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Update on Clinical Management with Neurovascular Stents

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Abstract

Endovascular stenting has continued to evolve given the new trials. Several new stents have recently been developed to address specific purposes. In this focused review, we discuss the concepts of neurointerventional stents and address the clinical implications. Furthermore, each type of stent is discussed with supporting evidence for clinical utility. In the final component, we argue for continued development and utilization.

Keywords: Neurovascular stents, Clinical utility, Emerging technology, Advances, Intracranial atherosclerosis, Intracranial aneurysms, Flow diversion, Stent assisted coiling

Introduction

Endovascular stenting is a relatively new, but quickly evolving technique for the neurointerventionalist given the advent of multiple novel devices being introduced every year.

While the current indication of intracranial stenting primarily revolves around the management of intracranial aneurysms, there is ongoing research around the use of stenting for patients with intracranial atherosclerosis. On one end, the VISSIT and SAMPRIS trials demonstrated that aggressive medical management may be associated with better outcomes, suggesting that stenting not be appropriate for this indication [1,2]. There are other studies, however, that demonstrate superiority of stenting in symptomatic middle cerebral artery (MCA) stenosis as compared to aggressive medical therapy [3]. For the purposes of inclusivity, this review will address both the different stents available for the management of intracranial atherosclerosis, and also intracranial aneurysms.

The clinical utility of SAC (stent-assisted coiling) for aneurysms is more widespread—a 2016 survey of physicians performing surgical and/or endovascular treatments for intracranial aneurysms showed that over 40% prefer treating basilar apex aneurysms with SAC [4]. With the large variety of currently available devices, however, the clinical and angiographic outcomes of SAC can differ across patients depending on the device used. A recent multi-center analysis of over 800 patients demonstrated that device choice was associated with variability in both short and long-term outcomes, with specific procedure-related and post-procedural complications such in-stent thrombosis, stroke, and rupture rates differing across devices [5].

Given this diversity in clinical outcomes, the aim of this paper is to explore the currently available stent types, and address their clinical utility, paying mind to specific advantages and disadvantages unique to each device. Specifically, we will address stents used in the management of intracranial atherosclerosis (Wingspan, PRO-Kinetic Energy, and D+Storm), intracranial aneurysms (Enterprise, Neuroform, Leo, LVIS, and SOLITAIR AB), and flow diversion (Pipeline Embolization device, Silk device, Surpass device, and the Flow Redirection Endoluminal device).

Intracranial Stent Devices by Indication

Intracranial Atherosclerotic Stenosis (ICAS)

There are currently three unique stents available to use for

the management of intracranial atherosclerosis. These include the Wingspan stent, which is self-expandable. The other two stents, which are balloon-expandable include the PRO-Kinetic Energy stent, and the D$^+$ Storm stent [6].

The Wingspan stent, which is self-expanding, allows for greater flexibility and less rigidity when compared to the PRO-Kinetic Energy and D$^+$ Storm stents. The combination of greater flexibility and low rigidity allows the stent to be deployed in areas where the vasculature may be tortuous, requiring maneuverability to deploy the stent in the correct location. The major down-side is that calcification of vessels becomes a greater issue when using a less rigid stent. With the balloon-expandable stents, the increased rigidity allows for the stent to be deployed in areas with heavy calcific burden. Thus, the choice between these two stents is a balancing act between how tortuous the vessel is, compared to how heavy the atherosclerotic burden is [7].

The wingspan stent: As mentioned above, the value of this stent is its maneuverability in traversing tortuous vasculature given its flexibility [1]. The Wingspan stent is composed of two elements: the self-expanding stent coupled with an angioplasty balloon. The overall design of the stent is very similar to the Neuroform stent, which will be discussed later. Namely, the stent design (specifically, the cell pattern) features an open cell design where some of the cells are not connected to each other. This unique feature allows for greater flexibility of the stent, and traversal through tortuous vasculature. On top of the flexibility afforded by the open-cell design, a key feature of the wingspan stent in comparison to the Neuroform stent is a greater radial force (or rigidity), mostly imparted by its overall thicker dimensions. This allows the Wingspan stent to be successfully used for atherosclerotic disease, where there is an important balance between the flexibility of the stent, and its outward radial force [8].

Balloon-expandable stents (Pro-Kinetic Energy / D$^+$Storm stents): Overall, the balloon-expandable stents behave similarly to each other. Both stents are deployed using an expandable balloon, and the stent composition is made of a cobalt chromium alloy, which is unique when compared to the nitinol alloy of the Wingspan stent. The Pro-Kinetic Energy and D+Storm stents do differ slightly in cell design (the Pro-Kinetic Energy stent uses a 12-crown design with a double-helix strut, while the D$^+$Storm stent features a 6 and 8-crown design with waved struts), but both feature open-cell design. Compared to the Wingspan stent, both the balloon-expandable stents demonstrate more favorable wall-apposition, likely due to a higher radial force achieved by the balloon expandable method of delivery [6]. This supports the notion that balloon-expandable stents are favorable in vessels with greater calcific burden, as the radial stiffness is better when compared to the self-expanding Wingspan stent. The trackability of the stent is also important, and paradoxically in a study by Park et al., it was found that the balloon-expandable stents (specifically the D$^+$Storm stent) actually performed better than the Wingspan stent. The authors suggest that the model used may not mimic clinical conditions exactly, however, so clinical judgment should be used when interpreting this data—the conventional understanding in clinical practice is that the Wingspan stent offers better conformability and trackability due to its more favorable strut dimensions when compared to the balloon expandable stents [9].

Intracranial aneurysms

The Enterprise stent: The Enterprise stent is self-expandable and features a closed cell design. Retrieval of the device can be accomplished up until two-thirds of the device has been deployed, thus allowing for repositioning and retrieval up to a certain extent [10]. Since the device features a closed cell design, there is a stronger radial force afforded for better aneurysm neck scaffolding when performing stent-assisted coiling [11].

The Neuroform stent: This was the original stent specifically created to manage intracranial aneurysms. It has an open-cell design, however its main drawback is that the device cannot be retrieved [12]. The Neuroform stent is one of the most widely used stents currently. The stent itself is composed of a nitinol tubular mesh designed in a "zig-zag" pattern. The stent is available in a multitude of diameters and lengths allowing for greater flexibility in the management of aneurysms (**Table 1**) [6].

The Neuroform stent has undergone several improvements since 2002, when it was first approved for the management of wide-necked intracranial aneurysms. Originally, the stent suffered from a low radial force (recall that the Wingspan stent improved on the design of the Neuroform stent by increasing its strut thickness). This resulted in occasional issues where there was not enough structural integrity to maintain the coil within the aneurysm, as well as stent migration issues. The Neuroform stent has since been revised numerous times, with the Neuroform2 stent released in 2003, followed by the Neuroform3 stent released in 2005, and most recently, the Neuroform EZ stent in 2010.

Leo stent: The Leo stent is a self-expanding stent used for the management of intracranial aneurysms. It features a closed cell pattern and can be re-sheathed or re-positioned at up to 90% of its deployment, making it very versatile for fine-tuning the location of deployment in challenging anatomical vasculature. One thing that is unique about the Leo stent is a large metal surface area. This allows for an effect like flow-diversion (where blood flow is re-routed away from the aneurysm, allowing for obliteration of the aneurysm as well as restoration of normal anatomy through neo-intimal growth), and thus can provide a favorable adjunctive effect when managing intracranial aneurysms. The device has undergone revision, and a newer generation device (Leo+) is available for use. The device comes in a variety of lengths, extending as far as 75 mm, making it very versatile (**Table 1**).

Table 1. Summary of the devices used for intracranial aneurysms, and their respective characteristics.

	Leo	**Neuroform**	**Enterprise**	**Solitaire AB**	**LVIS**
Company	Balt, Montmorency France	Boston scientific, USA	Cordis corporation, USA	EV3, Irvine, USA	Microvention corporation, Tustin, USA
Approval	2003	2002	2007	2012	2018
Stent type	Self-expendable	Self-expendable	Self-expendable	Self-expendable	Self-expendable
Overall design	Braided design, nitinol wires (16 braided wires)	6-8linked radiolucent nitinol cells	Laser cut Made of nitinol with flared end	Laser cut, made of nitinol in honeycomb pattern	Nitinol exterior and platinum core with flared end
Cell design	Closed	Open	Closed	Closed	Closed
Surface coverage	14%	6.5-9.5%	10%	5-7%	17-23%
Markers	2 radiopaque wires that extend along its length	4 on each end	4 on each end	One proximal and 3 distal markers	4 on each end with double strand to assist full length visualization
Retrievability %	Up to its 90% deployment	Not retrievable	70%	100% (can be retrieved even when fully deployed)	80%
Diameter	2.5, 3.5, 4.5, 5.5 mm	2.5-4.5 mm	4.5 mm only	4 mm and 6 mm	2.5, 3.5, 4 mm
Length	12, 18, 28, 30, 35, 40, 50, 60, 75 mm	10-30 mm	14, 22, 28, 37	15, 20, 30 mm	15, 17, 25, 35, 41, 49
Other generation	Leo+, Leo+baby	Neuroform2, Neuroform3, Neuroform EZ,Neuroform atlas			LVIS Jr LVIS EVO
Clinical Advantages	Large metal surface area allows for "flow diversion like" adjunctive effect. Many different device lengths allow for flexibility. Can be retrieved at up to 90% deployment	Increased flexibility and trackability. Multitude of diameters and lengths allow for variability in management options.	Retrievable at up to 66% deployment. Strong radial force allows for good neck scaffolding.	Only stent with 100% retrievability. Can be deployed and retrieved by single operator.	Intraluminal visualization allows for precise targeting due to the tantalum being interwoven into the mesh. Also provides "flow-diversion" effect like Leo.
Clinical Disadvantages	Closed cell pattern makes the stent more rigid and increases radial force	Cannot be retrieved	Stiff closed cell design makes the stent less maneuverable	Fewer length and diameter options than other stents	Closed cell design reduces maneuverability

The LVIS device: The Low-profile Visualized Intraluminal Support (LVIS) device is a newer generation device that was FDA approved in 2014 for the indication of stent-assisted embolization to treat intracranial aneurysms. The device itself is a self-expanding stent made of nitinol, however it is created by the tight braiding of a single wire. It features a closed cell design, and thus has the benefit of a strong radial force, and good wall apposition. Into the mesh is woven tantalum wire, a novel radiopaque marker, which serves as the guide for allowing for intraluminal visualization during stent-assisted coiling. The device is available in a multitude of lengths, as well as stent diameters (**Table 1**) [6]. Like the Leo stent, the high surface coverage of the stent promotes a flow-diversion effect which aids to obliterate the aneurysm as an additive effect on top of coiling.

Solitaire AB (aneurysm bridging) device: The Solitaire device is a uniquely designed tool that is used for stent-assisted coil embolization of intracranial aneurysms. It is a self-expanding device that has the unique capability of allowing for complete deployment and retrieval by a single operator, until the device is detached. The device can be re-positioned even after 100% deployment up to two times. The device is then detached from its push wire using an electrolytic system with a separate device [13].

Flow diversion

Flow diverters are fine-mesh stents that are placed at the neck of intracranial aneurysms in the parent vessel. Their function is to re-direct blood flow away from the aneurysm and back into the parent artery, thus, they reduce aneurysmal blood flow eventually obliterating the aneurysm. Over time, the parent vessel is reconstructed with neo-intimal growth promotion from the stent material, which aids in restoring normal anatomy [14].

Currently, there are four available flow diversion devices for use (although not all the devices are available in every country): the Surpass device, The Pipeline Embolization Device (PED), the Flow Redirection Endoluminal Device (FRED), and the Silk device. As with the nature of flow-diversion, each of these device's function in primarily the same method—they all act as stents that divert blood flow away from the aneurysm, eventually leading to obliteration of the aneurysm, and promotion of neo-intimal growth along the parent vessel. The devices vary in the method of deployment, and the overall design of the stent, which leads to flexibility for the operator given unique variable anatomy across many patients [14].

Silk flow divertor: The Silk device is currently not approved for use in the United States; however, this device deserves mention as it was the first ever flow-diversion device available for the management of intracranial aneurysms, gaining approval in Europe in 2008 for routine clinical use. It functions as a self-expandable stent with a closed cell design made of nitinol. The closed cell design lends itself to being re-deployment friendly—it can be re-sheathed at up to 90% deployment. The porosity of the device is roughly 45-60%, corresponding with a 30-35% arterial wall coverage, which is typical across all the flow-diversion devices [13].

Pipeline embolization device: In the United States, the Pipeline device is an FDA approved flow-diversion device available to use for the management of intracranial aneurysms. It was approved in the United States in 2011 when the Pipeline for Uncoilable and Failed Aneurysms trial (PUFS) demonstrated that flow-diversion with the Pipeline device was both safe (low risk of stroke or death) and effective (high rate of complete aneurysm obliteration without flow-limiting stenosis) in the management of large unruptured intracranial aneurysms that had failed prior endovascular treatment [15]. The device itself features a self-expanding deployment and is composed of a mixture of three-quarters chromium-cobalt, and one-quarter platinum tungsten alloy. As with other flow-diverters, it covers approximately 30-35% of the arterial wall surface, with a porosity of about 65-75% [15]. There is a newer generation of the PED, which is called the Pipeline Flex Embolization Device or PED Flex and was approved by the FDA in 2015. This device has the added benefit of being resheathable [16].

Surpass: The Surpass flow diverter device has recently been FDA approved for the management of intracranial aneurysms following the results of the *Surpass Intracranial Aneurysm Embolization System Pivotal Trial to Treat Large or Giant Wide Neck Aneurysms* (SCENT) trial, which demonstrated that the device was both safe and effective when deployed for wide-necked, large fusiform, saccular, and blister aneurysms in the supraclinoid and distal ICA segments [17]. The device itself features a self-expanding design with a braided stent. The porosity of the device is 70% with arterial surface coverage of roughly 30%. A key benefit of the Surpass device is the ability to recapture, re-sheath, and reposition the device while maintaining the position of the distal wire [18].

Flow-redirection endoluminal device (FRED): FRED obtained CE Mark approval in Europe in 2013 and was recently afforded FDA premarket approval in 2020 for the management of intracranial aneurysms. It is currently indicated for use in wide-necked saccular/fusiform aneurysms that arise from parent vessels with diameter between 2 and 5 mm. The device is composed of a self-expanding mechanism made of braided nitinol but is unique for what is known as a "stent-within-a-stent" design. That is, there is an outer high-porosity layer of 16 nitinol wires, as well as an inner lower-porosity layer of 48 nitinol wires. The inner and outer layers of the device are merged by a double helix of tantalum, which allow for visibility of both layers under fluoroscopic visualization. Overall, the device offers a surface coverage of 30%, which is on par with other devices, however it also has the greatest variability in length compared to the other 3 flow-diversion devices (**Table 2**) [19].

Table 2. Summary of the devices used for flow diversion, and their respective characteristics.

	PED	SILK	Surpass	FRED
Company	EV3, Irvine, USA	Balt, Montmorency France	Stryker neurovascular, Fermont, CA, USA	Microvention corporation, Tustin, USA
Approval	FDA approval 2011	CE mark approval in 2008	CE mark approval in 2010	CE mark approval 2013 FDA approval 2020
Mesh design	cylindrically shaped, com- posed of 48 braided strands in a standard pattern, and made of 75% chromium-cobalt and 25% platinum-tungsten alloy microfilaments.	a self-expanding stent designed as a closed-cell mesh cylinder composed of 48 interwoven nitinol strands and 4 platinum microfilaments with flared ends.	Its design keeps the porosity relatively constant (70%) while the wire struts increase across all diameters, the 2 mm stent has 48 wires, the 3 and 4 mm stents have 72 wires, and the 5 mm stent has 96 wires.	The FRED device has a unique dual-layer design made of a nickel-titanium alloy. It consists of a low-porosity inner mesh (48 nitinol wires) and a high-porosity outer stent (16 nitinol wires).
Surface coverage %	30-35	30-35	30	30
Diameter	2-5 mm	2-5 mm	2-5 mm	3-5.5 mm
Length	10-35mm	15-40 mm	12-50 mm	7-56 mm
Clinical Advantages	Multiple generations of devices, and is re-sheathable	Can be re-sheathed at 90% deployment	Distal wire position can be maintained while re-sheathing/repositioning the device	Greatest variability in length among the flow diverters
Clinical Disadvantages	Limited length options compared to other flow divertors	Closed cell design affords less maneuverability compared to other devices	Less well studied in clinical trials compared to other stents (FDA approval in 2020)	Only re-sheathable to 50% of deployment

Clinical Utility of SAC for Intracranial Aneurysms

The utility of stents in the treatment of intracranial aneurysms has undergone considerable evolution since the ISAT trials gave way to the recommendations of endovascular coiling as first-line management [11,20]. However, coiling alone is not suitable for many complex aneurysms. In particular, treatment of wide-neck bifurcating aneurysms have been historically challenging with traditional endovascular coiling due to coil instability and risk of protrusion and migration [21]. Due to limitations, a number of assistive and novel endovascular methods have been developed [11]. Stent-assisted coiling (SAC) is an adjunctive method to coiling which has proven efficacious in treating aneurysms of both complex morphology and location [22]. The use of stents for intracranial aneurysm trapping can generally be divided into two main categories - SAC and stent monotherapy, also known as flow diversion [11]. Although flow diversion is advantageous in many regards - such as in its ability to treat wide-neck side wall aneurysms - its use in bifurcating aneurysms remains controversial due to risk for inadequate neck occlusion [23]. Further, the recent introduction of the Woven EndoBridge (WEB) device has indeed proven effective in treating wide-neck bifurcating aneurysms, however, falls short in its ability to treat aneurysms with extremely unfavorable neck sizes (<4mm) and dome-to-neck ratios (<1) [24]. In this regard, SAC techniques have proven quite effective in treating aneurysms of such complex anatomical morphologies and locations that are not amenable to coiling, flow diversion or WEB alone [22]. Specifically, SAC is an attractive technique for the treatment of wide-neck bifurcating aneurysms, such as those seen in the middle cerebral artery and basilar apex [23,25,26].

Stent jailing is one form of SAC that is considered especially suitable for wide-necked aneurysms [27]. In stent jailing, a coil delivery microcatheter is fed into the aneurysm followed by a second catheter which deploys a stent across the aneurysm neck [27]. At this point, the microcatheter is nudged securely between the stent and vascular wall. Coils are then deployed while the stent creates a barrier to prevent coil herniation. The microcatheter is then retrieved leaving the coils and stent in place. Stent jailing provides an advantage of imparting greater microcatheter stability within complex aneurysms into which insertion may otherwise be difficult [28]. In addition, Y-stenting

is another form of SAC suitable for bifurcating aneurysms and can be used in conjunction with stent jailing methods [25,26]. Y-stenting involves the use of two stents and is associated with very good long-term stability in the treatment of complex bifurcating aneurysms [25,26]. Further, when a bifurcating aneurysm neck incorporates more than one daughter vessel, Y-stenting can more reliably protect daughter vessels from coil embolization as compared to single-stent techniques [25].

Following stent-assisted coiling, it is essential to obtain follow up imaging at multiple intervals [29]. Immediately, angiograms are indicated to evaluate for aneurysm occlusion and obliteration and is recommended by the AHA following treatment of all aneurysms [20]. Early and delayed follow-up is also essential to assess for risk of recanalization and future hemorrhage, as well as for in-stent stenosis [29,30]. Although no established guidelines currently exist for such follow-up, it is generally recommended to obtain early follow up around 3 to 6 months and long term follow up at 12 to 24 months, as well as at 3 to 5 years [29]. Follow-up during the first two years is especially critical as most recurrences reveal during this time [31]. Digital subtraction angiography is considered the gold-standard imaging method due to high sensitivity for recurrent flow detection and lack of device-related imaging artifact [29]. However, magnetic resonance angiography is a less invasive and suitable alternative that, despite lower sensitivity for recurrent flow, can still effectively detect aneurysm recurrence, as well as in-stent stenosis [29,32-34].

Overall, SAC is associated with favorable angiographic outcomes, including both occlusion and recanalization rates [35]. However, occlusion rates do appear to vary across studies when looking at difficult to treat aneurysms [24]. In a meta-analysis of SAC-treated unruptured intracranial aneurysms with wide necks, periprocedural and postprocedural occlusion rates were 50.2% and 68.83%, respectively [36]. However, in the ATLAS IDE trials, wide-neck intracranial aneurysm of the anterior circulation treated with a laser-cut stent, achieved complete and adequate occlusion of 88.2% and 96.1%, respectively, at 12 months follow up [37]. In another study evaluating the use of a braided stent, complete and near complete occlusion at 12 months were 70.6% and 92.1%, respectively [38]. Although it is difficult to compare efficacy between various endovascular approaches due to high study heterogeneity – including variations in aneurysm complexity - slightly reduced, yet comparable, postprocedural occlusion rates are seen in SAC when compared to meta-analyses of alternative endovascular techniques [23,39-41] **(Table 3).** Finally, recanalization rates appear to be relatively low in SAC-treated aneurysms. Recanalization can be used as a surrogate marker for aneurysm rupture risk [11]. In meta-analyses of unruptured aneurysms, the recanalization rate of SAC-treated aneurysms was 7.07% as compared to 24.4% in coiling alone [36,42].

Despite favorable angiographic outcomes, SAC is associated with non-negligible risk for post-intervention mortality and neurologic-related complications, including thromboembolism, in-stent stenosis and intra-/postoperative aneurysm rupture [36,43,44]. Perioperative thrombosis is reported to be the most common complication and is especially concerning, as the risk of aggressive treatment and postoperative hemorrhage must be carefully balanced [44,45]. In a meta-analysis comparing SAC versus coiling alone in the treatment of ruptured intracranial aneurysms, a higher overall perioperative complication rate was found in the SAC group, although no significant difference in mortality at discharge [46].

It is important to note that the use of SAC in ruptured aneurysms is known to be associated with a greater risk of complications - often attributed to the use of dual anti-platelet therapy - and, according to several authors, should generally be avoided in such populations [47-50]. In this context, a recent meta-analysis investigating morbidity and mortality in SAC-treated unruptured intracranial aneurysm with wide necks, demonstrated an estimated pooled rate of mortality and overall neurologic complications to be 0.02% and 4.33%, respectively [36]. This is compared to 1.2% and 4.8% for coiling alone and 1.7% and 6.7% for clipping alone in the treatment of unruptured intracranial aneurysms [42,51]. Thus, it is possible that overall morbidity and mortality may achieve more favorable rates when utilized in appropriate settings **(Table 3).**

Clinical Utility of SAC for Intracranial Atherosclerosis

Stenting for intracranial arteriosclerosis was previously abandoned largely due to a high risk of in-stent thrombosis. However, it is important to note that a select few types of

Table 3. Morbidity, Mortality and Postprocedural Occlusion Rates Among Endovascular Techniques.

Technique	Morbidity (%)	Mortality (%)	Postprocedural Occlusion (% of all aneurysms)	Reference
Coiling	4.8	1.2	71.4	Naggara 2010 [42], Xin 2019 [40]
Woven EndoBridge	2.85	0.93	83.3	van Rooji 2020 [39]
Stent-Assisted Coiling	4.33	0.02	68.8	Papadopoulos 2020 [36]
Flow Diversion Stenting	9.8	3.8	77.9	Ye 2016 [41]

stents were utilized in the studies that have noted these poor outcomes, particularly early self-expanding and balloon expandable stents [7,52]. One study that highlighted the negative outcomes using these types of stents was the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) randomized controlled trial (RCT) in 2015, which compared patients with symptomatic intracranial stenosis who received balloon-expandable stent plus medical therapy vs. medical therapy alone. This study was terminated early due to increased stroke or transient ischemic attack (TIA) rates in patients that received a balloon-expandable stent at both 1-year post-intervention and 30-day post-intervention, in the same vascular territory or in any vascular territory, respectively [1]. Similarly, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial in 2016 demonstrated negative results using the Wingspan stent, a metal-based, self-expanding stent [53,54]. In this RCT, a total of 451 patients who recently experienced a stroke or TIA accompanied by a 70-99% stenosis of a major intracranial artery was randomized into receiving medical management only or medical management plus stenting. Results indicated that patients who received stenting with this self-expanding stent had higher rates of subsequent stroke or death (p=0.0252), as well as increased rates of intracranial hemorrhage (p=0.0009), compared to those who received medical management only [54]. Thus, the poor outcomes associated with these types of stents subsequently necessitated exploration into the possibility of using other types of stents in order to improve clinical outcomes. The primary type of stent being studied in this manner are drug-eluting stents.

Success in decreasing restenosis rates in coronary arteries using drug-eluting stents was initially proposed decades ago and has now been purported as superior to many of their previous counterparts, such as bare-metal stents [55-57]. The initial proposal of using drug-eluting stents in both the intracranial and extracranial circulation began over a decade ago, after some success had been demonstrated with their use in the coronary arteries [58-60,61]. In 2010, Ogilvy et al. demonstrated decreased occurrence of vertebral artery restenosis in 2/12 (17%) patients who received drug-eluting stents compared to 9/24 (38%) patients who received non-drug-eluting stents. Further, 7 out of the 9 restenotic patients who received non-drug-eluting stents required angioplasty, whereas neither of the 2 restenotic patients who received drug-eluting stents required angioplasty [62]. Although lacking statistical significance between these outcomes, these results set an important precedent for future studies to build upon. A similar, larger study in 2020 examining vertebral artery ostium stenting outcomes demonstrated a statistically significant reduction in restenosis rates in patients who received drug-eluting stents compared to patients who received bare metal stents (p=0.021) [63]. This success with drug-eluting stents has since been demonstrated in intracranial arteriosclerotic lesions. In 2020, Kim et al. demonstrated successful drug-eluting stent placement in 12 patients with intracranial arteriosclerotic stenosis, none of which experienced restenosis in a follow-up period of approximately 43 months [64]. A 2019 meta-analysis examined restenosis rates in 336 intracranial arteriosclerotic stenosis patients who received drug-eluting stents, reporting a restenosis rate of only 4.1% [65]. Authors further reported that this evidence suggests both relative safety and efficacy when compared to the non-drug-eluting stents used in the SAMMPRIS and VISSIT trials [54,54,65]. Most recently, a RCT published in 2022 randomized 263 patients with intracranial arteriosclerotic stenosis into one group who received a drug-eluting stent and another group who received a bare-metal stent. Results at one-year post-intervention demonstrated significantly reduced restenosis rates in patients who received drug-eluting stents compared to those who received bare-metal stents (p<0.001) [66]. Results also showed reduced rates of ischemic stroke recurrence between one month and one year post-intervention in patients who received drug-eluting stents (p<0.03) [66]. In all, these results show great potential for the efficacy of drug-eluting stents, especially when compared with the relatively poor overall outcomes seen with the advent of several types of early non-drug-eluting stents. However, further evaluation using additional, larger-scale trials are needed in order to increase the confidence in these results and validate a clear recommendation for the use of drug-eluting stents over non-drug-eluting stents for this patient population.

Although the drug-eluting stent is currently demonstrating the most promise as a new treatment option for intracranial arteriosclerotic stenosis, it is important to note that investigation into the modification of other, previously used stents is still ongoing. The use of several different models of the Neuroform stent, traditionally used for aneurysm stenting, has recently started to be investigated as a treatment option for intracranial arteriosclerosis. A recent study including 45 medically refractory intracranial arteriosclerosis patients underwent re-stenting with the Neuroform EZ stent model with a technical success rate of 100% and no incidence of restenosis at the average follow-up of 7.3 months [67]. A similar recent study using 71 intracranial arteriosclerosis patients also yielded a 100% technical success rate, with an incidence of restenosis of 16.9% [68]. The Neuroform Atlas model is also being evaluated, with demonstration of some early success in intracranial stenting for arteriosclerotic lesions [69]. In addition, new techniques aimed at reducing morbidity are also being explored, such as deployment of the Neuroform Atlas stent using a balloon microcatheter [70]. However, investigation is still in the early stages for the Neuroform models in either regard or further investigation, particularly using RCTs, is warranted.

Regardless of stent placement, a standard antiplatelet regimen needs to be employed in these patients. Dual antiplatelet therapy in the early symptomatic stages of intracranial arteriosclerosis has generally been recommended, based on the relatively elevated recurrent stroke risk associated

with early aspirin monotherapy in these patients [71]. Several different options for dual antiplatelet therapy have been suggested over the years. A 2015 RCT showed that aspirin plus cilostazol was superior to aspirin monotherapy in slowing progression of symptomatic intracranial arterial stenosis [72]. Another study showed no significant difference in the efficacy of aspirin plus cilostazol and aspirin plus clopidogrel in slowing progression of intracranial atherosclerotic stenosis [73]. However, aspirin plus clopidogrel as dual antiplatelet therapy specifically has historically been primarily recommended, largely based on results from the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial which demonstrated significant risk reduction of stroke in minor stroke or TIA patients who received clopidogrel and aspirin together compared to those who received aspirin monotherapy (p=0.006) [74]. Thus, as it currently stands, in patients who have sustained either a TIA or stroke attributed to intracranial atherosclerosis of 70-99%, dual antiplatelet therapy with aspirin plus clopidogrel is recommended for up to 90 days, followed by long-term aspirin monotherapy. Recommendations for dual antiplatelet therapy using aspirin plus cilostazol or aspirin plus ticagrelor are not yet made, mainly due to limited generalizability and lack of comparative data.

Although evidence is currently not sufficient to recommend as a first-line treatment option, the drug-eluting stent appears to show much promise in the way of significantly improving clinical outcomes in patients with intracranial arteriosclerosis, particularly when compared to outcomes with previously used non-drug-eluting stents. Further investigation into their utility is warranted. More recently developed non-drug-eluting stent models, along with the addition of innovative new methods of delivery, are also being evaluated in this context. Regardless of stent outcomes, recommendations for antiplatelet therapy must be upheld.

Conclusions

Stent technology has continued to evolve at a rapid pace in the neuroendovascular space. Several new types of stents such as flow diverters have recently emerged. Given the rapid developments, the need for a consolidated and user-friendly guide is indicated. This review offers a snapshot of current situation with emphasis on continued development.

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