication from each major class of antihypertensive agents (goal SBP < 140; 130 if diabetic). Patient compliance and risk factor management were managed at each site by a team including a neurologist, a study coordinator, and a lifestyle coach (17). Compliance with medical regimens was closely monitored by the study coordinator including counting patients' anti-platelet medications. The lifestyle coach met with the patients to develop personal action plans and contacted the patients every 2 weeks for the first 3 months and then monthly thereafter. Additional help was provided for difficult-to-manage patients from a central director.

There is little question that aggressive medical management of ICAD has a profound effect on the natural history of the disease. While we should try to achieve the medical management parameters set forth in SAMMPRIS, this degree of oversight is costly and it is quite likely that medical management applied long-term to "real-world" situations might result in event rates for symptomatic intracranial stenosis that were higher than those seen in SAMMPRIS. In addition, it should be pointed out that the "low" event rate in SAMMPRIS left more than 1 in 10 patients with a death or a stroke in the territory of the symptomatic artery at 1 year. The endovascular comparator in SAMMPRIS was stent placement with a self-expanding stent and this clearly raises the question whether another endovascular strategy such as angioplasty alone may provide better results.

INTRACRANIAL ANGIOPLASTY

Angioplasty used in the setting of symptomatic intracranial stenosis has been performed for more than two decades and was motivated by the poor natural history of ICAD despite medical therapy. While the first successful intracranial angioplasty was reported by Thoralf Sundt in 1980, early results showed high complication rates. For example, Higashida et al. treated eight symptomatic patients and encountered three major complications (38%) (18).

Subsequent technical advances reduced these early complications. One very important contribution to the safety of balloon angioplasty was the concept of "sub-maximal angioplasty" first promoted by Connors et al. (19). They examined three time periods in their angioplasty experience based on the technique used. In early experience, the angioplasty balloon size approximated the vessel size with rapid angioplasty. In the middle experience oversizing of the balloon was permitted with rapid angioplasty. In the final time period, an under-sized balloon was used with slow inflations. Numbers in the groups were small and both variables (inflation times and balloon size) were not controlled for. Nevertheless, these data indicated procedural complications rates may be reduced by slow expansion of a balloon smaller than the native artery.

Table 1 reports the technical success of several groups (19–26) and suggests the 30-day major complication rates are ≤6%. Many of these same investigators also show low post-procedure stroke rates over time and this ultimately drives the case for angioplasty in patients with symptomatic intracranial atherosclerosis (**Table 2**).

Clark and Yoon demonstrated notable results in studies of 17 and 32 patients, respectively (20, 22) with the latter study reporting a single TIA event (**Table 2**). The two largest series – Marks et al. (23) and Wojak et al. (24) – also showed favorable stroke rates. Marks et al. had a 3.2% rate of death and stroke in the territory corresponding to treatment (42-month follow-up) and Wojak et al. had an annual stroke rate of 1.8% (45-month follow-up). Although their follow-up was only 3 months and no annual stroke rate could be reported, Nguyen et al. (25) had only one stroke in the territory ipsilateral to the treated vessel. However, four major procedure-related strokes occurred in this multi-center study.

In a study published in response to SAMPRISS, Dumont et al. (26) queried their database of 41 patients [many of whom were ineligible for SAMPRISS and Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT)] who underwent intracranial submaximal balloon angioplasty procedures between January 2007 and July 2011. These patients had >70% stenosis and many presented with an acute ischemic event. In 32 patients with at least

Table 1 | Technical success and 30-day major complications of angioplasty.

Series	*N* (cohort size)	Complication rate (%)	Technical success (%)
Higashida et al. (18)	8	38	
Clark et al. (20)	17	9.1	
Marks et al. (21)	23	4.3	
Connors et al. (19)	50	6	98
Yoon et al. (22)	32	6	91
Marks et al. (23)	120	5.8	93
Wojak et al. (24)	60	4.8	91
Nguyen et al. (25)	74	5.0	92
Dumont et al. (26)	41	4.9	

Table 2 | Long-term stroke rates following angioplasty.

Series	*N* (cohort size)	Mean follow-up (months)	Annual stroke rate (%)
Clark et al. (20)	17	22	0
Yoon et al. (22)	32	20	0
Marks et al. (23)	120	42	3.2
Wojak et al. (24)	60	45	1.8
Nguyen et al. (25)	74	3	N.R.
Dumont et al. (26)	41	12	3.1

12 months of follow-up, only 1 ischemic event (a TIA) in the vascular distribution of the treated vessel occurred between 30 days and 1-year after the procedure. However, the 1-year event-free survival rate was 91% (29 of 32 patients) as two patients had peri-procedural morbidity.

It cannot escape attention that the angioplasty studies show substantially lower 30-day peri-procedural complications when compared to stent treatment arm of the SAMMPRIS study. In addition, the post-treatment annual stroke rates discussed above are superior to the natural history reported in those patients treated with aggressive medical therapy in SAMMPRIS. However, randomized data comparing a strategy of primary angioplasty with best medical management alone are lacking.

PATIENT SELECTION AND TECHNIQUE

In our current post-SAMMPRIS practice, we generally follow three tenets when applying angioplasty to the treatment of symptomatic ICAD. The patient should fail best medical therapy (dual antiplatelet, statins, and risk factor reduction). The operator must use sub-maximal angioplasty technique. The operator should only select those lesions likely to respond to balloon dilatation. SAMPRISS demonstrated the profound impact of best medical therapy and we have discussed sub-maximal angioplasty technique. Perhaps equally important is the issue of lesion selection. Failure to appreciate the impact of lesion morphology or employ sub-maximal angioplasty technique would be a serious oversight by the endovascular surgeon.

Mori et al. (27) hypothesized lesion morphology would affect lesion response to angioplasty and thus categorized atherosclerotic lesions as short, concentric and <5 mm long (Mori A), 5–10 mm long and may be eccentric (Mori B), and >10 mm and may have excessive tortuosity (Mori C). As predicted, Mori found higher rates of death, ipsilateral stroke, or subsequent ipsilateral bypass after angioplasty by lesion type; Type A (8%) versus Type B (26%) versus Type C (87%). While two studies found no outcome differences between lesions >7 or <7 mm (28, 29), a number of other studies support the Mori data and have found lesion length or morphology an important variable in determining procedural success and restenosis rates (30–34).

THE FUTURE OF INTRACRANIAL ANGIOPLASTY

Despite the low 1 year stroke rates following intracranial angioplasty, restenosis remains a possible weakness of primary angioplasty. Symptomatic and angiographic restenosis (23, 24, 26) occur at 6 months in approximately 5–30% of patients treated with angioplasty alone. The re-angioplasty rate was in excess of 20% in the most recent study in which sub-maximal technique was rigorously employed.

The drug-eluting balloon (DEB) may alter this problem. The DEB is an emerging technology with meaningful accumulated data in coronary arteries and femoropopliteal disease. The sina qua non-for this technology is effective transfer, absorption, and circumferentially uniform effect of the drug on the diseased vessel segment during the short period the balloon is inflated against an atherosclerotic plaque. Excipient technology (the balloon coating that helps deliver the drug) is in its infancy and one should expect a plethora of proprietary formulas in years to come. Paclitaxel is favored as it is highly lipophilic and allows for passive absorption through cell membranes with sustained effect within a treated vessel wall.

Data regarding the use of DEB's in the small vessels to which we are accustomed are scant. In a single-arm study, Schmidt et al. (35) treated patients with infra-popliteal disease and 70% stenosis with a paclitaxel-eluting balloon (In.Pact Amphirion, Medtronic, Minneapolis, MN, USA) with pre-dilatation and 1 min inflation times. The 3-month restenosis rate (available for 84 of the 109 limbs treated) was 27.4%, which compares quite favorably with the 60–70% restenosis rate typically seen with uncoated balloons. There have been two reports by one endovascular group of DEB use for intracranial atherosclerotic lesions (36, 37). In their first report, they compared DEB and conventional angioplasty balloons for the treatment of in-stent recurrent stenosis and found DEB's reduced subsequent restenosis fivefold (9 versus 50%) (36). In their most recent report, 52 patients with high-grade ICAD lesions underwent primary angioplasty and stenting with the Enterprise stent. Angioplasty with the DEB was performed in >80% of patients and in 33 patients with an average follow-up of 8.9 months only 1 (3%) recurrent stenosis was seen (37).

A possible dilemma for DEB intracranial angioplasty will be the need to balance "sub-maximal angioplasty" (slow inflation of under-sized balloons) with effective circumferential coating of the diseased vessel with excipient and drug. Furthermore, the risk and consequence of embolization of excipient and drug to intracranial branches beyond the ICAD lesion is, at present, unknown.

CONCLUSION

The first line of therapy for symptomatic ICAD patients is dual anti-platelet therapy and aggressive management of blood pressure, blood sugar, and lipids. The SAMMPRIS trial gave us useful information in that even with aggressive, highly monitored medical management, there is still a concerning 12.2% combined 30-day stroke and death rate or ipsilateral stroke rate beyond 30 days in the first year of treatment. The results of the SAMMPRIS trial should not stop further investigation of endovascular therapy for severe symptomatic intracranial stenosis. With appropriate lesion selection and technique, intracranial angioplasty should be a technically safe procedure with a low complication rate. Furthermore, single center series suggests there is a low annual stroke rate in these patients. However, no randomized data exists to show a benefit compared to medical therapy. The impact of DEB's on post-treatment stroke rates and restenosis rates is eagerly awaited.

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Intracranial angioplasty and stenting before and after SAMMPRIS: "from simple to complex strategy – the Chinese experience"

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Intracranial atherosclerotic disease (ICAD) accounts for 33–50% of all ischemic strokes in the Asian population (1) and represents an important public health issue in China. The results of the SAMMPRIS trial alarmed most experienced interventionalists in China for two reasons. Firstly, the high complication rate in the stenting arm (20% the first year) was higher than expected. Secondly, the recurrent stroke rate in the aggressive medical treatment arm at 12.2% during the first year was unacceptably high, not to mention the fact that such tight vascular risk factor control is difficult to achieve for many patients in real life clinical experience, at least in China. The experience of treating ICAD in China, gained over the last two decades, is very rich and promising. We intend to highlight these past experiences and address future trials and trends in China. We will also address our criticism of the SAMMPRIS trial design in order to better design a future trial.

Keywords: ischemic stroke, intracranial atherosclerotic disease, angioplasty, balloon, stenting, medical therapy

INTRACRANIAL STENTING FOR ICAD IN CHINA BEFORE SAMMPRIS

The warfarin–aspirin symptomatic intracranial disease (WASID) study showed that the role of medical therapy for intracranial atherosclerosis (≥70%) is less effective, with the 1-year risk of ischemic stroke remaining as high as 23% in patients who presented with stroke and 14% in patients who presented with transient ischemic attack (TIA) (2). Inspired by experience from the treatment of the coronary artery disease, Chinese doctors began treating patients with symptomatic intracranial artery stenosis refractory to medical therapy with endovascular treatment since the 1990s. The devices initially used were the coronary balloons Magellan (Balt Co., Montmorency, France) and SeQuent (B. Braun, Melsungen, Germany). Different stents including Coroflex or Coroflex Blue (B. Braun, Melsungen, Germany), BiodivYsio (Biocompatibles Ltd., Farnham, UK), S660 (AVE, Galway, Ireland), and Firebird (MicroPort, Shanghai, China) were also used. Initial reports were all single-center, self-reported studies, with varying degree of success (96.46–97.6%) and low complication rates (4.42–10%). When examined together, these studies included a total of 528 patients (3–9), which constituted a rich database. When compared with the expected natural history of the disease, the consensus at that time was that these results supported the use of the coronary stents as a mean for stroke prevention in patients with intracranial atherosclerotic disease (ICAD).

With the dramatic increase of new cases, new devices specifically designed for ICAD were developed. The Wingspan stent system (Stryker, Kalamazoo, MI, USA) was the first commercially available device since 2005 (10) and was introduced to China after approval by the State Food and Drug Administration (SFDA) in 2007 (11). The Apollo balloon-mounted stent (MicroPort, Shanghai, China) was also approved by the SFDA the following year. Since then, a series of registries followed their introduction to the market, showing promising results for both the Wingspan and Apollo stent systems (11, 12).

The current Chinese experience was summarized best in the last Tiantan International Stroke Conference (TISC). A poll analysis was presented on 1372 treated lesions between March 2005 and November 2011 using different devices (13). The distribution of these lesions was as follows: 91 (7%) at the distal internal carotid artery (ICA), 795 (58%) at the M1 segment of the middle cerebral artery (MCA), 239 (17%) at the basilar artery (BA), and 247 (18%) at the intracranial vertebral artery (VA). Devices used included 323 coronary stents, 109 specially made intracranial balloon-mounted stents (Apollo), 638 Wingspan stents, and 38 cases of balloon angioplasties alone. The success rate was promising with an average rate of 96% (92–100%). The complication rate within 30 days was 8% (from 3.2 to 14.8%) (13).

We also independently reported our prospective registry focused on symptomatic MCA stenosis, which demonstrated a relatively high 1-year complication rate of 19.4%, compared to the medical group of 17.6% ($p = 0.85$) (14). This result was very similar to the later published SAMMPRIS study. Then, the general consensus was that stenting is feasible, but its effectiveness at preventing recurrent stroke with high grade symptomatic intracranial stenosis still needed validation (7, 9, 10, 12, 13, 15).

SINCE SAMMPRIS

The publication of the SAMMPRIS (16) results, the first and only prospective randomized trial to date, demonstrated high complication rates in the first 30 days following the Wingspan stenting in one arm and lower than expected stroke risk in the aggressive medical treatment (AMT) arm. This changed the accepted belief of the

efficacy of intracranial stenting as a measure of stroke prevention, and there is no reason to believe that a similar prospective trial using the same device will have different results in China. Based on the results, it is estimated that for intracranial stenting to remain a promising measure for stroke prevention in these patients, the peri-procedural complication rate within the first 30 days needs to be <4% (7, 13). From our personal experience, and reviewing the above highlighted Chinese experience, we believe that in order for us to obtain such a low complication rate we need to enact a few important changes. Firstly, a different patient selection criterion should be employed. Secondly, a more complex treatment strategy needs to be adopted (not all vessels or lesions are the same). Finally, we need a better device than the Wingspan stent system (7).

The most obvious conclusion of SAMMPRIS is that the device exclusively used (the Wingspan system) is not well suited for intracranial stenting. We can speculate as to why the Wingspan system ended up not being suitable for intracranial stenting, such as the need for two steps (angioplasty then stenting) or the low radial force of the stent making its opposition to the arterial wall very limited, which has a tendency to encourage platelet aggregation and clot formation beneath the stent (17, 18). Besides the stent itself, we believe that there was another shortcoming in the trial design (19). Dissection following angioplasty has been shown in a prospective registry to predict a higher stroke rate in the peri-procedural period (20, 21). Since the slow inflation technique of the angioplasty balloon was not included in the trial protocol, and no angiogram following the angioplasty was obtained prior to the stent placement, we can speculate that some of the complications in SAMMPRIS were due to unaccounted dissections caused by suboptimal angioplasty technique (7, 13, 17, 19). Secondly, in SAMMPRIS all the vessels were grouped together without distinction between vessels with perforators (BA, MCA) and those without perforators (VA, ICA), despite their known different complication rates (20, 21). Thirdly, the SAMMPRIS protocol did not take into account the Mori classification, yet there are numerous papers showing that lesions with different characteristics as classified by Mori carry different risks during intracranial endovascular revascularization (IER) (20–26). However, we still believe that SAMMPRIS was an important study because at least it forced us to examine the question: how safe is IER?

Building on prior literature, future trials need to take into account the following points:

1. *Improve patient selection*: which group of patients will most likely benefit from IER? It is suggested that patients with poor collaterals stand a higher chance of benefit from IER than patients with excellent collaterals (22). Poor collateral circulation is determined as ≥40% decrease in cerebral blood flow (CBF) at the stenotic arterial territory compared to CBF at the reference area by CT or MRI perfusion (reference area being defined as the contralateral hemisphere for anterior circulation lesions or anterior circulation territory for posterior circulation lesions); or a ASITN/SIR collateral flow grading system score <3 as confirmed by diagnostic cerebral angiogram (2–26).
2. *Improve device selection:* we believe that different lesions respond better to different devices.
   a. For Mori A lesions with straightforward arterial access, the balloon-mounted stent is our first choice, since no exchange maneuver is needed and requires shorter procedural time (3, 27–29).
   b. For Mori B or C lesions with tortuous arterial access, or lesions with a significant mismatch in the diameter between the proximal and distal segment, the gateway balloon plus Wingspan stent system is preferred because it is more flexible compared to the balloon-mounted stent system (6–12, 28, 29).
   c. For lesions near the perforator vessels (the mid-basilar artery and distal M1 segment), lesions with tortuous arterial access and Mori A classification, or lesions in a target vessel with small diameter (<2.5 mm), angioplasty alone is simpler and safer than stent implantation (28).

STUDIES IN CHINA SINCE SAMMPRIS

We recently published our new, prospective, single-center study applying the aforementioned criteria (28). Between November 2011 and October 2012, 158 patients were enrolled into the study

Table 1 | The efficacy endpoints of different therapy groups.

	BS group $n=81$	AG group $n=39$	AS group $n=38$	Total $n=158$	p
Primary endpoints					
Successful PTAS, *n* (%)	79 (97.5)	35 (89.7)	38 (100.0)	152 (96.2)	0.042
Secondary endpoints					
Any stroke or death	4 (4.9)	0 (0.0)	3 (7.9)	7 (4.4)	0.231
Any ischemic stroke	4 (4.9)	0 (0.0)	2 (5.3)	6 (3.8)	0.359
Any hemorrhagic stroke	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.6)	0.204
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
MI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
SAE	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.6)	0.204
mRS ≥ 3	2 (2.5)	0 (0.0)	2 (5.3)	4 (2.5)	0.339

BS group, balloon-mounted stent group; AG group, angioplasty group; AS group, angioplasty plus self-expanding stent group; MI, myocardial infarction; mRS, modified Rankin scale; PTAS, percutaneous transluminal angioplasty and stenting; SAE, serious adverse even (28).

and were divided into 3 groups: balloon-mounted stents (BS) group (81 patients, some patients were treated first with gateway balloon and then with the Apollo stent), angioplasty alone (AG) group (39 patients), and balloon angioplasty and Wingspan stenting (AS) group (38 patients). The primary endpoints were successful procedural rate and any vascular event within 30 days. Overall technical success rate was 96% (152/158). Intracranial stenting was successful in 97.5% (79/81) of patients in BS group, 100% (38/38) in AS group, and 89.7% (35/39) in AG group with significant differences between the three groups ($p = 0.042$). The 30-day composite stroke or death rate was 4.4% (7/158). Any stroke or death rate within 30 days in the BS group was 4.9%, in AS group was 7.9%, and 0% in angioplasty AG group (see **Table 1**). In this study, 59% of angioplasty cases needed secondary stenting due to large dissection. These results, especially in the angioplasty arm, are seemly very encouraging and point the merit of our IER strategy; the primary outcome was not satisfying and more than 50% require secondary stenting. There are more works we should do.

Currently, there are two ongoing multicenter clinical trials supported by both government agencies and medical device companies: Wingspan Stenting for Symptomatic Intracranial Artery Stenosis Registry study in China (WIRE-CHINA) and Apollo Balloon-Mounted Stent for Symptomatic Intracranial Artery Stenosis Registry study in China (AIRE-CHINA) (7, 13). These studies will be carried out in more than 20 centers. The primary objective is to evaluate the safety of intravascular stenting during the 30-day perioperative period in patients with symptomatic intracranial artery stenosis in the Chinese population using a specific device. Their results are eagerly awaited.

CONCLUSION

In patients with symptomatic intracranial atherosclerotic lesion, complex treatment strategy is needed. Different patients have different risk factors and indications, while different lesions respond better to different devices. Future trials are needed and we are very optimistic about their final outcome.

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Reviving intracranial angioplasty and stenting "SAMMPRIS and beyond"

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We review the methods and results of Stenting and Aggressive Medical Management for Preventing Recurrent Stroke (SAMMPRIS) and provide a critical review of its strengths and limitations. In SAMMPRIS, the aggressive medical treatment arm (AMT arm) did substantially better than the Wingspan Stenting plus aggressive medical management arm (WS+ arm). Complications in the first 30 days post intervention led to the disparity between treatment arms. A major contribution of SAMMPRIS was the added value that AMT and lifestyle change may provide, when compared to a precursor trial, Warfarin–Aspirin Symptomatic Intracranial Disease (WASID), designed to prevent stroke in persons with high-grade symptomatic intracranial occlusive disease, however, the results of neither of these two trials have ever been reproduced. On the other hand, we argue that technical limitations of the Wingspan stent system (WS System) and lack of an angioplasty only intervention arm may have led to a premature launch of the trial and early termination of the study. Future randomized trials with different devices and modified patient selection criteria are warranted.

Keywords: intracranial stenosis, best medical therapy, neurointervention, angioplasty, stenting, Wingspan stent

INTRODUCTION

Recently, an important intracranial stenting prevention trial in patients with symptomatic intracranial atherosclerotic occlusive disease (sICAD), Stenting and Aggressive Medical Management for Preventing Recurrent Stroke (SAMMPRIS), was published (1). SAMMPRIS showed that AMT alone was superior to the Wingspan system plus aggressive medical therapy (WS+ arm). The main findings were unexpected by some. The publication of the results, we believe, has reduced intracranial endovascular revascularization (IER) therapies leaving those patients with intracranial atherosclerotic stenosis who have failed medical management without an alternative treatment strategy despite a high risk of stroke, minimum 12.2%, in the first year. In this topical review, we discuss the main results and limitation of SAMMPRIS, and re-address the question as to whether or not the findings were really surprising based on prior scientific information. In addition, we discuss strategies to advance the field of IER.

BRIEF HISTORY OF CAROTID-ARTERY SURGERY AND ENDOVASCULAR INTERVENTIONS FOR STROKE PREVENTION: LESSONS LEARNED

Carotid-artery reconstructive surgery for aneurysms and invasive local cancers was carried out as early as 1916 with resection and end-to-end anastomosis (2). By 1952, anastomotic techniques were well-described when substantial portions of the common and internal carotid arteries had to be sacrificed in the presence of local cancer. At this time, there was recognition of the importance of collateral circulation in conjunction with these types of anastomotic surgeries, as well as the importance of autogenous vein grafting (2). Whereas thrombosis of the common carotid artery had been described as early as 1881 and predilection for atherosclerosis at the carotid bifurcation and carotid siphon described in the 1900s, C. Miller Fisher's report in 1951 has been considered the landmark article on this field (2). In this paper, a neuropathological correlation was emphasized. He argued for two stroke mechanisms: decreased flow by high-grade stenosis and embolic debris migrating downstream causing ischemic stroke. He also recognized the importance of collateral circulation in relation to permanency or occurrence of stroke symptoms and prophesized that surgical intervention might be possible (3).

Thromboendarterectomy was popularized in French literature in the 1940s (2), which consisted of resection of the intima and diseased media with the thrombus. However, it was not until the 1990s that carotid endarterectomy (CEA) was proven superior to medical management alone following several decades of surgical technique and instrumental refinements that also included a few failed trials that taught us how to improve our techniques and refine patient selection criteria (4, 5).

CAROTID BIFURCATION ANGIOPLASTY AND STENTING

Endovascular therapy for the cervical carotid-artery bifurcation with balloon angioplasty was reported in 1980 (6, 7) and it was shown to be safe and efficacious (8). Early experiences with balloon angioplasty, however, were complicated by the generation of embolic debris. Stenting was developed in response to the need for better outcomes after angioplasty and was proven to be effective by reducing the occurrence of plaque dislodgement, intimal dissection, elastic recoil of the vessel wall, and early and late stenosis (7).

The introduction of a protection device to catch the debris released during stenting, the basket, theoretically made the procedure safer and helped launch multiple studies comparing carotid-artery stenting (CAS) to CEA. Until recently, multiple trials comparing the efficacy and safety of endovascular stenting for carotid-artery bifurcation to CEA have been carried out with mixed results. The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) demonstrated similar efficacy and safety outcomes between the two methods, but only after device improvement and refinement of patient selection (8–10). We suspect that the history of IER and stenting will experience similar challenges along the way until we establish the correct device, technique, and patient selection criteria.

SAMMPRIS METHODS AND STUDY DESIGN

Stenting and Aggressive Medical Management for Preventing Recurrent Stroke is a Phase III, investigator-initiated, multicenter, randomized, open label, stroke prevention trial funded by National Institute of Neurological Disorders and Stroke (NINDS) to determine whether the WS System angioplasty and stenting arm (WS+ arm) and intensive medical therapy are superior to intensive medical therapy alone (AMT arm) for preventing stroke in recently symptomatic patients with severe intracranial atherosclerotic stenosis. The trial was initiated in October 2008 and was conducted at 50 sites in the United States. The details of the study protocol have been described elsewhere (11).

Patients were randomized if they had TIA or non-disabling stroke within 30 days prior to enrollment attributed to 70–99% stenosis of a major intracranial artery. Randomization was at a 1:1 ratio to intensive medical therapy alone or to the WS+ arm.

PRIMARY END POINT

The primary endpoint of the trial was stroke or death within 30 days following enrollment or after a revascularization procedure for the qualifying event during the follow-up period, or stroke in the territory of the qualifying event beyond 30 days.

ENDOVASCULAR INTERVENTION

The Gateway angioplasty balloon (Boston Scientific, Fremont, CA, USA) and Wingspan stent (Boston Scientific, San Leandro, CA, USA) were the only devices allowed in the WS arm of the SAMMPRIS trial. The WS System was the only stent in the SAMMPRIS trial because it was the only FDA-approved device for use at the time of study.

INTENSIVE MEDICAL THERAPY

Intensive medical therapy in both intervention arms of the study consisted of aspirin (325 mg/day) for the entire follow-up period, clopidogrel (75 mg/day for 90 days) after enrollment, and aggressive risk factor management primarily targeting blood pressure to less than 130/80 mm Hg and low-density lipoprotein-cholesterol (LDL-C) concentration to <70 mg/dL by administration of antihypertensive agents and rosuvastatin, respectively. A neurologist, study coordinator, and lifestyle coach closely monitored patients. Medication compliance was closely monitored by the study coordinator and included pill counts and monitoring of the patients if they were taking antiplatelet medications, statin therapy, and other medications.

Patients were examined at enrollment, 30 days, and then every 4 months following enrollment. If blood pressure was not within target range, adjustments in medical treatment were made and the patient returned in 30 days for a follow-up visit (1).

STATISTICAL ANALYSIS

Based on the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) study, the final projected rate of the primary endpoint in the medical management group was 24.7% at 2 years taking into account a 15% relative risk reduction based on the influence of aggressive medical management. It was then estimated that 382 patients would be needed in each treatment arm to have 80% power to show a relative reduction of 35% favoring the WS arm (1).

SAMMPRIS RESULTS

The 30-day rate of stroke and death was 14.7% in the WS arm (12.5% non-fatal stroke, 2.2% fatal stroke) and 5.8% in the medical arm (5.3% non-fatal stroke, 0.4% non-stroke death, $p = 0.002$), which resulted in the study being stopped prematurely. There were five stroke-related deaths in the WS arm and one non-stroke-related death in the medical arm within 30 days following enrollment. The 30-day rate of primary endpoint in the WS arm was higher than what the study investigators had anticipated (5.2–9.6%). Although there was no difference in main outcomes after 30 days of stroke (same territory, 13 patients in each arm), Kaplan–Meier curves were significantly different with 1-year rates of the primary endpoint between the WS arm (20.0%) and medical arm (12.2%, $p = 0.009$). When the study was stopped, 451 (59%) of the planned 764 patients had been enrolled; 227 were randomized to the treatment medical arm, and 224 were randomized to the WS arm. A futility analysis showed that there was essentially no chance that the WS arm would be proven superior to medical therapy (1).

Of the 224 patients randomized to the WS arm who underwent stenting ($n = 219$) or angioplasty alone ($n = 5$), 13 had hemorrhagic strokes. Seven of the 13 were intraparenchymal bleeds (IPH), all remote from the stented vessels. A subgroup analysis of the IPH showed its association with higher degrees of intracranial stenosis, administration of a preoperative clopidogrel loading dose of 600 mg, and high procedural activated clotting time of >300 s. Amongst the other hemorrhagic strokes, a total of four cases were subarachnoid hemorrhages (SAH).

DISCUSSION

SAMMPRIS AMT ARM AND PRIOR MEDICAL LITERATURE

Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) demonstrated that subsequent stroke risk in patients with sICAD was related to the degree of vascular stenosis and the clinical presentation. A subsequent stroke risk in those patients was much higher than previously reported in other trials. In the WASID population, patients with >70% stenosis and TIA had a stroke rate in the first year equal to 14%, and 22.5% if they presented with stroke and for patients who presented with TIA or stroke and >70% stenosis, the combined stroke rate was 18% (12). Surprisingly in the SAMMPRIS AMT arm, the stroke rate was 12.2% in the first year, much lower than the results reported in WASID. Therefore, based on the above information, there are two possible

explanations for the discrepancy with the WASID results. Either the WASID data exaggerated the true risk of symptomatic ICAD and SAMMPRIS results came to highlight this fact, or the WASID data were not generalizable to the SAMMPRIS patients.

In SAMMPRIS, however, AMT was applied to both the WS+ and AMT arms. Therefore, if aggressive medical therapy were to explain the difference between the results in the two treatment arms (WS+ arm vs. AMT arm), the effect of medication would have to differ between these two groups, favoring the AMT arm. We do not have a complete understanding of the profile and effect of medical risk factor control in the two treatment arms as long-term follow-up of study patients is currently underway. For there to be a differential effect in one treatment arm, control of key risks (e.g., glycosylated hemoglobin, hypertension, lipids, and physical exercise) would have to differ between the two arms thereby placing the WS+ arm at a disadvantage. Thus far, we have seen baseline and 4-month data in relation to key medical factors and the following observations have been made in the medical arm vs. WS+ arm at 4 months: systolic/diastolic blood pressure (134.8/77.3 vs. 133.1/76.2 mm Hg); LDL cholesterol (72.8 vs. 75.9 mg/dL); HDL cholesterol (41.9 vs. 43.2 mg/dL); non-HDL cholesterol (90.0 vs. 94.3 mg/dL); glycosylated hemoglobin (7.5 vs. 7.8%); current smoking (20.4 vs. 17.3%); moderate or vigorous exercise (56.6 vs. 56.1%). Thus, some of these factors slightly favor one treatment arm. Additional analyses and follow-up time will be required to determine the possible influence that these factors may have on the study outcomes. We are skeptical that these modest risk factor control differences between the intervention arms will have major influence on the primary study outcome.

One may consider the effect of combination therapy with aspirin plus clopidogrel on the results of SAMMPRIS. Since combination antiplatelet therapy was administered to patients in both treatment groups for the same period of time in this trial, the expected effect should be constant in both groups unless there was a differential negative effect, for example, in the WS+ arm, which does not seem to be the case. Several other aspects of combination antiplatelet therapy are of interest for further discussion. First, such combination therapy benefited smokers but not non-smokers in a non-primary analysis of the SAMMPRIS data. This may be an effect of more efficient conversion of the pro-drug clopidogrel to its active form by the 450 cytochrome system and has been observed in other studies (9, 13). Second, the rate of recurrent stroke in SAMMPRIS was about one-half that of the precursor study, WASID, which compared high-dose aspirin vs. warfarin (12.2 vs. 25%) (1, 14). However, if we exclude the perioperative strokes in SAMMPRIS then the rate of subsequent ischemic strokes in the territory of the qualifying artery was almost the same in the WS+ and medical arms. The 30-day rate of stroke or death in the angioplasty and stenting group was 14.7%, which is substantially higher than the rates previously reported ranging 4.4–9.6% (1). Therefore, we conclude that the SAMMPRIS medical regimen may be more advantageous than the WASID medical treatment regimen, and more careful control of vascular risk factors in SAMMPRIS was associated with lower risk of subsequent stroke (1, 14).

On the other hand, before the publication of the WASID study, the stroke rate in patients with intracranial atherosclerotic disease was on the order of 10–12% per year in multiple other studies (15, 16). Contrary to this data, WASID reported a much higher stroke rate (18%) per year for the patients with 70–99% stenosis (17). Although we do not know the precise degree of stenosis in the prior study, it is curious that the medical arm in SAMMPRIS found the same 12.2% rate of stroke, and we doubt the majority of cases in the prior study had <70% stenosis. As previously discussed, we wonder whether the WASID results were not generalizable to the SAMMPRIS study patients and thus, overestimated the real risk of subsequent stroke per year in patients with symptomatic ICAD in SAMMPRIS. However, one should interpret the findings with caution since neither the results of WASID nor those of SAMMPRIS have been reproduced in other studies as of yet. Therefore, at the present time such comparisons may not be valid, and their results still need to be validated by subsequent study. However, we believe that the risk of stroke in the first year in the vascular territory of symptomatic ICAD is at least 12% with best available AMT.

COMPLICATIONS RATE OF THE WS STENT PRIOR TO LAUNCHING SAMMPRIS

At a 14.7% complication rate within the first 30 days, the SAMMPRIS WS+ arm procedural complication rate was higher than anticipated. It was almost 2.5 times higher than that observed for stenting of symptomatic extracranial carotid-artery stenosis in CREST (8–10). The actual periprocedural complication rate was in the range of approximately 5–10 absolute percentage points higher than anticipated. However, we believe that the literature prior to the SAMMPRIS trial launch anticipated the actual complication rate. An early paper dealing with the complication rate of the WS System reported a 6.1% major periprocedural neurological complication rate (18). The important modifier "major" needs interpretation as all operators know that major complications are always less frequent than minor complications, triggering an expectation of an at least a 15% total complication rate (assuming major complications represent approximately 40% of all complications). This point was further validated in other studies (Al-Ali et al., May 2008, International Intracranial stenting conference. Ankara. Turkey), reporting their periprocedural complication rates at 3.6% major, 10.9% minor (total of 14.5%), and at 19.5% stroke/TIA rate at 1 year. In August of the same year, The NIH Multicenter Wingspan, Intracranial Stent, Registry Study results were reported and despite being retrospective and self-reported the stroke rate was at 14% at 6 months (19). Thus, concurrent available data on complication and outcome rates of stenting were generally higher than projected in SAMMPRIS and suggest the need for a different set of statistical calculations for the SAMMPRIS trial to avoid failure of the WS+ arm.

IMPROVING THE DESIGN OF SUBSEQUENT TRIALS

A trial to test the merit of IER for stroke prevention in patients with symptomatic ICAD was, and is still needed. In this text, we have previously articulated certain reservations about the SAMMPRIS trial design, such as use of the WS system as the sole device allowed in the trial, despite the high complication rate previously reported in the literature and highlighted above. In addition, other reservations about SAMMPRIS include:

PATIENT SELECTION

There has been debate about whether high enough risk patients were enrolled in the study. Based on the WASID findings, we understand that those patients with 70–99% stenosis and TIA or stroke within 30 days before enrollment had the highest rate of ischemic stroke in the territory of the symptomatic artery (14). The WASID risk of TIA or stroke was 22.9% at 1 year and 25.0% at 2 years (14). SAMMPRIS was designed using risk estimates from this subgroup of the WASID trial. We agree that based on the WASID trial, the aforementioned patient risk profile was a reasonable one for choosing patients for eligibility in SAMMPRIS (11).

LESION MORPHOLOGY

The "Mori classification" [type A <5 mm in length, concentric or moderately eccentric, smooth stenosis; type B, 5–10 mm in length, extremely eccentric, or angulated (>45°), or irregular stenosis, or total occlusion (<3 months old); type C, >10 mm in length, extremely angulated (>90°) stenosis, or total occlusion (>3 months old), or lesion with a number of neovasculatures all around] was not clearly elucidated in the study design eligibility criteria, despite the fact that it has been well-documented in the literature (20). It has been shown that lesion length and morphology correlate with outcome following IER (20–22). For example, the intrastent multicenter registry showed much lower rates of neurological complications in patients with lesions <5 vs. 5- to 10-mm lesions or >10 mm lesions (23). Zhu et al. found a 12% rate of in-stent restenosis in Mori A lesions and a 50% rate in Mori C lesions (24). Another recent multicenter report of 670 treated lesions showed Mori A lesions were safer to treat and were less likely to develop restenosis (25). The lesions treated in the SAMMPRIS trial were either 14 mm in length or less (11, 26) but there was no stratification of the lesions along Mori or other system criteria to select for favorable lesions to treat.

FRAGILE PLAQUE AND COLLATERAL CIRCULATION STATUS

The presence of numerous micro embolic signals (MES) on Doppler ultrasound was found to predict a higher risk of subsequent stroke (27). Also, the WASID study revealed that patients with poor collateral circulation distal to the stenosis had higher risk of subsequent stroke. The SAMMPRIS trial did not include criteria taking into account MES or collateral circulation status. The impact of these factors on such a trial is not clear but needs to be further defined.

TECHNIQUE

Proper angioplasty technique "slow submaximal balloon inflation" was described in the late 1990s (28). The authors reported their experience and noticed that when they started using a smaller balloon 0.5 mm less than the diameter on the diseased vessel at its normal section and inflating it slowly over a period of 3–5 min to achieve nominal pressure, their complication rate dropped dramatically. The authors attributed this lower complication rate to decrease in frequency of large dissections at the angioplasty site. The findings were later confirmed in a major case series demonstrating that large dissection following angioplasty was associated with a statistically significant occurrence of stroke in the periprocedural period, and restenosis at follow-up (29). In SAMMPRIS, operators were encouraged to down size the balloon angioplasty by 0.5 mm, but this was not a requirement, nor was the slow inflation axiom. Since these data are not documented and not every patient had an angiography study following angioplasty and prior to stent placement, it is impossible to know with certainty the impact of the technique on the final trial results.

LESSONS LEARNED FROM SAMMPRIS TRIAL

We discuss below further insights from and since the publication of SAMMPRIS in relation to possible means to heighten the success of IER:

VESSEL SIZE

Stenting and Aggressive Medical Management for Preventing Recurrent Stroke included vessels that were 2–4.5 mm in diameter. Vessel diameter was not a predictor of outcome.

VESSELS WITH PERFORATORS VS. VESSELS WITH NO PERFORATORS

Stenting and Aggressive Medical Management for Preventing Recurrent Stroke demonstrated a higher risk of ischemic stroke during intervention in vessels with perforators (PV) than in those with no perforating vessels (nPV). For example, IER to the basilar artery had a higher complication rate than any other vessel. The importance of this distinction between PV vs. nPV has been confirmed and in direct comparison of outcomes following IER, it was found that different vessels carry a very different risk following IER. Vessels with perforators carried significantly higher risk following IER (MCA 16.3%, basilar artery 20.3%) than when there were nPV (vertebral artery 8.3%, internal carotid artery 4.9%) (29). Future trials should take this important information into consideration, by either avoiding PV until newer generation devices emerge, or by restricting intervention in some patients to balloon angioplasty using a significantly smaller diameter balloon and a shorter one.

ROLE OF OPERATOR AND SITE EXPERIENCE

It is important to determine if the higher than expected rate of endovascular complications in the SAMMPRIS trial was related to the operator or site experience. The SAMMPRIS analysis showed that neurointerventionalists with less Wingspan experience did not have a higher rate of periprocedural strokes in the trial. Neurointerventionalists with a more than a 10-Wingspan case experience actually had higher rates of 30-day events than those with less than a 10-case experience (19.0 vs. 9.9%, $p = 0.11$). Moreover, high enrolling study sites in this trial had lower rates of hemorrhagic stroke; 9.8% at sites enrolling <12 patients vs. 2.7% at sites enrolling ≥12 patients ($p = 0.04$). The exact cause of this difference is not clear but most likely is related to factors other than the operators' expertise, such as poor blood pressure control after stenting and reperfusion injury (30). Final review of SAMMPRIS results found no association between the operators' exact prior experience and the outcome. Other authors have looked at the importance of the "learning curve" using the WS system (29). In their series, they observed that complications did not cluster at the beginning of their use of the WS system but rather, occurred along the whole period of their registry experience. This observation suggests that the notion of "increased

familiarity with the stent or more selective choice of the operators would have altered the final results of the SAMMPRIS" is probably inaccurate.

CHALLENGES OF THE WS STENT

THE WINGSPAN STENT

First, the WS stent most likely contributed to the complication rate in SAMMPRIS. The WS has numerous shortcomings including the need for an exchange length micro-wire that must be kept in place while exchanging the balloon catheter to the stent delivery catheter. This invariably causes back and forward motion of the micro-wire tip and possible vessel perforation. Second, the pusher used to stabilize and help deploy the stent that was very rigid and invariably causes tension and motion on the wire tip causing it sometimes to abruptly jump. Third, the stent delivery catheter is bulky (3.5 French) and advancing such a bulky catheter through the fresh angioplasty site would, at least theoretically, cause further injury to the blood vessel wall. Thus, a smaller delivery catheter is needed. Lastly, the opposition of the stent at the angioplasty site is suboptimal due to its lower WS stent radial force as compared to the balloon-mounted stent. This suboptimal stent opposition to the vessel wall can allow the persistence of tiny spaces between the stent strut and the vessel wall allowing for platelet aggregation. This may help explain the curious phenomenon seen with the use of WS stent, which is the occurrence of small strokes, days following the intervention. It is not always in the immediate aftermath of stent placement as it is customary when using the balloon angioplasty catheter or the balloon-mounted stent where delayed stroke almost always equates to stent thrombosis.

CONSIDERATIONS FOR FUTURE TRIALS

From the aforementioned information, we believe that we should now be able to improve the design of future IER trials based on better imaging techniques, patient and lesion selection, and improved procedural techniques. We make the following summary recommendations:

IMAGING

Digital conventional angiography

Degree of stenosis. Over the last several years, many reports have demonstrated that lesions more than 70% stenosis have higher risk of future stroke or TIA. Therefore, we can restrict our lesion selection to above 70% stenosis.

Lesion morphology. It has been shown repeatedly that Mori C lesions have a very high complication rate; hence, we believe these lesions should be excluded from intervention. Numerous reports have confirmed that lesions in the perforator vessels such as in the basilar or middle cerebral arteries have much higher complication rates than those in non-perforator vessels, and it could be that lesions in the perforator artery presenting with perforant territory stroke are riskier than those presenting in the perforator artery with distant stroke (31, 32). This point needs to be clarified before embarking on a new trial, as we mentioned above. We recommend a change in the device selection by restricting intervention in these lesions to angioplasty using balloon with smaller diameter and shorter length.

Magnetic resonance imaging

Magnetic resonance perfusion imaging is capable of demonstrating the patient with a focal area of relatively lower perfusion, indicating less robust collaterals. In the WASID study, these patients were shown to have a higher likelihood of subsequent stroke. Any future trial should consider including equal numbers of these patients in both treatment arms to decrease their potential-cofounding effects.

Doppler ultrasound

Since increase in number of MES correlates with increased chances of further stroke, taking this finding into account may help refine the selection of patients and lesions.

TECHNICAL FACTORS

Stenting and Aggressive Medical Management for Preventing Recurrent Stroke demonstrated that most of the complications were periprocedural ones. Hence, working hard to decrease these complications should impact any future trials in a positive way. We believe the following points are valid based on personal experience and review of the literature:

Guiding catheter positioning

It should be as close to the lesion as safely possible; intracranial internal carotid artery, or at C1/C2 level for the vertebral artery. Our rule of thumb "never more than four curves between the tip of the guiding catheter and the lesion." This will decrease the jerky movement of the micro-wire tip during crossing the lesion and during any exchange of the micro-catheter system if it becomes needed. We believe that this requirement is so important that failure to place the guiding catheter in an acceptable position should be considered an exclusion criterion.

Angioplasty

Intracranial angioplasty can be performed relatively safely in most of the patients with intracranial stenosis. It appears that angioplasty has a much lower complication rate than any available stent on the market today. We believe that angioplasty should be the first line of intervention. Should it be attempted, we believe it should follow the axiom of submaximal, slow inflation technique. Currently available stents should be used only as a bail out for large dissection or significant recoiling of the lesion following angioplasty (29, 33, 34).

IMPROVING THE AVAILABLE STENT DESIGNS

Safer, more sophisticated stents are needed to improve outcomes of stenting procedures.

FUTURE DIRECTIONS

The Wingspan self-expanding device used in the SAMMPRIS trial has potential technical drawbacks, and trials with newer stents and an angioplasty only arm are warranted. Overtime, more effective and safer endovascular procedures may be developed and further trials will be needed to determine if these procedures with advanced technology lower the risk of stroke compared with aggressive medical therapy in high-risk subgroups. Until the next stent generation emerges, angioplasty alone might be an option

in some of the patients with intracranial stenosis and recurrent stroke after failure of best medical therapy. Moreover, several subgroups of patients with intracranial stenosis are at high risk of recurrent TIAs and strokes in spite of being on a best medical therapy such as those with posterior circulation involvement and high-grade stenosis, and others with recurrent ischemic events especially with blood pressure fluctuations (35). These patients may need neurointerventional procedures during the course of their intracranial stenosis management in spite of being on a best medical therapy due to recurrent ischemic events. Therefore, it is important to identify subgroups of patients who are at high risk of stroke despite being on an aggressive medical therapy protocol. However, it can be challenging as any neurointerventional procedure that aims to improve this outcome must have a low periprocedural complication rate and be able to lower the stroke rate over time when compared with the best medical therapy. The SAMMPRIS trial results encourage further research to investigate and find innovative ways of using endovascular therapies to treat severe symptomatic intracranial stenosis patients.

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REVIEW
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Acute ischemic stroke treatment, part 1: patient selection "The 50% barrier and the capillary index score"

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The current strategy for intra-arterial treatment (IAT) of acute ischemic stroke focuses on minimizing time from ictus to revascularization and maximizing revascularization. Employing this strategy has yet to lead to improved rates of successful outcomes. However, the collateral blood supply likely plays a significant role in maintaining viable brain tissue during ischemia. Based on our prior work, we believe that only approximately 50% of patients are genetically predisposed to have sufficient collaterals for a good outcome following treatment, a concept we call the 50% barrier. The Capillary Index Score (CIS) has been developed as a tool to identify patients with a sufficient collateral blood supply to maintain tissue viability prior to treatment. Patients with a favorable CIS (*f*CIS) may be able to achieve a good outcome with IAT beyond an arbitrary time window. The CIS is incorporated into a proposed patient treatment algorithm. For patients suffering from a large stroke without aphasia, a non-enhanced head CT should be followed by CT angiography (CTA). For patients without signs of stroke mimics or visible signs of structural changes due to large irreversible ischemia, CTA can help confirm the vascular occlusion and location. The CIS can be obtained from a diagnostic cerebral angiogram, with IAT offered to patients categorized as *f*CIS.

Keywords: acute ischemic stroke, patient selection, the 50% barrier, intra-arterial treatment, capillary index score, revascularization, stroke outcome

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Introduction

The current strategy for acute ischemic stroke (AIS) treatment is based on two pillars: time from ictus to revascularization (TIR) and revascularization success as measured by the modified thrombolysis in cerebral ischemia scale (mTICI). The assumption is that clinical outcome following AIS is dependent on the interaction of these two factors. The shorter the TIR and the higher the mTICI, the better the outcome. It follows that the strategy behind current intra-arterial treatment for acute ischemic stroke (IAT-AIS) is the faster and more complete the revascularization, the better the clinical outcome. However, despite the recent impressive improvement in revascularization rates and decrease in time to revascularization, until recently the clinical improvement rate remained unchanged at approximately 40–45% (**Table 1**) with a ratio of good clinical outcome (GCO) in treatment vs. control arms of approximately 1.7 (1–11). Recent trials have published GCOs above 50% in the treatment arm, but with the same ratio of GCOs between the treated and untreated arms around 1.7 (12, 13). How we can explain this consistency? A fresh look at our strategy and selection criteria is obviously warranted.

TABLE 1 | Clinical outcomes across IAT-AIS trials.

Trial	% mRS 0–2 (3 months)	Time to IAT (h)	% TIMI 2, 3
PROACT II	42.3[a]	4.5[b]	58
IMS I	43	3.05 ± 0.8[b]	56
IMS II	46	n/a	64
IMS III	40.8	3.5[b]	81[d]
SYNTHESIS	41.9	3.45[c]	n/a
SWIFT	37	4.9[b]	83
TREVO 2	39.9	4.7[c]	90
MR CLEAN	32.6	4.3[c]	58.7[d]
EXTEND-IA	71	3.5[c]	86[d]
ESCAPE	53	3.1[c]	72.4[d]

[a] *Barthel Index 9 and 10.*
[b] *Mean.*
[c] *Median.*
[d] *TICI 2, 3 for M1 occlusion.*

Physiological Background and the 50% Barrier

Normal cerebral blood flow (CBF) is 50–55 ml/100 g/min (14, 15). AIS induces a rapid and sustained reduction in CBF. Clinical signs of ischemia generally become apparent when CBF drops below 23 ml/100 g/min (16). If residual CBF (rCBF) further decreases to 15–16 ml/100 g/min, the cortical-evoked potential ceases within seconds (16). The rate of depression of the evoked potential (EP) amplitude (expressed in units of percent of control/min) is highly correlated with the residual flow, following a linear relationship with the regression line intercepting the flow axis at 15.2 ml/100 g/min (17). The data strongly suggest a threshold-like relationship also exists between the amplitude of the EP and local blood flow. If flow is greater than approximately 16 ml/100 g/min the EP is not affected, but at flows less than approximately 12 ml/100 g/min the EP is abolished (17). Neither the clinical signs of ischemia nor cessation of the EP is synonymous with cell death, but cessation of the EP is one of the final stages before irreversible injury (infarction). Its physiological purpose is to conserve energy by decreasing cell metabolism to the minimal level possible; however, cell death ensues thereafter.

Similarly, the relationship between time to irreversible damage and rCBF is well-documented (18). In one study, rCBF in monkeys was measured in the ischemic area with time after occlusion until irreversible tissue damage occurred (16). An infarction threshold was observed relating the rCBF to time between the initial drop in CBF to irreversible ischemia (**Figure 1**). This work confirmed prior studies using the neuronal EP and showed that when rCBF reached a low level of around 10 ml/100 g/min, the available time to salvage the brain tissue was extremely short (<1 h) (16).

The depth of ischemia, i.e., the level of rCBF, will vary from patient to patient depending on the available retrograde pial collaterals to the ischemic area. The major determinants of the amount of collateral perfusion are the number and diameter of these pial collaterals, plus perfusion pressure and resistance above and below the collateral network. Greater collateral numbers and diameters sustain a higher rCBF, thus more salvageable brain and a smaller final infarct volume.

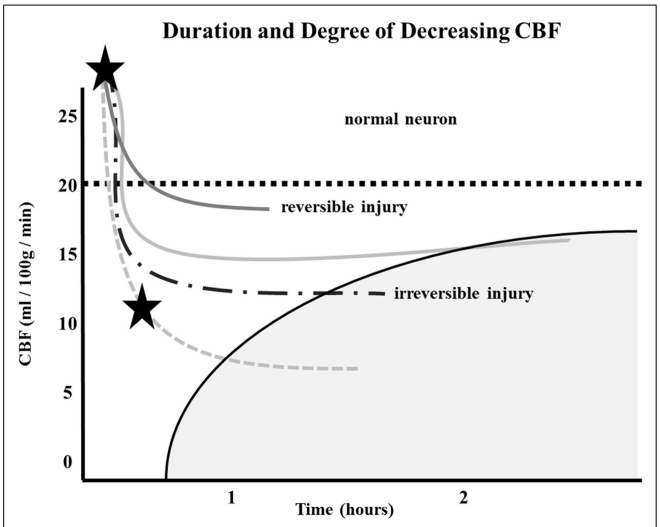

FIGURE 1 | Depth of ischemia and time to irreversible cerebral damage: time to irreversible cerebral damage depends on the depth of ischemia, which depends on the pial collateral supply to the ischemic territory. Since different patients have different collaterals, the depth of ischemia will vary among patients, as will the time available for therapy to salvage the tissue (16).

Following AIS, rCBF stays virtually unchanged if spontaneous recanalization of the occluded blood vessels does not occur (16, 18, 19). While the clinical symptoms of ischemia will often resolve if CBF is restored promptly, prolonged low levels of rCBF leads to irreversible brain tissue damage. Since the time of ischemia that the brain tissue can tolerate before irreversible damage ensues depends on the rCBF value, which is patient-specific and highly dependent on the collaterals, it follows that *every patient has his or her own time* (**Figure 1**) (16, 18, 19). Hence, if we correctly select patients that are optimal candidates (patients with ischemic but viable tissue) and are able to achieve safe, full, and timely revascularization (prior to irreversible ischemic damage occurring), the clinical symptoms of a stroke should improve significantly and rather quickly.

Given this information, the most logical explanation for the remarkably consistent results of the different IAT-AIS trials, with <50% GCOs (modified Rankin Score, or mRS, $\leq$2), is that around half of treated patients have poor pial collaterals, thus causing them to have a relatively low rCBF such that they enter into irreversible ischemia *before* therapy can be administered, even when *timely* (within 6 h) revascularization is achieved. This observation implies a potential ceiling effect for IAT-AIS; we call this phenomenon *the 50% barrier* (**Figure 2**).

The Genetic Factor?

Why is there such variability in collateral-dependent flow in patients with AIS, as exemplified by the above and many other studies? (21) Could the number and diameter (i.e., extent) of cerebral collaterals vary among individuals? While we do not have answers for humans yet, recent studies in mice suggest the answer may be yes and that genetic background may be important. In mice, pial collaterals form late in gestation, after the cerebral

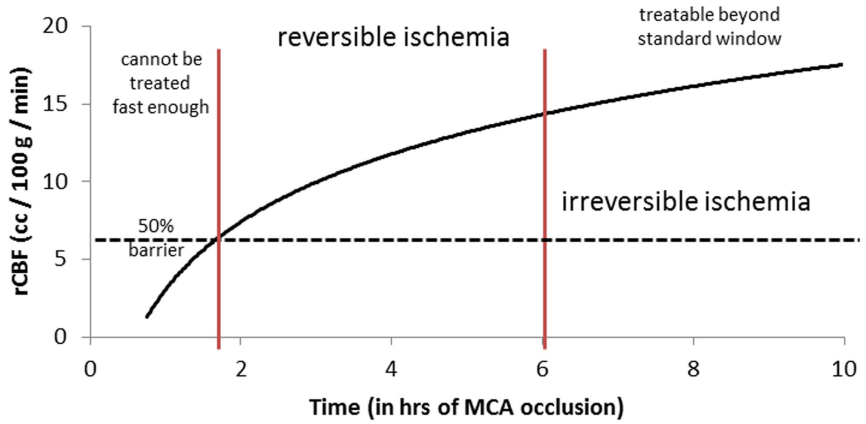

FIGURE 2 | Logarithmic time curve: the infarction threshold distinguishing between reversible and irreversible ischemia as a function of rCBF and time from ictus. Time window here is an approximation. The vertical lines are an approximation and have not yet been validated (20).

artery trees are well-established (22, 23). Likewise in humans, the middle cerebral artery (MCA) tree is already well-established by 9 weeks gestation, with pial collaterals beginning to appear by 14 weeks (24, 25). Collateral formation occurs by a unique process, termed collaterogenesis, that differs significantly from development of the general arterial–venous circulation; moreover, this process determines the collateral extent present in the adult (22, 23). Interestingly, naturally occurring differences in genetic background, which have no discernible effect on formation of the general circulation or its extent and function in the adult, have profound effects on collaterogenesis (23, 26). Thus, the extent of the pial collaterals in the neocortex varies by 56-fold among 21 mouse strains with different genetic backgrounds, resulting in a 30-fold variation in infarct volume after MCA occlusion (27–29). A single polymorphic locus on chromosome 7, denoted, "Determinant of collateral extent-1 (*Dce1*)," has been identified as *causal* for more than 80% of this variation, as exemplified in the two index strains (30). In that study, congenic methods were used to replace the at-risk allele of *Dce1* in the strain with poor collaterals with the allele from the strain with abundant collaterals. This restored the poor collateral phenotype to nearly that in the good strain, i.e., 83% correction of low collateral extent, and – after MCA occlusion – a 4.5-fold increase in blood flow in the territory at risk and 85% reduction of final infarct volume. Thus, ischemia and infarct volume were strongly reduced by exchanging a single genetic locus (30). These findings demonstrate that the *Dce1* locus harbors a critical link in the pathway that controls collaterogenesis. Although the causative genetic element(s) at *Dce1* is not yet known, several candidate genes have been identified (30). Since the pathways that control vascular development in the embryo are highly conserved among vertebrates, the same or a closely related gene(s) is likely to contribute to the wide variation in collateral status in humans. A prospective multi-center study, "Genetic Determinants of Collateral Status in Stroke (GENEDCSS) has been initiated to test this hypothesis (31). This study will determine if variation in collateral score, stroke severity, functional recovery, and other outcomes are linked to a polymorphism(s) at human *Dce1* and/or at several related candidate genes in patients with acute MCA stroke.

One's genetic background may not be the only factor that causes variation in collateral extent. Environmental factors also cause collateral insufficiency, at least in mice, although the magnitude of their impact has thus far not approached that of genetic background. Thus, aging (32), other cardiovascular risk factors such as hypertension, metabolic syndrome, and diabetes (33), as well as endothelial dysfunction *per se* (34), cause loss of pial collaterals and reduced diameter of those that are still present (collateral rarefaction). This rarefaction is accompanied by substantial increases in infarct volume after MCA occlusion. These findings have recently found support in patients with AIS(21).

It is also important to note that variation in the extent of the anterior communicating artery (ACom) and posterior communicating artery (PCom) collaterals is well-known to exist in humans, including those with acute stroke. The contributions of genetic, environmental, and stochastic factors to this variation are unknown, although they are currently under investigation in mice (JE Faber, personal communication). Moreover, the extent to which such variation combines with variation in pial collaterals to impact rCBF remains to be determined.

How might identification of a "collateral gene" like *Dce1* in mice benefit patients with acute stroke? A biomarker for collateral extent would provide a rapid point-of-care test to aid imaging methods, used during stroke triage to measure collateral status (e.g., conventional angiography and CT/MR perfusion), to help tailor the time-window for treatment with intravenous and/or endovascular recanalization therapies. A genetic marker of collateral abundance would also help stratify patients to reduce the presumed large contribution of collateral differences to the variability seen in past trials, and help more accurately assess the merit of the treatment used (e.g., intra-venous vs. intra-arterial vs. embolectomy). Identifying a risk allele for collateral insufficiency in humans would also be prognostic, adding to our understanding of why some patients do worse than others. Eventual identification of the causal gene(s) at *Dce1* may also provide therapeutic targets

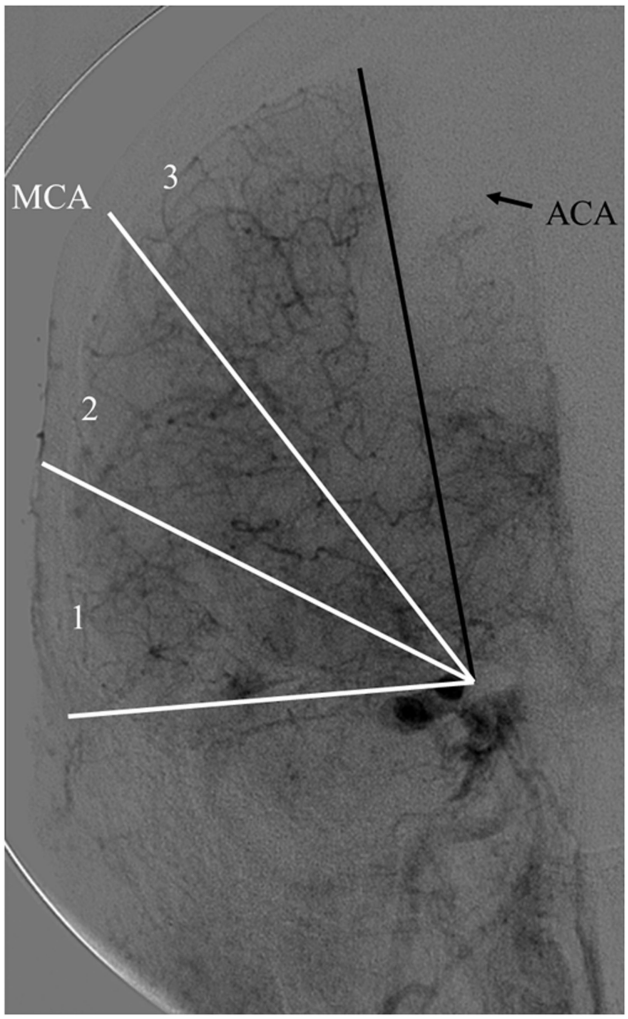

FIGURE 3 | Calculating the capillary index score (CIS). A frontal view of normal diagnostic cerebral angiogram. The territory of the middle cerebral artery (MCA) is being used as an example of an ischemic territory. The ischemic territory is divided into three equal sections; each section is given a 1 if it exhibits capillary blush, or a 0 if no capillary blush is present. The CIS is the sum of these three numbers. CIS can range from a score of 0 to 3 (20, 61).

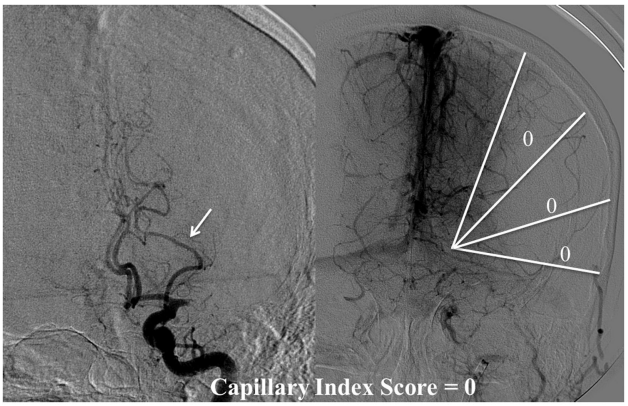

FIGURE 4 | CIS = 0. In this patient with proximal left middle cerebral artery occlusion, we can calculate the CIS from this injection only since the only other potential collateral to the MCA territory is from the left posterior cerebral artery (PCA), which is filled in the injection through the posterior communicating artery (Pcom, arrow). If we divide the ischemic territory (Lt MCA territory) into three sections, none of these sections exhibit a capillary blush, late in the venous phase; therefore, the CIS = 0.

aimed at the collateral circulation for future development. Healthy individuals carrying the risk polymorphism could be encouraged to adopt lifestyles and treatments to avoid acquiring risk factors for cardiovascular disease and stroke that have been found in animal studies (22, 30, 31) [with support coming in human studies (4)] to cause progressive loss of collaterals and increased severity of stroke.

Patient Selection

Current Imaging Selection Tests: Non-Invasive Neuroimaging

Diffusion MRI

Diffusion MRI is the best available method for the early detection of infarct core (35–38). Acute infarction produces a high contrast abnormality on diffusion-weighted images (DWI), the volume of which is relatively simple to quantify (39). The high contrast-to-noise (CNR) ratio of DWI makes it accurate. DWI abnormalities sometimes reverse (40), but this is rare (41) and when it occurs it usually involves only a small part of the lesion (42). Additionally, a DWI reversal is often a pseudo-reversal in that such tissue proceeds to infarction despite apparent temporary normalization of the DWI signal abnormality (42).

Studies have shown that a DWI abnormality volume of >70 ml is highly specific for a poor outcome (43, 44), and that this threshold volume is useful in selecting patients for endovascular intervention (45, 46). This threshold was successfully employed in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study II (DEFUSE II) trial (42). The use of early infarct "core" identification for triage decisions is supported by the observations that the final infarct volume is the single best predictor of good outcome at 90 days (39, 40). As has been shown (47), good outcomes are observed in nearly half such patients when the final infarct volume is 60 ml or less. The rate of good outcomes rapidly declines with infarcts that are larger. The use of a 70 ml DWI volume threshold (48) to successfully guide endovascular treatment was recently independently verified in a study at the Cleveland Clinic (49).

CT

CT is a front-line imaging modality for acute stroke because it is reliable for detecting hemorrhage. Moreover, CT angiography (CTA) may be subsequently acquired. However, non-contrast CT is unreliable for detecting the early infarct core (50, 51). It is highly specific for infarction when a hypodensity is clearly visible, but such changes typically occur late.

CT Perfusion

Much research has been devoted to developing CTP techniques for identification and quantification of the early infarct core. However, it is not sufficiently reliable for this purpose. This is

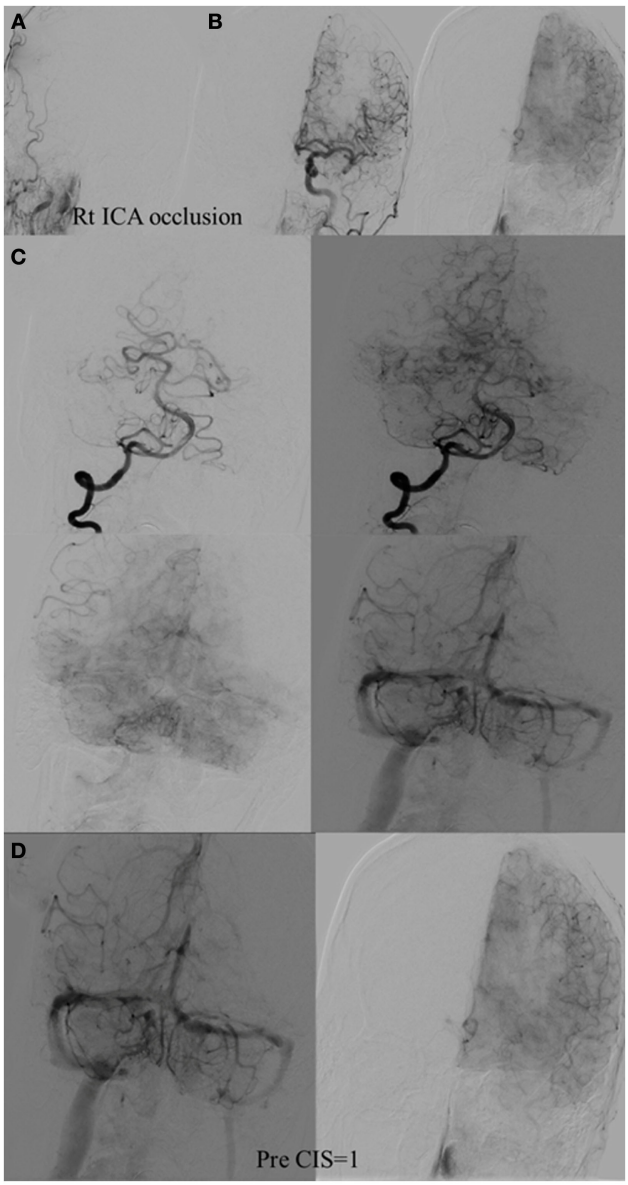

FIGURE 5 | CIS = 1. **(A)** Occlusion of intracranial right ICA. **(B)** Injection of the left ICA demonstrates absence of the Acom; hence, no cross filling to the right hemisphere from this injection (ischemic territory = right middle and right anterior carotid arteries). **(C)** Injection of the right vertebral artery demonstrates partial opacification of the temporal and parietal lobes through the right PCA via pial collaterals. **(D)** Delayed combined venous phase of the left internal carotid and right vertebral showing only one-third of the ischemic territory (right middle cerebral and interior cerebral arteries) territory demonstrates capillary blush. CIS = 1.

because it is a method that has inherently low signal-to-noise ratio (SNR) and CNR, producing "noisy" images with high measurement error (46, 52). Proponents of CTP may have been misled by correlation and regression studies of CTP-derived parameters in comparison to DWI or another gold standard. These studies typically show statistically significant correlations. Some investigators extrapolate a high correlation in a population of measurements to high accuracy of the measurement in an individual. This is not valid (53). A recent evidence-based analysis of diffusion and perfusion imaging in stroke by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology found that diffusion MR was a Level A/Class I method, but found insufficient evidence to even classify perfusion imaging (37). Furthermore, CTP typically only encompasses a limited number of slices and often fails to capture even half the tissue volume at risk for infarction that one is interested in determining infarction volume in.

There is no consensus on how to best apply CTP. A variety of acquisition parameters have been used, as well as many different data processing methods. Additionally, different parameters (e.g., cerebral blood volume, CBV, or CBF thresholds) have been proposed for defining infarcted tissue (54). It is thought that standardization and validation will make CTP viable (53). However, CTP is unlikely to become a reliable method (46, 52). Theory informs us that CBV may be elevated or depressed in core tissue and thus it is not useful. This has been empirically confirmed (55). CBF is more capable of estimating the infarct core. The reasoning is that below a certain CBF threshold, brain tissue is very likely to be viable only for a short period of time. However, there are major problems that are related to the underlying imaging physics: the CNR of infarct cores on CTP-derived CBF images are very low (52). At its current state, the errors in CTP-derived estimates of CBF are too high to be used to reliably guide treatment in an individual patient with a severe anterior circulation stroke.

The Limitations of Non-Invasive Testing

Despite its promise, the merit of any non-invasive imaging test in patient selection for AIS treatment has yet to be proven in a multicenter, prospective, randomized clinical trial. Furthermore, the issue of what is considered acceptable sensitivity, specificity, and positive predictive value of these screening tests has not yet been addressed.

In a recent paper, Alberta Stroke Program Early CT (ASPECT) score was not found to help in patient selection in AIS to predict outcome (56). Even MRI diffusion and perfusion imaging did not demonstrate a strong enough positive predictive value where only approximately half of patients with AIS, who were selected for endovascular treatment, achieved GCO following successful revascularization (42, 49). We believe that the low positive predictive value (50%) of these tests is due to the inability of different non-invasive tests to distinguish between normal and ischemic (but viable) cerebral tissue on one hand, and its inability to distinguish between ischemic tissue and irreversible ischemia early on, on the other hand, due to the time delay needed for the structural changes of cerebral infarction to become readily apparent (42, 49, 56, 57).

For a screening test to be a useful patient selection tool, it must be highly correlated to the functional clinical outcome. In our opinion, existing non-invasive tests do not meet this requirement. This relatively low positive predictive value of the different imaging techniques used has multiple implications. First, it hinders our ability to develop an accurate prognosis for the patient and his or her family. Second, we may proceed with a costly treatment without benefit (futile recanalization). In some cases, the patient may experience worsening clinical symptoms due to increasing

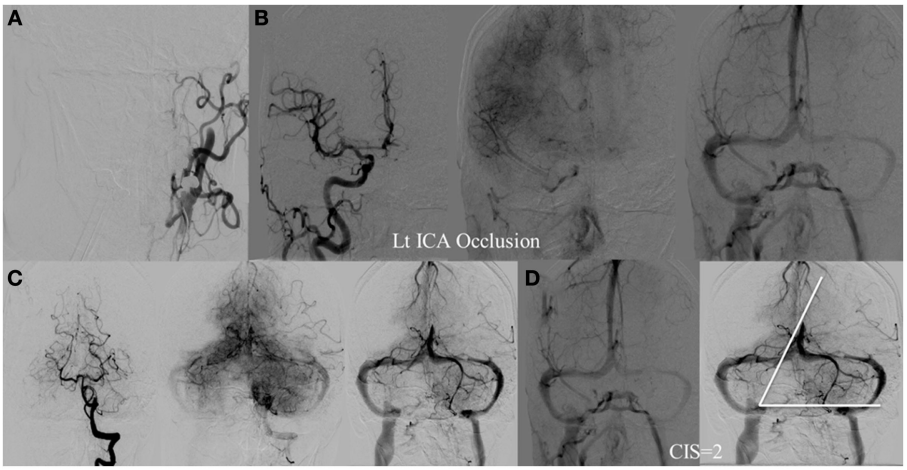

FIGURE 6 | CIS = 2. (A) Occlusion of the left ICA. **(B)** Injection of the right ICA demonstrates filling of the left ACA territory through the Acom with partial opacification of the fronto–parietal lobes via pial collaterals. **(C)** Injection of the left vertebral artery demonstrates partial opacification of the left temporal lobes via pial collaterals. **(D)** Delayed venous phase of the right ICA and left vertebral showing approximately two-third of the ischemic territory (left middle MCA) to demonstrate capillary blush.

the cerebral injury by reperfusion-mediated vasogenic edema, or perhaps even hemorrhagic transformation by forcing blood into the infarcted area (harmful revascularization). Finally, and more importantly, we may deny the treatment to patients based on an artificial time window, for whom IAT may still be beneficial. Increasing the accuracy of patient selection is clearly needed.

The Capillary Index Score

The role of collaterals in improving clinical outcome in patients with AIS is now widely accepted (58–60). Recently, using the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral score (58), the Interventional Management of Stroke (IMS) III investigators were able to confirm the previous reports on the positive effect of better collaterals on revascularization and clinical outcome (59).

The Capillary Index Score (CIS) was first introduced from the Borgess Medical Center-Acute Ischemic Stroke Registry (BMC-AIS Registry) data (61) with the aim to improve the criteria for patient selection in AIS. The presence of capillary blush was proposed to be a *marker of residual viable tissue*, with its absence implying irreversible ischemia. The CIS is a simple 4-point scale ranging from 0 to 3. The ischemic territory on the frontal view of a diagnostic cerebral angiogram (DCA) is divided in three equal segments (**Figure 3**). If a segment does not demonstrate a capillary blush it is assigned 0 points, whereas it is assigned 1 point if it exhibits capillary blush. The final CIS is the sum of these three segmental scores (**Figures 4**–**7**). Therefore, CIS of 0 means no angiographic capillary blush was found in the whole ischemic territory, whereas a CIS of 3 signifies that the whole ischemic area exhibits capillary blush. CIS 2 or 3 ($\leq$1/3 of the ischemic area has no capillary blush) is considered favorable CIS (*f*CIS) and it was found to be a *prerequisite for a GCO* in BMC-AIS registry (61). A CIS of 0 or 1 was considered a poor score CIS (pCIS), and no patients with *p*CIS had a GCO despite good revascularization (61). The merit of the CIS as a method for patient selection was further validated in a recent IMS I and II subgroup analysis (20). Of patients with *f*CIS and good revascularization (mTICI, score 2b or 3), 100% achieved GCO, while patients with *p*CIS invariably did worse than the natural history of the disease estimated at 25% GCO, as shown by the PROACT II study, independent of revascularization status (**Table 2**) (3). Recently, we applied the CIS to a subgroup of IMS III cohort and found almost identical findings (Al-Ali, Firas et al. Relative Influence of Capillary Index Score, Revascularization and Time on Stroke: Outcomes from the IMS III trial. Submitted to *Stroke* February 2015).

The percentage of *f*CIS, which was a prerequisite for GCO, was found to be 42% in the BMC-AIS registry and 46% in the IMS I, II subgroup analysis (20, 57), all hovering around 50%, which strengthens our belief in "the 50% barrier" hypothesis.

Ischemic Territory vs. the Site of Vascular Occlusion

Central to the concept of CIS is the concept of *ischemic territory*. We define ischemic stroke by the ischemic territory instead of the site of vascular occlusion since we believe that it gives a more accurate estimation of stroke extension. The *ischemic territory* is defined as the *area of the brain that lacks antegrade flow. All or a portion may receive its blood supply in retrograde fashion through pial collaterals*. For example, in a patient with internal carotid artery (ICA) occlusion, a few radically different scenarios are possible. In one scenario, the patient has congenital absence of the Acom and the Pcom arteries (**Figure 8**). This patient's ischemic territory will include the entire ipsilateral middle and anterior cerebral artery territories. In a different scenario with the exact same ICA occlusion, but with Acom artery present and well-developed, the anterior cerebral artery territory ipsilateral to the vascular occlusion will receive an antegrade blood supply

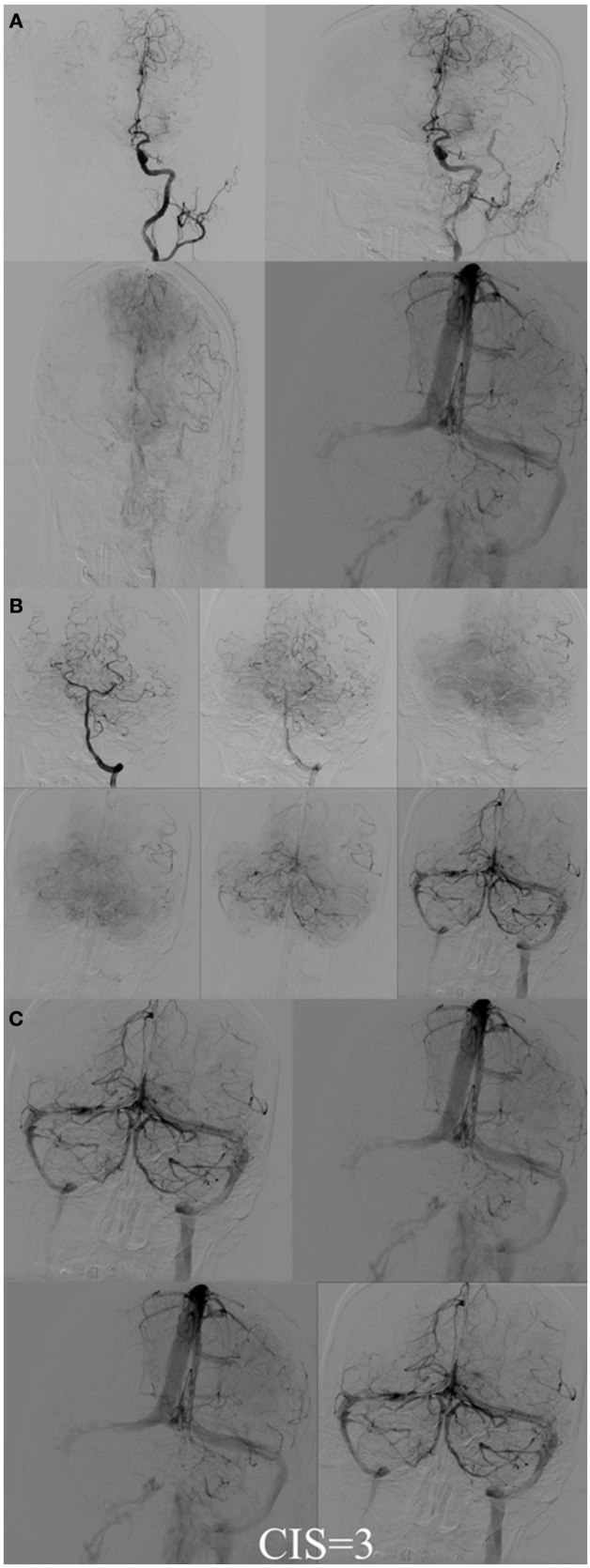

FIGURE 7 | CIS = 3.

FIGURE 7 | Continued
(A) Injection of the left ICA demonstrates occlusion of proximal left MCA (ischemic territory = left MCA) with partial opacification of the left fronto-parietal lobes via pial collaterals of the left ACA. **(B)** Injection of the left vertebral artery demonstrates partial opacification of the left temporal lobes via pial collaterals. **(C)** Delayed venous phase of the left ICA and the left vertebral artery. All the ischemic territory (left MCA) demonstrates capillary blush. CIS = 3.

TABLE 2 | CIS vs. Outcome.

	*f*CIS:% of mRS, 0–2	*p*CIS:% of mRS, 0–2
BMC-AIS (TIMI 0,1)	0	0
BMC-AIS (TIMI 2,3)	60	0
BMC-AIS (TIMI 3)	83	0
IMS I, II (TIMI 0,1)	33	0
IMS I, II (mTICI 2,3)	86	13
IMS I, II (mTICI 2b,3)	100	20

from the counter lateral ICA, through the patent Acom artery so the ischemic territory will encompass only the MCA territory (**Figure 9**). Hence, due to multiple possible scenarios when using the site of vascular occlusion to describe the ischemic stroke, we believe that defining the stroke by its territory is a more accurate approach.

The CIS Limitation

The main limitation of the CIS is the need to perform a full DCA during intervention. However, we believe the significant information obtained through the CIS by examining the DCA, mainly how to guide patient selection combined with the elimination of an arbitrary time window greatly outweighs the minimal risk associated with adding a few injections for a required DCA during intervention.

CIS vs. Non-Invasive Testing

Interestingly, the *f*CIS and *p*CIS groups had almost identical values concerning time from stroke onset, the ASPECT score, and the National Institutes of Health Stroke Scale (NIHSS) scores in the BMC-AIS registry and the IMS I, II subgroup analysis (20, 61). The relationship between CIS and different perfusion imaging parameters was evaluated in the DEFUSE II trial. Although there was a good general agreement between the CIS score and the time to maximum values >6 and >10 (Tmax > 6 and Tmax > 10), low CIS correlated with high Tmax > 6. There was a significant overlap between the different CIS and the Tmax values, which makes it impossible to differentiate between the *f*CIS and *p*CIS based solely on the MRI perfusion parameter. (Oral presentation at the International Stroke Conference, San Diego, CA, USA, February 2014). These findings imply that the CIS provides different information than currently available from non-invasive tests, which cannot be extrapolated with confidence. Furthermore, none of these non-invasive tests has a similar threshold to the CIS (*f* vs. *p*CIS) that can be used confidently in patient selection. As shown, even with the most useful non-invasive test today, MRI diffusion/perfusion

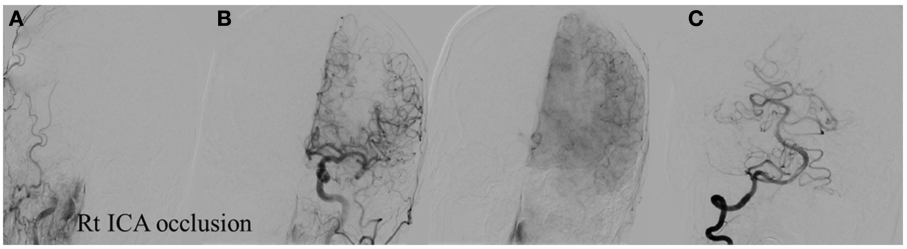

FIGURE 8 | Vascular occlusion and ischemic territory. This patient has occlusion of the right ICA and a congenital absence of the anterior and posterior communicating arteries (Acom, Pcom). The resulting ischemic territory is the right MCA and ICA. **(A)** Frontal view of the injection of the right common carotid artery demonstrating no intracranial capillary blush. **(B)** Frontal view of the injection of the left common carotid artery demonstrating no collateral flow to the right hemisphere through the interior cerebral artery. **(C)** Frontal view of the injection of the right vertebral artery demonstrating no collateral flow to the right interior carotid artery territory.

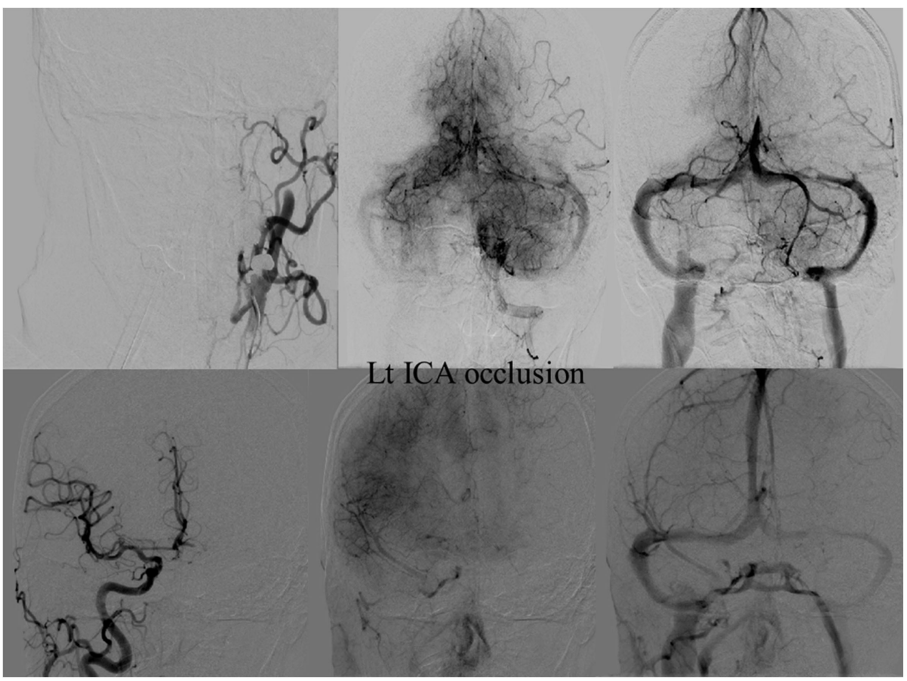

FIGURE 9 | Vascular occlusion and ischemic territory. This patient has occlusion of the left internal carotid artery (ICA), but has a well-developed anterior communicating artery (Acom). The resulting ischemic territory is only the left MCA territory.

imaging, only 50% of patients who achieve good revascularization have a GCO (49).

The Relative Importance of CIS, Revascularization, and Time

Several important observations were made after applying the CIS retrospectively on different registries and trials [(20, 61), Al-Ali, Firas et al. Relative Influence of Capillary Index Score, Revascularization and Time on Stroke: Outcomes from the IMS III trial. Submitted to *Stroke* February 2015]. First, *f*CIS was almost a prerequisite for GCO following revascularization. In other words, when good revascularization (TIMI 2, 3) was achieved on patients with *p*CIS, it was futile (no clinical improvement). Revascularization mattered *only* when patients had excellent collaterals, as indicated by *f*CIS. Next, and despite the fact that *f*CIS was almost a prerequisite for GCO, its presence alone was not sufficient to guarantee GCO. In the IMS I and II, patients with *f*CIS had 100 vs. 38% GCO with or without good recanalization, respectively (20). These observations demonstrate the concomitant importance of recanalization and the fact that *f*CIS is an indicator of ischemic but contemporaneously viable tissue, but not an indicator of perpetually viable tissue. Recanalization is still required. If these observations are supported in a prospective trial, it may significantly change the AIS treatment algorithm, where IAT could be offered to all patients with *f*CIS but not patients with *p*CIS, regardless of time of ictus. This will constitute a radical shift of the present approach and liberate the decision making from an arbitrary time window, in favor of a more physiological basis.

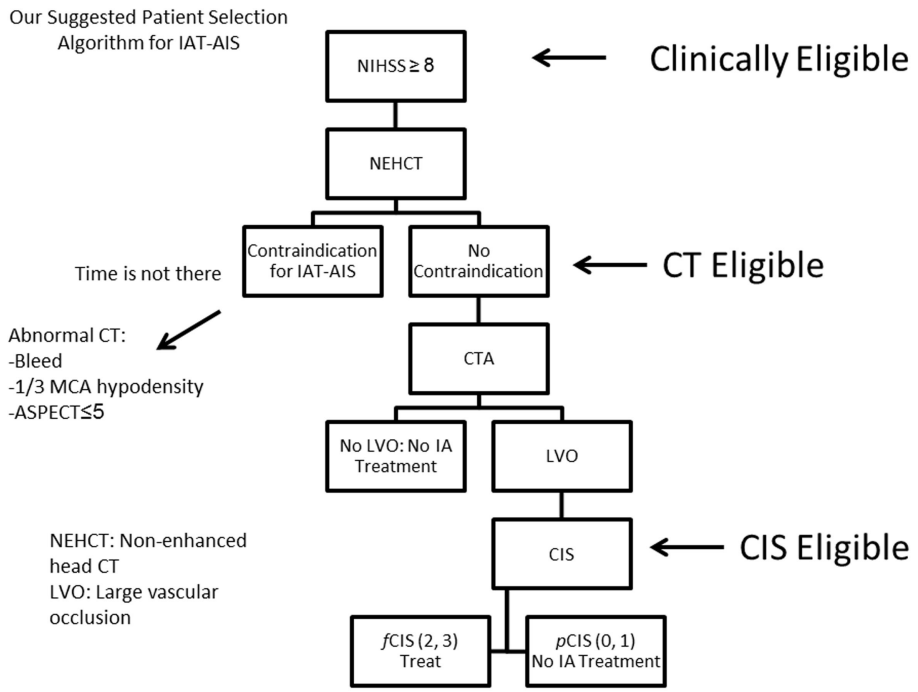

FIGURE 10 | Proposed patient selection algorithm for AIS.

Proposed Patient Selection Algorithm

We recognize that the merit of the CIS still needs to be proven in a multicenter prospective study; however, we believe the CIS hypothesis will be proven true due to its ability to explain the results of ischemic stroke trials.

Since most patients will improve to a variable degree with time and physical therapy, we believe that IAT should be offered to patients suffering from a large stroke (NIHSS < 8), with the only exception being aphasia (**Figure 10**). Of those patients who are *Clinically Eligible,* a non-enhanced head CT is obtained followed by CTA. These non-invasive tests can first rule out stroke mimics and identify patients with already visible signs of structural changes due to large irreversible ischemia (i.e., hypodensity in $>1/3$ MCA territory on head CT). If no such findings are identified, CTA will help confirm the vascular occlusion and its location. Patients with no counter-indication to treatment and proven large vessel occlusion (*CT Eligible)* are offered IAT. A full DCA is performed on these patients to obtain the CIS. Only patients who demonstrate *f*CIS (*CIS Eligible*) should be offered IAT since revascularization on patients with *p*CIS will be futile and possibly harmful (**Figure 10**). If these steps are taken, we predict a significant increase in the ratio of GCOs between treated and untreated patients on the order of 5–6, instead of the current 1.6–1.7 ratio that exists currently (3, 10–13), by the virtue of significantly decreasing the percentage of futile and harmful revascularization.

Conclusion

The current approach for treating AIS is based on arbitrary time windows and revascularization, but we believe collaterals also need to be taken into account. We argue that only approximately 50% of all patients with AIS have robust enough collaterals to permit GCOs following treatment, a concept we call *the 50% barrier*. Previous and ongoing genetic work should shed light on this interesting possibility in the near future. The CIS can identify patients with viable tissue, who are therefore candidates for treatment, and dispose of the arbitrary time window.

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REVIEW
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Acute ischemic stroke treatment, part 2: Treatment "Roles of capillary index score, revascularization and time"

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Due to recent results from clinical intra-arterial treatment for acute ischemic stroke (IAT-AIS) trials such as the interventional management of stroke III, IAT-AIS and the merit of revascularization have been contested. Even though intra-arterial treatment (IAT) has been shown to improve revascularization rates, a corresponding increase in good outcomes has only recently been noted. Even though a significant percentage of patients achieve good revascularization in a timely manner, results do not translate into good clinical outcomes (GCOs). Based on a review of the literature, the authors suspect limited GCOs following timely and successful revascularization are due to poor patient selection that led to futile and possibly even harmful revascularization. The capillary index score (CIS) is a simple angiography-based scale that can potentially be used to improve patient selection to prevent revascularization being performed on patients who are unlikely to benefit from treatment. The CIS characterizes presence of capillary blush related to collateral flow as a marker of residual viable tissue, with absence of blush indicating the tissue is no longer viable due to ischemia. By only selecting patients with a favorable CIS for IAT, the rate of GCOs should consistently approach 80–90%. Current methods of patient selection are primarily dependent on time from ischemia. Time from cerebral ischemia to irreversible tissue damage seems to vary from patient to patient; so focusing on viable tissue based on the CIS rather than relying on an artificial time window seems to be a more appropriate approach to patient selection.

Keywords: acute ischemic stroke, intra-arterial treatment, revascularization, stroke outcome, capillary index score

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Introduction

The interventional management of stroke (IMS) III trial (1) showed non-superiority of intra-arterial (IA) revascularization combined with intra venous (IV) tissue plasminogen activator (tPA) treatment over IV tPA alone, and the systemic thrombolysis for acute ischemic stroke (SYNTHESIS) trial demonstrated similar lack of favorable clinical outcomes for IA versus IV tPA therapy (2). This is despite the high revascularization rate in the IA arms in these trials. The role of intra-arterial treatment for acute ischemic stroke (IAT-AIS) has been contested. Paradoxically, however, the benefit of revascularization to clinical outcomes is convincingly attested to in prior literature. In a recent meta-analysis of 998 patients with clinical follow-up at 3 months, good clinical outcome was found in 58% of revascularized patients as compared to 24.8% in non-revascularized patients (3).

When revascularization occurred within the first 6 h, good clinical outcomes (GCOs) were found in 50.9% of revascularized patients as compared to 11.1% in non-revascularized patients. Other authors reached similar conclusions. Even in the IMS III trial, better revascularization using the modified thrombolysis in cerebral infarction (mTICI) score led to better outcomes than those for patients who achieved lesser revascularization (1). This data were recently resolved with the publication of newer trials. In MR CLEAN, EXTEND-IA, and ESCAPE, good recanalization rates were achieved in 58.7, 86, and 72.4% of patients, respectively, with accompanying GCO rates at 32.6, 71, and 53%, respectively (4–6). While these results demonstrate IA superiority with higher recanalization rates than with IVT, there are still a significant number of patients who achieved good and timely revascularization that did not also achieve GCOs. So if better revascularization improves outcome and IA treatment has a better revascularization rate than IV treatment, how can we explain the lack of GCOs in some of these patients?

Revascularization and Outcome

Revascularization is defined as the restoration of anterograde blood flow to the ischemic area through the recently occluded artery. Currently, this is reported using the mTICI score, with mTICI of 2b or 3 being considered successful revascularization (7). The aim of revascularization is to produce clinical improvement through restoring the cerebral blood flow (CBF) level to greater than the critical threshold of 23 ml/100 g/min of viable brain tissue (8). This should translate into a permanent resolution of AIS symptoms by saving the ischemic tissue *before* it progresses to irreversible damage. So if perfect revascularization is achieved (mTICI = 3) in a *timely* manner, i.e., before ischemia becomes irreversible, clinical improvement should be achieved for almost all patients, as well as for the majority of patients with less effective revascularization (mTICI = 2b). However, review of the literature reveals that only around 50% of patients in whom we obtained timely recanalization (mTICI 2b, 3) will achieve a good clinical outcome (**Table 1**) (1, 2, 9–13). Attempting to solve the paradox regarding why all technically successful revascularizations do not translate into GCOs should help us improve our revascularization strategy.

Revascularization Rate

Revascularization rate depends heavily on the mode of treatment used (3). Spontaneous recanalization is estimated at 24% within the first 24 h (3). By comparison, overall data suggest that IV tPA results in recanalization in 46% of patients, as compared to 63% for IA thrombolysis, and 68% when the combined therapies (IV + IA) are utilized. Mechanical thrombectomy achieved the highest recanalization rate at 84% (3). It is estimated that revascularization is associated with a four to fivefold increase in good clinical outcome rates. Since higher revascularization rates correlate with better outcome in the literature and mechanical thrombectomy has the highest revascularization rate, it is now the preferred method for most operators.

TABLE 1 | Clinical outcomes across IAT-AIS trials.

Trial	% mRS 0–2 (3 months)	Time to IAT (h)	% TIMI 2, 3
PROACT II	42.3[a]	4.5[b]	58
IMS I	43	3.05 ± 0.8[b]	56
IMS II	46	n/a	64
IMS III	40.8	3.5[b]	81[d]
SYNTHESIS	41.9	3:45[c]	n/a
SWIFT	37	4.9[b]	83
TREVO 2	39.9	4.7[c]	90
MR CLEAN	32.6	4.3[c]	58.7[d]
EXTEND-IA	71	3.5[c]	86[d]
ESCAPE	53	3.1[c]	72.4[d]

[a] *Barthel index 9 and 10.*
[b] *Mean.*
[c] *Median.*
[d] *TICI 2,3 for M1 occlusion.*

Mechanical Thrombectomy

The original method of mechanical thrombectomy was microwire and micro-catheter clot manipulation during IA tPA or pro-Urokinase infusion. In Asia, balloon angioplasty is used frequently as a mechanical method with an excellent recanalization rate of 80% (3). In the Western hemisphere, while balloon angioplasty is used, the predominate mode of mechanical recanalization is either a stent retrieval or the Penumbra system.

Stent retrieval systems are designed to restore blood flow by catching the thrombus through the stent struts. Flow cessation is then induced in the internal carotid artery using a balloon-mounted guiding catheter. At this time, the clot is removed by dragging it through the guiding catheter while applying suction on the guiding catheter to decrease the chance of a clot fragment migrating downstream. There are two available stent retrieval systems in the market today: the Trevo™ Pro Vu™(Stryker, Kalamazoo, MI, USA) and the Solitaire™(Covidian, CA, USA). Both devices are constructed of Nitinol with a laser cut design that can be delivered through a standard 0.021 or 0.027-inch (internal diameter) microcatheter.

The Trevo™ ProVue™ consists of a flexible, tapered core wire with a shaped section at the distal end. Radiopaque platinum wires in the shaped section and a guide wire-like tip allow fluoroscopic visualization. It is constructed of a straight cut tube that includes a distal taper and wire. Its struts are constructed perpendicularly to the clot in an attempt to engage the thrombus. The Solitaire™, on the other hand, has a proprietary overlapping stent technology called Parametric™ Design that provides multiple planes of clot contact (Solitaire IFU). Both stents have demonstrated comparable and excellent revascularization rates in prospective registry studies. In a recent prospective study of 227 patients, the Solitaire™ system had excellent results of 71% mTICI 2b or 3 (14), while the Trevo™ Pro Vu™ demonstrated 86% TICI 2 or 3 revascularization in the Trevo versus Merci retrievers for a thrombectomy revascularization (TREVO 2) randomized trial (13).

The Penumbra System™(Penumbra Inc., Fremont, CA, USA) is an aspiration system that utilizes an entirely different mechanism of mechanical clot retrieval. The device uses a suction mechanism to retrieve the clot inside the catheter by lodging the tip

of the catheter in the proximal end of the clot while simultaneously hooking its hub to a suction machine creating pure suction (−29 mm Hg at sea level). In the initial pivotal study that included 125 patients, recanalization rates utilizing the Penumbra system were 82% thrombolysis in myocardial infarction (TIMI) score of 2 or 3 (15), later confirmed by a second prospective trial with 87% revascularization rates (TIMI 2 or 3) (16).

From Technically Successful to Clinically Beneficial Revascularization

Technically successful revascularization does not always lead to good, i.e., beneficial, clinical outcomes. Some technically successful revascularizations are futile (not followed by clinical improvement) while others are outright harmful (cause clinical deterioration). Several factors may contribute to these variations:

Patient Selection: The Capillary Index Score

In patients who already suffered a large area of irreversible ischemic injury, reconstituting the anterograde blood flow will not be beneficial, and can actually be harmful by increasing the risk of vasogenic edema and/or hemorrhagic transformation, as well as possible herniation. We believe one reason why good revascularization does not always lead to good clinical outcome is poor patient selection, i.e., treating patients with already irreversible ischemia. The capillary index score (CIS) is a simple angiography-based scale for assessing viable tissue in the ischemic territory. The CIS is comprised of a 4-point scale ranging from 0 (no angiographic capillary blush) to 3 (the whole ischemic area exhibits capillary blush), with the presence of capillary blush proposed as a marker of residual viable tissue, with absence implying irreversible ischemia. Favorable CIS (*f*CIS) is defined as a score of 2 or 3 and was found to be nearly a prerequisite for a good clinical outcome (modified Rankin Scale, mRS, score of 2 or lower at 90 days) (17), whereas a poor CIS (*p*CIS) is defined as a score of 0 or 1. If the assumption that the presence of *capillary blush indicates viable tissue* and its absence implies irreversible ischemia is correct, then selecting only patients with *f*CIS for treatment should significantly increase the percentage of patients with GCOs following technically successful intervention. At the same time, by not offering treatment to patients with *p*CIS, there should be a significant decrease in the percentage of futile or harmful revascularization, further increasing the percentage of patients with GCOs. Indeed, in the Borgess Medical Center-acute ischemic stroke registry (BMC-AIS), 83% of patients with *f*CIS who achieved TIMI 3 revascularization had good clinical outcome (mRS 0–2) (17). In a subgroup analysis of IMS I, II trials using the CIS and TIMI scores, 100% of the five patients with a *f*CIS and good revascularization (mTICI 2b, 3) had good clinical outcome (18). To our knowledge, this represents the highest percentage of GCOs following good revascularization that has been reported, suggesting that the CIS is the most accurate tool, to date, for patient selection in AIS treatment.

Territory Selection: Complete Versus Optimal Revascularization

The current understanding of revascularization is that clinical benefits of revascularization increase with its extent (1, 19). In the IMS I and II trials, better revascularization led to better outcome – 46 versus 58% for TICI 2 or 3 versus mTICI 2b or 3, respectively (19). Even in the IMS III, despite its overall results, better revascularization in the IA arm translated into better clinical outcomes (**Table 2**) (1). However, if we accept the assumption that capillary blush indicates viable tissue, we should not be guided solely by the desire to obtain as complete revascularization as possible. Rather, the aim of revascularization should be to reconstitute anterograde flow *solely* to the territory with persistent capillary blush through the pial collaterals (viable tissue), while resisting the temptation to establish an anterograde flow to the territory void of capillary blush (non-viable tissue). In other words, and counter-intuitively, for a technically successful revascularization to be clinically beneficial, it does not necessarily need to be as complete as possible, but rather it should aim to restore an anterograde flow *only* to the area with persistent capillary blush. Following revascularization, *one should not see capillary blush that did not exist prior to intervention.*

TABLE 2 | IMS III results – clinical outcome and revascularization status (1).

mTICI	mRS 0–2 at 3 months (%)
0	12.7
1	27.6
2a	34.3
2b	47.9
3	71.4

Complication Rates

All forms of intervention, no matter how simple, carry the risk of complications. IAT-AIS is a very complex and technically demanding procedure, and at times it requires clinicians to cross occluded vessels blindly without any road mapping or prior knowledge of the patient's anatomy. Furthermore, most of these patients are advanced in age and have difficult vessels to navigate. Complications related strictly to the revascularization attempts certainly exist; some of them are obviously device-specific. Unfortunately, information is lacking about the actual complication rate during IAT-AIS. Since these patients are already symptomatic prior to intervention, it is difficult to reliably determine how much an unsuccessful intervention contributed to overall patient symptoms or functional outcome impairment during their hospital stay. The only prospectively available data on complication during the revascularization procedure comes from the Penumbra™ aspiration system with a 13% total complication rate in the Pivotal study (3% deemed serious) and 6% in the post study (15, 16). Complication rates of 3% with the Solitaire™ system were reported in a review article involving 13 prior papers comprised of 262 patients (20). This included five subarachnoid hemorrhages, two self-detachments of stent, one entanglement of stent, and one in-stent thrombosis. Currently, no published data regarding Trevo complications are available, but the rates are likely similar to the other devices. We can thus conclude that mechanical intervention devices carry approximately 5% complication rate, which would ultimately negatively affect the overall odds ratio of better outcomes following IAT-AIS. Decreasing the complication rate is mandatory if we want to increase the percentage of treated patients with GCOs.

The Different Forms of Revascularization

There are three forms of technically successful revascularizations: beneficial, futile, and harmful. We believe that beneficial revascularization, i.e., revascularization followed by clinical improvement, occurs when revascularization is completed only on the areas with persistent capillary blush via collaterals (prior to intervention). The role of revascularization here is simply to reverse the retrograde flow supplying the ischemic area to anterograde flow and by doing so raise the CBF above the critical threshold of ischemia. Therefore, technically *successful and beneficial, revascularization* can be defined as: *reversing the flow to an ischemic area with persistent capillary blush, from retrograde to antegrade without complications*.

The other forms of revascularization are futile (no clinical improvement) and harmful (followed by clinical deterioration). These occur when revascularization is performed on an area void of capillary blush prior to intervention, i.e., to non-viable cerebral tissue, or due to a complication during a revascularization attempt.

In order to enhance the benefit of intra-arterial treatment (IAT), we need first to redefine our revascularization strategy by minimizing the performance of futile and harmful revascularization. To achieve this goal, we propose the following strategy: select patients correctly with *f*CIS and obtain as complete and timely revascularization as safely possible, *solely* to the viable tissue, i.e., the areas with persistent capillary blush.

Intra-Arterial Versus Intra-Venous Treatment

The recent results of the IMS III (1) and SYNTHESIS (2) trials are most likely due to poor patient selection and high percentages of futile or harmful revascularizations. By adapting the CIS for patient selection and a more nuanced strategy for revascularization, we should consistently approach the 80–90% clinical improvement rate in the treated subgroup, as we saw in the BMC-AIS registry and the subgroup analysis of IMS I, II. This percentage cannot be reached using IV treatment alone due to the lower revascularization rate associated with IV treatment and its inability to assess the collateral supply prior to treatment, which will invariably lead to a higher percentage of futile and harmful recanalization.

Time to Revascularization and Outcome

The Relationship of Time to Revascularization and Outcome: Is it Linear?

Selection Bias

A linear relationship between time from ictus to revascularization and outcome is suggested from few previous trials (21–25). However, it is important to note that a selection bias exists in these trials since a significant portion of patients are excluded either due to the presence of imaging evidence of counter-indication for AIS treatment (signs of irreversible brain damage) or due to an artificial time window. Hence, even if the relationship between time from ictus to recanalization and outcome is perfectly linear in this subgroup of patients, we cannot deduce from it the overall relationship between time and outcome for all patients presenting with AIS.

Literature Review

The suggested linear relationship between time and outcome is not supported by empirical data when we reviewed the recent IAT-AIS trials. Reviewing the most recent large, prospective trials, the IMS III (1) and SYNTHESIS (2), as well as the two most recent device studies, solitaire with the intention for thrombectomy (SWIFT) and Trevo 2, reveal an almost identical clinical improvement rate despite significant differences in time from ictus to treatment across these studies (**Table 1**) (1, 3, 12, 13). The SWIFT and the Trevo 2 trials had similar results with a percentage of good clinical outcome (mRS $\leq$2) at 37 and 40%, respectively; the mean time from ictus to treatment was 4.9 h in the SWIFT study, and the median for Trevo 2 was 4.7 h (12, 13). Both trials included patients up to 8 h from ictus (12, 13). Meanwhile, in the IMS III trial, the IV treatment had to start within 3 h from ictus, while the IA treatment had to start within 5 h and finish by 7 h post ictus; yet, the study operators reported almost identical results with 40.8% mRS 0–2 at 3 months (1). In addition, the SYNTHESIS trial had a shorter time from ictus to treatment (median of 3:45 h; range 3:14–4:20) with a similar percentage of mRS 0–2 at 42% of mRS 0–2 (2). If the relationship between outcome and time from ictus to revascularization was linear, we would expect a higher percentage of mRS improvement in the SYNTHESIS trial than the IMS III trial, and a higher percentage in the IMS III trial than the SWIFT and Trevo 2 trials; yet, all reported an almost identical good clinical outcome rate. Furthermore, there are numerous series reporting almost identical percentages of GCOs (around 40%) on patients treated after the traditional 6-, even up to 8-h window (25, 26). It is difficult to reconcile these observations with a linear relationship between time from ictus to revascularization and outcome.

The Collateral Supply and the Logarithmic Curve of Time to Outcome

Crowell et al. have shown that following the arterial occlusion there is a sudden and abrupt drop in CBF (27). However, ischemia is never total and residual flow to the ischemic areas invariably persists through pial collaterals. Residual CBF (rCBF) will remain stable until revascularization occurs or cell death ensues. Studies have shown that time until ischemia becomes irreversible is heavily dependent on the rCBF, which varies depending on the collaterals present (8, 27). In other words, following cerebral ischemia, different patients will have varying amounts of time before cell injury becomes irreversible (**Figure 1**).

As we argued in a previous paper (18), when we consider a large cohort of patients with acute ischemic stroke we can grossly divide them into three groups depending on their rCBF. The first group will have such a low rCBF value that they will experience irreversible ischemia within an hour or two of ictus. For these patients, time to revascularization and its degree are irrelevant since the cerebral tissue will be irreversibly damaged by the time the patient arrives at the hospital. They are either not enrolled in studies due to evidence of ischemia on a computed tomography (CT) scan and other imaging modality, or do not improve following treatment despite timely and good revascularization (futile revascularization). We propose that approximately half of all AIS patients do

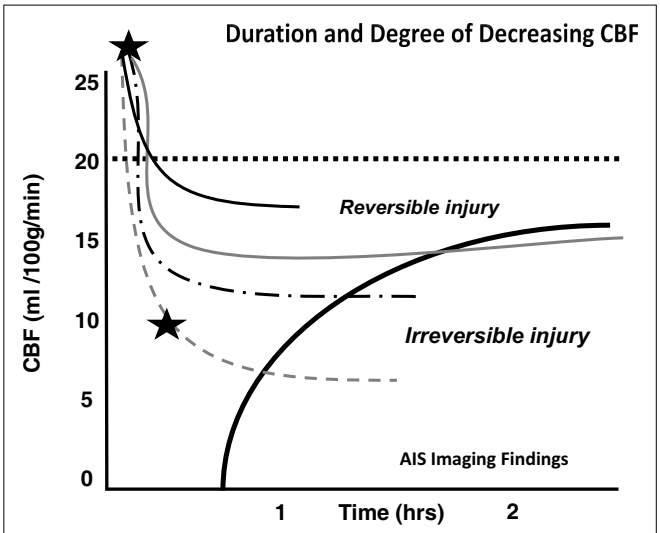

FIGURE 1 | Depth of ischemia and time to irreversible cerebral damage: time to irreversible cerebral damage depends on the depth of ischemia, which depends on the collateral supply. Since different patients have different collaterals, the depth of ischemia will vary among patients, as will the time available for therapy to salvage the tissue (8). Adapted with permission from Jones et al., (8). Permission has been obtained from the American Association of Neurological Surgeons.

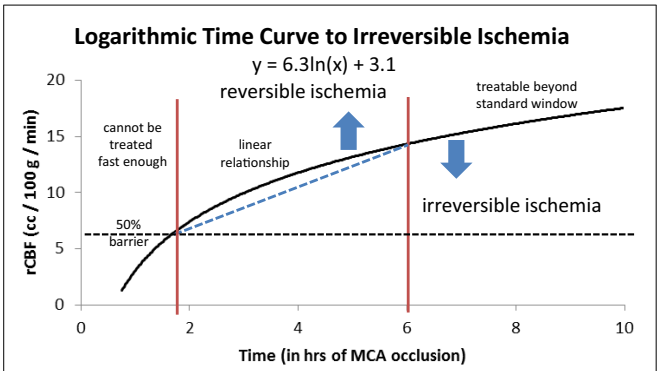

FIGURE 2 | Logarithmic time curve: the infarction threshold distinguishing between reversible and irreversible ischemia as a function of rCBF and time from ictus. The vertical lines are an approximation and have not yet been validated (18). Reproduced with permission from Al-Ali et al. (18). Permission has been provided by Wolters Kluwer Health, Inc.

not have sufficient collaterals to sustain ischemia until revascularization, no matter how fast it can be achieved, called "the 50% barrier." A second group of patients will present with intermediate rCBF that will follow an approximately linear relationship between time to revascularization and outcome (a subtle gradual decrease). These patients are most often included in trials and registries. Finally, a third group has a higher rCBF than the others, but still below the critical symptomatic level of 23 ml/100 g/min (8). This group will exhibit a more asymptotic, flat curve relating time to revascularization and outcome, but they are usually excluded from studies when presenting outside the artificial time window. If we assemble these three groups as a whole, the relationship between time from ictus to revascularization and outcome will resemble a logarithmic function (**Figure 2**). In other words, if the patient has poor pial collaterals, no time will be fast enough. On the other hand, if pial collaterals are present and robust, we have longer time to revascularize the patient [not measured in minutes, but in hours (28)]. Simply put, if the patient has good collaterals they have time; if a patient has no collaterals they have no time.

Patient Selection

The obvious implication of this logarithmic understanding of the time curve is the abandonment of any artificial time window to treatment since *each patient will have his or her own time* until irreversible ischemia occurs. Relying heavily on an arbitrary time window will significantly decrease the accuracy of patient selection in AIS treatment, either by including patients with irreversible ischemia just because they presented within the traditional time window and thereby leading to futile revascularization, or by denying treatment to patients who may still have viable tissue simply because they presented outside the traditional window. We propose a different patient selection algorithm, based more on objective signs of cerebral ischemia as opposed to an arbitrary time window.

Proposed Patient Selection Algorithm

We recognize that the merit of the CIS still needs to be proven in a multicenter prospective study; however, we believe the CIS hypothesis will be proven true due to its ability to explain the results of the different ischemic stroke trials.

Since most patients will improve to a variable degree with time and physical therapy, we believe that IAT should be offered to patients suffering from a large stroke (NIHSS >8), with the only exception being aphasia (**Figure 3**). Of those patients who are *Clinically Eligible*, a non-enhanced head CT is obtained followed by CTA. These non-invasive tests can first rule out stroke mimics and identify patients with already visible signs of structural changes due to large irreversible ischemia (i.e., hypodensity in >1/3 MCA territory on head CT). If no such findings are identified, CTA will help confirm the vascular occlusion and its location. Patients with no counter-indication to treatment *and* proven large vessel occlusion are offered IAT, *CT Eligible*. For these patients, a full DCA is performed to obtain the CIS. Only patients who demonstrate *f*CIS should be offered IAT since revascularization on patients with *p*CIS will be futile and possibly harmful, *CIS Eligible*. If these steps are taken, we predict a significant increase in the percentage of treated patients with GCOs by virtue of significantly decreasing the percentage of futile and harmful revascularization. It is important to note that time from ictus to presentation is not included in this proposed algorithm. Since we believe that as long the patients advance successfully from clinical, to CT, to CIS eligibility, they are good candidate for intervention, regardless of time from ictus to presentation.

Conclusion

Revascularization is the best hope for AIS patients. It should aim to reverse the flow to an ischemic area with persistent capillary blush

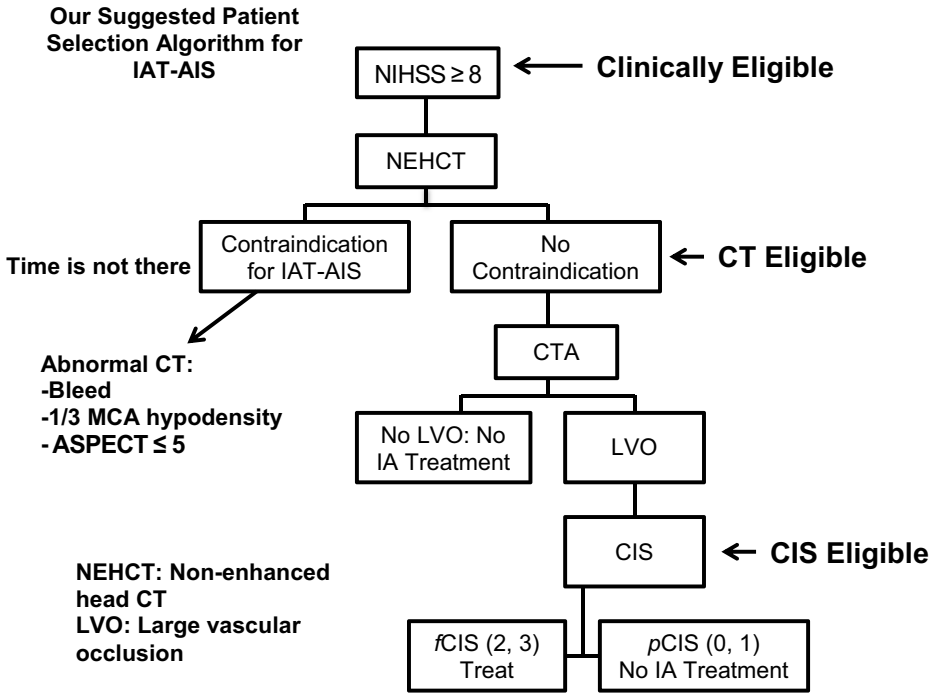

FIGURE 3 | Proposed patient selection algorithm for AIS.

from retrograde to anterograde without complications. Time from cerebral ischemia to irreversible damage varies from patient to patient and depends on their pial collaterals. In other words, the importance of time is secondary to the presence of collaterals. We believe that the relationship between time from ictus to revascularization and outcome is not linear, but logarithmic. Every patient has his/her own time before irreversible ischemia is reached, so it is critical to dispose of the artificial time window.

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