JVIN Journal of Vascular and Interventional Neurology

OFFICIAL JOURNAL OF ZEENAT QURESHI STROKE INSTITUTE

Experience with the Onyx Frontier Zotralimus-Eluting Stent: Outcomes for the Interventional Treatment of Intracranial Atherosclerotic Disease

Mina Al-Ani, MBBCh[1,2], Mossum Sawhney, MD[1,2], Kevin Shah MD3 ,Timothy G. White MD[3], Thomas Link MD[3], Neda Sedora-Roman MD[1,2], Henry Woo MD[3], Ina Teron MD[3]

[1] Departments of Radiology, SUNY Downstate Health Science University, Brooklyn, New York

[2] Department of Radiology, Kings County Hospital Center, Brooklyn, New York

[3] Department of Neurology and Neurosurgery North Shore University Hospital, Long Island, New York

Abstract

Background— Intracranial atherosclerotic disease (ICAD) is a common cause of stroke worldwide. Aggressive medical therapy is the first line of treatment, which includes dual antiplatelet therapy for the initial 90 days followed by a single agent, in addition to controlling the associated risk factors. Previous trials demonstrated that endovascular treatment with stenting was inferior to medical management due to significant increased risk of perioperative stroke. However, some patients with ICAD are at risk of stroke recurrence despite appropriate medical management. Therefore, endovascular management can be considered on a case-by-case basis. Currently, there is still controversy regarding endovascular options for symptomatic ICAD. In this manuscript, we present our initial experience with the new generation Onyx Frontier drug-eluting stent in the treatment of symptomatic ICAD.

Methods— Retrospective review of patients who underwent placement of Onyx Frontier drug-eluting stents for the treatment of symptomatic ICAD at our center from May 2022 to November 2022.

Results— Six patients were identified. 9 Onyx Frontier stents were deployed for 7 distinct intracranial atherosclerotic lesions. Four patients had mRS of 0 at 90 days, one patient had mRS of 6 (from significant brainstem stroke) and one patient was lost to follow-up.

Conclusion— Our study demonstrates the utilization of the Onyx Frontier drug-eluting stent in the treatment of refractory symptomatic ICAD. The majority of post-treatment results were favorable except for one case of fatal brainstem stroke. Large prospective multicenter studies are needed to formally evaluate the use of drug-eluting stents in refractory symptomatic ICAD.

Keywords— ICAD, Intracranial atherosclerotic disease, interventional neuroradiology, neuroradiology, Neurointervention, Onyx, Onyx Frontier, Onyx Frontier stenting, angioplasty, stenting, angioplasty.

BACKGROUND

Intracranial atherosclerosis disease (ICAD) is a leading cause of cerebrovascular ischemia worldwide with a racial predilection towards Asian, Hispanic, and African populations.[1] Aggressive medical therapy is the mainstay for management, which includes dual antiplatelet therapy for the initial 90 days after a cerebrovascular accident (CVA) followed by single-agent therapy in addition to intensive management of risk factors.[2] Historically, the SAMMPRIS (Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis) and VISSIT (the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) trials demonstrated that endovascular treatment (ET) with stenting was inferior to medical therapy for the initial management of symptomatic ICAD (sICAD) due to significantly increased risk of perioperative stroke and death in patients undergoing ET.[3,4] On the other hand, a randomized controlled trial in China and the more recent CASSISS (China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis) trial concluded that in patients with a transient ischemic attack (TIA) or ischemic stroke due to severe sICAD, percutaneous transluminal angioplasty (PTA) and stenting in addition to medical therapy did not result in a significant difference in the risk of stroke or death compared to medical therapy alone.[5,6] However, these studies did not establish the superiority or additional benefit of ET over conventional medical therapy. Furthermore, the multicentric WEAVE (Wingspan Stent System Post Market Surveillance) trial demonstrated an improved safety profile of ET with stenting for treatment of severe sICAD in a strictly selected group of patients who underwent the procedure by experienced interventionalists and following the on-label usage guidelines.[7] Based on these results, ET has been implemented as a treatment option for medically refractory sICAD, with the Wingspan Stent System

Vol.14, No. 2, pp. 53-57, Published February, 2024.

*Corresponding Author: Firas Al-Ali, MD. E-mail: falali@OhioStroke.com, Cell phone: 330-780-3406, www.OhioStroke.com,

(WSS) being the only FDA-approved stent for this indication to date.

In-stent restenosis (ISR), and hence stroke recurrence, is a major complication of intracranial stenting with self-expandable stents (SES) due to the technically demanding step of over-the-wire exchange.[8] Therefore, balloon-mounted stents (BMS) have been implemented to successfully lower the risk of intracranial ISR.[9] The drug-eluting subtypes of BMS, further reduce the risk of ISR by releasing anti-proliferative and anti-migratory substances to the vascular smooth muscles.[10] Their stiff profile, however, rendered their navigation difficult in the tortuous intracranial arteries and injurious to the thinner intracranial vascular media and adventitia as most are intently designed for intracoronary use.[11,12] Second-generation DES (Everolimus/Zotarolimus drug-eluting stents) were then developed with a more flexible stent profile, facilitating their use intracranially.[13] Multiple studies specifically discussed the promising results of the Resolute Onyx™ (R-Onyx) (Medtronic, Santa Rosa, CA) balloon-mounted DES.[14,15,16] We aim to present a case series demonstrating the early utility of the new-generation Onyx Frontier™ DES (Medtronic, Santa Rosa, CA) for the treatment of sICAD with a favorable periprocedural outcome profile.

MATERIALS AND METHODS

A retrospective review, approved by the Institutional Reviewed Board (IRB), of the prospectively maintained neurointerventional surgery log from May 2022 through November 2022 was performed at North Shore University Hospital Northwell Health. The following dates were selected for review due to their coinciding with the U.S. Food and Drug Administration (FDA) approval of the Onyx Frontier™ drug-eluting stent on May 13, 2022, for the treatment of coronary artery disease. The "off-label" or non-FDA approved utility of the Onyx Frontier system for treatment of refractory intracranial ischemia was performed under the accepted principle of exercising physician-discretion in life-threatening or severely debilitating medical situations, where there are no established alternative treatment options, and the acuity of the situation renders prior-IRB approval unfeasible. The feasibility and safety profile of the previous generation R-Onyx DES for the treatment of sICAD, has been well documented in the literature 10,11.

Patients were included in the study if they had an Onyx Frontier DES placed for symptomatic intracranial atherosclerosis. A baseline mRs of 0-2 was used as a cutoff for inclusion.

A total of 6 procedures were performed under general anesthesia. Deployments of 9 stents were completed successfully. Femoral access was used for all cases via an 8-French 80 or 90 cm Benchmark BMX96 sheath (Penumbra, Alameda, CA, USA). A 5 French Sofia EX (Medtronic, Irvine, CA, USA) was used as a support intermediate catheter in 5 cases and there was 1 case where no intermediate was required. During the intervention, all patients were heparinized. The stents that were deployed at an M1 segment or further were placed across the area of stenosis over an exchange length microwire.

Onyx Frontier DES (Medtronic) Zotarolimus-Eluting Coronary Stent system is a BMS composed of a single sinusoid-formed wire and a laser-fused stent. The stent design is the same as R-Onyx DES consisting of a platinum-iridium core and a cobalt alloy shell, optimizing its radiopacity. It uses an Over-the-Wire or Rapid Exchange delivery system. Unlike the previous generation R-Onyx DES, Onyx Frontier DES possesses enhanced catheter flexibility and a thin dual-flex balloon that enables a smaller crossing profile which enhances stent delivery by 16%. The stent was recently approved by the FDA for the treatment of non-left main coronary artery bifurcation lesions owing to the technically improved deployment in regions of complex bifurcation anatomy. The stent is available in varying sizes ranging from 2.0 mm to 5.0 mm with expansion up to 6.0 mm. The Zotarolimus drug coating inhibits neointimal proliferation while the BioLinx ™ biocompatible polymer promotes faster healing and more sustainable drug release, reducing systemic toxicity.[17]

RESULTS

Of the sixty-one subjects, the core lab was

A total of 6 patients were identified for review. The average age at presentation was 65.6 years (range 53-81 years) with a predominance of males to females (5:1); 16.6% (1) were identified as Caucasian, 16.6% (1) as African American, 33.3% (2) as multiracial and 16.6% (1) as Asian and 16.6% (1) unknown. All six patients presented with stroke or stroke-like symptoms, of which 3 (50%) presented with a recurrent stroke event despite maximum medical therapy, including dual antiplatelet or anticoagulation in addition to blood pressure augmentation. One patient of the total cohort underwent initial treatment with thrombectomy.

In total, 9 Onyx Frontier BMS were deployed for 7 distinct intracranial atherosclerotic lesions in the following distribution: cavernous segment of the internal carotid artery: 5, supraclinoid segment of the internal carotid artery: 1, M1 segment of the middle cerebral artery: 2, basilar artery: 1. The smallest stent size was 2.0 x 8 mm and the largest stent utilized was 4.0 x 18 mm. The average vessel diameter was 2.88 mm with an average caliber of stenosis of 0.89 mm (69.52%). The residual stenosis was 2.65 mm (94.98%). There were two complications resulting in cavernous-carotid fistulas, neither with clinical consequences; one was treated with a covered stent and the other self-resolved. Of these cases, a single periprocedural mortality was incurred in a patient with basilar artery occlusion, which in spite of successful reperfusion after rescue stenting, resulted in a fatal brainstem infarct (Table 1, Figure 1).

At 3 months, the clinical evaluation concluded an mRs of 0 in four out of five patients. One patient had an mRs of 6 and one patient was lost to follow-up.

DISCUSSION

Appropriate device/stent selection plays a crucial role in determining peri-operative and long-term sequelae of intracranial intervention for sICAD and the use of BMS or SES may be considered. As compared to SES, BMS help mitigate the risk of ISR, which is one of the major risks implicated in stroke recurrence following intracranial vascular stenting.[8] Contrary to SES, BMS are placed at the same time as angioplasty, foregoing the risk of an over-the-wire exchange which can prove to be a technically difficult

TABLE 1: Patients' demographics, risk factors, lesion characteristics, stent specifics, and outcome. ICA, internal carotid artery; MCA, middle cerebral artery.

ID	Age	Gender	Race	HTN/ HLD/ DM	Smoker	Presenting Symptom	Stenting Location	Proximal Vessel Diameter (mm)	Distal Vessel Diameter (mm)	Stenosis (mm)	Percent Stenosis	Residual Stenosis (mm)	Percent Residual Stenosis	Stent Size	Sheath	Intermediate	Immediate Complication	MRS at 3 Months
1	66	Male	Caucasian	Yes	Yes	Stroke	Cavernous ICA	Occluded	Occluded	Occluded	N/A	N/A	N/A	4.0 x 15/ 4.0 x 12/ 4.0 x 18	BMX	None	None	0
2	61	Female	African American	Yes	No	Recurrent stroke	MCA M1	2.02	2.10	0.21	89.6%	2.11	104.5%	2.0 x 8	BMX	SOFIA 5F EX	None	Unknown
3	67	Male	Multiracial	Yes	Yes	Recurrent stroke	Supraclinoid ICA	2.80	2.36	1.41	49.6%	2.07	73.9%	2.0 x 15	BMX	SOFIA 5F EX	None	0
4	81	Male	Asian	Yes	Yes	Stroke	Cavernous ICA	3.90	4.00	1.55	60.3%	3.72	95.4%	4.0 x 8	BMX	SOFIA 5F EX	CC Fistula	0
5	53	Male	Unknown	Un-known	Un-known	Stroke	Basilar	Occluded	Occluded	Occluded	N/A	N/A	N/A	2.75 x 8	BMX	SOFIA 5F EX	None	6
6	66	Male	Multiracial	Yes	No	Recurrent stroke	Cavernous ICA	3.96	2.92	0.94	76.3%	3.98	100.5%	4.0 x 12	BMX	SOFIA 5F EX	CC Fistula	0

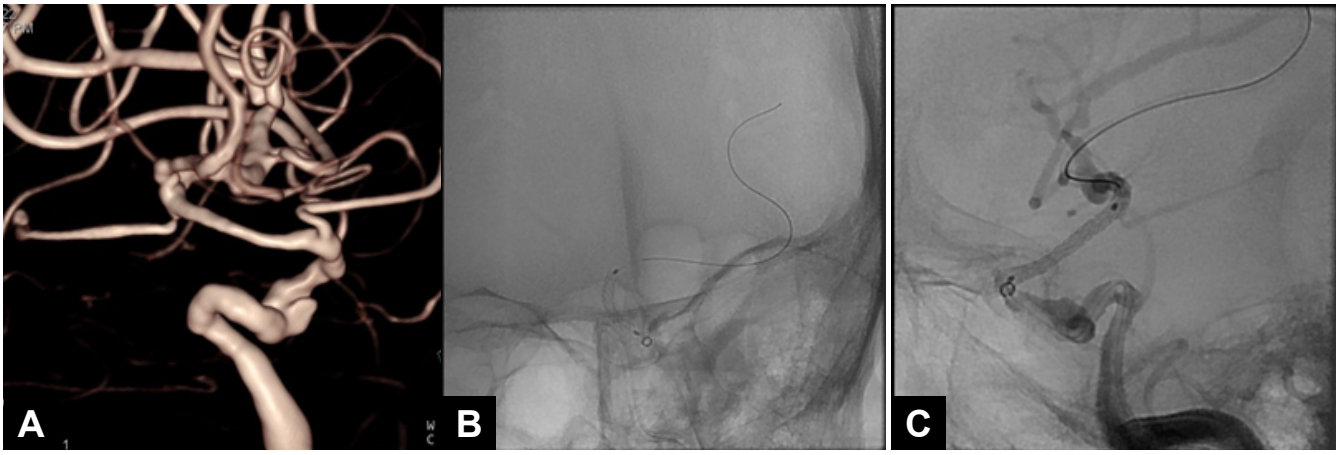

FIGURE 1: 67-year-old male presents with recurrent stroke. (A) 3D reconstruction of lateral projection digital subtraction angiography demonstrates severe stenosis of the left internal carotid artery (ICA) supraclinoid segment. (B) Intraprocedural native image shows the Onyx-Frontier stent placed at the site of stenosis (arrow). (C) Angiography obtained post stenting using an Onyx-Frontier 2x15 mm drug eluting stent shows no significant residual stenosis.

procedural step. In addition, the use of BMS may reduce the risks of vascular injury due to their easier maneuverability and shorter cone tips which increased their ability to navigate through small and tortuous vessels distal to the target lesions. BMS also generate increased optimal luminal dilation due to their higher radial forces, further mitigating the risk of periprocedural complications.[9] Furthermore, DES subtypes reduce the risk of ISR due to the release of anti-proliferative and anti-migratory drugs which act on the vascular smooth muscles, preventing proliferation while allowing re-endothelization.[10] While first-generation DES utilize Sirolimus or Paclitaxel drugs, second-generation DES employ Everolimus or Zatrolimus drug coatings, with the latter having been deemed clinically superior in preventing restenosis.[18] Collectively, these characteristics render a favorable profile for the off-label use of balloon-mounted DES for the treatment of refractory sICAD , with promising results.[14,19]

The R-Onyx stent is intently designed and approved for coronary arterial intervention. However, for over two decades, balloon-mounted coronary stents (BMCS) have been utilized with varying degrees of success for intracranial vascular intervention owing to the path paved by coronary percutaneous transluminal revascularization,[11,20] and justified by the similarities between the coronary and intracerebral atherosclerotic plaques.[21] One main limitation of these stents has been their stiffness which renders navigation in the tortuous intracranial arteries difficult, with injurious potential due to the thinner media and adventitia of intracranial vasculature.[12] This limitation was overcome with the advent of new stent technology of the second-generation BMCS resulting in higher flexibility, navigability, and deliverability,[13] providing reassuring technical safety in neurointerventional procedures.[22] One trial reported significantly lower preprocedural complications with R-Onyx versus WSS (1.7 vs 6.3 in stroke during the first 72 hours, 0% vs 8.9% in stroke beyond 72 hours, and 4.9% vs 22.8% in TIA, respectively). The incidence of in-stent restenosis was 1.7% with the use of R-Onyx system versus 21.4% with the use of WSS.[15] More recently, a larger trial of 132 patients with sICAD revealed significantly lower morbidity and mortality when treated with R-Onyx stent compared to the results of the SAMMPRIS trial.[16] It must be mentioned however, that angioplasty alone without the deployment of an intracranial stent, is another option for ET of sICAD and can be successfully performed for selected patients,[23] after accounting for the risk of vessel elastic recoil and restenosis and vessel dissection.[24]

In our cases, we utilized the more recent Onyx Frontier DES which retains the same stent platform as the R-Onyx system with some notable changes. It offers enhanced catheter flexibility, a smaller crossing profile, and improved stent delivery compared to the previous iteration, rendering an overall safer device profile. In addition to the more efficacious Zotarolimus drug-coating, the Onyx Frontier stent also contains BioLinx biocompatible polymer that promotes faster healing and more sustainable drug release, reducing systemic toxicity.[17]

Our study limitations include a small sample size of 6 participants, which significantly limits the generalizability of our findings.

As evidenced in our limited single-center, retrospective analysis, of a small 6-patient cohort, endovascular treatment with stenting, especially with the utility of newer-generation drug-eluting BMS Onyx Frontier system may offer at least a preliminarily initial viable treatment option, in patients with medically refractory sCIAD, with a relatively safe interventional profile as demonstrated by a single periprocedural complication of fatal brainstem ischemia in the setting of basilar artery reperfusion. With the progressive advancement of technology and design of such stents, the safety profile of ET for sICAD will continue to increase with early promising results, as seen in our case series, and may facilitate future official, "on-label" utility of such devices for the treatment of sICAD, especially in patients with medically refractive sICAD; with the additional prospective potential for mitigating long-term disease-associated morbidity and mortality.

CONCLUSION

Our case series demonstrates the utilization of the Onyx Frontier DES in the treatment of refractory sICAD. The vast majority of post-treatment results were favorable except for one case of fatal brainstem ischemia. Large prospective multicenter studies are needed to formally evaluate the use of DES in refractory sICAD.

REFERENCES

1. Wong LKS. Global burden of intracranial atherosclerosis. Int J Stroke 2006;1(3):158–9.
2. Wong KSL, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. The Lancet Neurology 2010;9(5):489–97.
3. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011;365(11):993–1003.
4. Zaidat OO, Fitzsimmons B-F, Woodward BK, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. JAMA 2015;313(12):1240–8.
5. Miao Z, Jiang L, Wu H, et al. Randomized Controlled Trial of Symptomatic Middle Cerebral Artery Stenosis. Stroke 2012;43(12):3284–90.
6. Gao P, Wang T, Wang D, et al. Effect of Stenting Plus Medical Therapy vs Medical Therapy Alone on Risk of Stroke and Death in Patients With Symptomatic Intracranial Stenosis. JAMA 2022;328(6):534–42.
7. Alexander MJ. Response by Alexander et al to Letter Regarding Article, "WEAVE Trial: Final Results in 152 On-Label Patients." Stroke 2019;50(7):e223–e223.
8. Jia B, Zhang X, Ma N, et al. Comparison of Drug-Eluting Stent With Bare-Metal Stent in Patients With Symptomatic High-grade Intracranial Atherosclerotic Stenosis: A Randomized Clinical Trial. JAMA Neurol 2022;79(2):176–84.
9. Mohammaden MH, Nogueira RG, Tekle W, et al. Safety and efficacy of balloon-mounted stent in the treatment of symptomatic intracranial atherosclerotic disease: a multicenter experience. J Neurointerv Surg 2022;14(8):756–61.
10. Ma X, Wu T, Robich MP, et al. Drug-eluting stents. Int J Clin Exp Med 2010;3(3):192–201.
11. Fiorella D, Chow MM, Anderson M, et al. A 7-year experience with balloon-mounted coronary stents for the treatment of symptomatic vertebrobasilar intracranial atheromatous disease. Neurosurgery 2007;61(2):236–42; discussion 242-243.
12. Bae HJ, Yoon B-W, Kang DW, et al. Correlation of coronary and cerebral atherosclerosis: difference between extracranial and intracranial arteries. Cerebrovasc Dis 2006;21(1–2):112–9.
13. Spione F, Brugaletta S. Second generation drug-eluting stents: a focus on safety and efficacy of current devices. Expert Rev Cardiovasc Ther 2021;19(2):107–27.
14. Hassan AE, Mohammaden MH, Rabah RR, et al. Initial Experience With the Next-Generation Resolute Onyx Zotarolimus-Eluting Stent in Symptomatic Intracranial Atherosclerotic Disease. Front Neurol 2020;11:570100.
15. Hassan AE, Khalil M, Desai S, et al. Resolute onyx stent more effective than wingspan stent at preventing procedural complications and long-term restenosis. Interv Neuroradiol 2023;29(6):691–5.
16. Siddiq F, Nunna RS, Beall JM, et al. Thirty-Day Outcomes of Resolute Onyx Stent for Symptomatic Intracranial Stenosis: A Multicenter Propensity Score-Matched Comparison With Stenting Versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial. Neurosurgery 2023;92(6):1155–62.
17. Van Dyck CJ, Hoymans VY, Haine S, et al. New-generation drug-eluting stents: focus on Xience V® everolimus-eluting stent and Resolute® zotarolimus-eluting stent. J Interv Cardiol 2013;26(3):278–86.
18. Navarese EP, Kowalewski M, Kandzari D, et al. First-generation versus second-generation drug-eluting stents in current clinical practice: updated evidence from a comprehensive meta-analysis of randomised clinical trials comprising 31 379 patients. Open Heart 2014;1(1):e000064.
19. Hassan A, Khalil M, Desai S, et al. Abstract TP162: Long-term Experience With Resolute Onyx Balloon Mounted Stent For Medically Refractory Intracranial Atherosclerotic Disease Evaluated By Wingspan Stent System Post Market Surveillance (WEAVE) Methodology. Stroke 2022;53.
20. Morris PP, Martin EM, Regan J, et al. Intracranial deployment of coronary stents for symptomatic atherosclerotic disease. AJNR Am J Neuroradiol 1999;20(9):1688–94.
21. Chung JW, Bang OY, Lee MJ, et al. Echoing Plaque Activity of the Coronary and Intracranial Arteries in Patients With Stroke. Stroke 2016;47(6):1527–33.
22. White TG, Shah KA, Koul P, et al. The resolute Onyx drug eluting stent for neurointervention: A technical series. Interv Neuroradiol. Published online 2022.
23. Nguyen TN, Zaidat OO, Gupta R, et al. Balloon angioplasty for intracranial atherosclerotic disease: periprocedural risks and short-term outcomes in a multicenter study. Stroke 2011;42(1):107–11.
24. Dumont TM, Sonig A, Mokin M, et al. Submaximal angioplasty for symptomatic intracranial atherosclerosis: a prospective Phase I study. J Neurosurg 2016;125(4):964–71.