Stent technology in ischemic stroke

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Atherosclerotic disease of the cerebral vasculature is a major cause of stroke worldwide. Atherosclerosis that is refractory to best medical management may require revascularization. In these instances, endovascular treatment provides a popular and safe alternative to open surgical techniques. The authors provide an overview of stent technology in the treatment of ischemic stroke, discussing the major studies evaluating stenting for extracranial carotid artery, vertebral artery, and intracranial atherosclerotic disease. The authors describe the commonly used stents with respect to their individual characteristics and technical limitations. Current and future developments in stent technology are also discussed, with areas for further innovation and clinical research.

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EACH year, approximately 800,000 people in the US will experience a new or recurrent stroke, of which 87% are ischemic in nature.⁴⁷ A large proportion of these strokes are secondary to vascular atherosclerotic disease, some of which can be refractory to best medical management. To treat atherosclerotic disease, endovascular revascularization with the use of stents has gained increasing popularity and acceptance as a safe and less-invasive alternative to open surgical revascularization procedures. In this review, we discuss studies that have attempted to validate the use of various stents for different indications, as well as the individual devices themselves with their specific characteristics. Finally, because stent technology is constantly evolving, current areas of research and development, and pharmacological strategies for minimizing stent restenosis are discussed.

Review of Current Stents

Extracranial Carotid Artery Stents

Atherosclerotic disease of the extracranial carotid artery accounts for approximately 30% of all ischemic strokes. Level 1 evidence from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrates that carotid endarterectomy (CEA) decreases the

risk of stroke in patients with severe stenosis, although this technique carries the typical risks of open surgery.⁵¹ Since the 1980s, endovascular techniques and devices have been developed as an alternative to CEA (Fig. 1), and multiple prospective randomized trials have evaluated their individual safety and efficacy.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) compared angioplasty, angioplasty plus stenting, and CEA and showed that while minor strokes that lasted less than 7 days were more common in the endovascular group (3.2% vs 0.4%), the number of other strokes in any territory or deaths was the same.²⁶ Carotid artery stenting (CAS) was used in only 26% of the endovascular treatment group, but its use resulted in a significantly lower incidence of restenosis. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized high-risk surgical patients (significant cardiac disease, recurrent stenosis, and age > 80 years) to either CAS with mandatory embolic protection devices or CEA, and found that the CAS group had a lower major adverse event rate at 30 days (4.8% vs 9.8%) and 1 year (12.2% vs. 20.1%).⁶⁹ High-risk patients were excluded in the International Carotid Stenting Study (ICSS), which showed no difference in the number of fatal or disabling strokes or in the modified

ABBREVIATIONS BMS = bare-metal stent; BVS = bioresorbable vascular scaffold; CAS = carotid artery stenting; CAVATAS = Carotid and Vertebral Artery Transluminal Angioplasty Study; CCA = common carotid artery; CE = Confirmité Européenne; CEA = carotid endarterectomy; DEB = drug-eluting balloon; DES = drug-eluting stent; ISR = in-stent restenosis; PED = Pipeline Embolization Device; SAMMPRIS = Stenting and Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis; TZD = thiazolidinedione; VAS = vertebral artery stenosis; WASID = Warfarin–Aspirin Symptomatic Intracranial Disease.

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FIG. 1. **A:** Digital subtraction angiography (DSA) showing severe narrowing of the left internal carotid artery at the carotid bulb in a 63-year-old woman. **B:** A 7 × 30-mm Precise carotid stent was deployed over the area of stenosis. **C:** Follow-up angiogram showing significant improvement in vessel caliber.

Rankin scale scores at 1- and 5-year follow-up.⁸ Patients in the CAS group did have a higher risk of nondisabling strokes than those in the CEA group (15.2% vs 9.4%).

The largest randomized controlled trial (2502 patients), the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), demonstrated CAS can be as effective as CEA for preventing strokes in both symptomatic and asymptomatic patients with carotid artery stenosis (7.2% vs 6.8% 4-year risk of stroke, myocardial infarction, or death).¹¹ The protocol specified the use of the RX Acculink stent (Abbott Vascular) as well as the RX Accunet embolic protection device whenever feasible in the CAS group. There was a higher risk of periprocedural stroke in the stenting group (4.1% vs 2.3%) but a higher risk of myocardial infarction in the endarterectomy group (1.1% vs 2.3%). As a result of these studies, the Centers for Medicare and Medicaid Services currently recommends CAS with embolic protection devices in patients at high risk for CEA, defined by factors such as significant cardiac comorbidities, contralateral carotid occlusion, previous CEA with recurrent stenosis, and prior neck radiation.

Stents used for CAS are self-expanding stents that can be closed cell or open cell, have a straight or tapered design, and are made of various metallic materials. The common CAS devices are listed in Table 1, with these factors described. The self-expanding nature allows the stent to expand against the plaque and exert an outward radial force that resists compression. The force depends on the stent design, as well as size of the stent chosen compared with the final vessel caliber (oversizing a stent). Open-cell stents tend to have greater radial force because their cells can freely open; however, excessive radial force can cause stent impaction and plaque protrusion.

Closed-cell stents have regularly spaced open spaces (cells) that are completely separated from other cells by tines, whereas open-cell stents are connected to other cells through incomplete tines. This allows closed-cell stents to have smaller cell areas that provide better wall coverage but tend to be more rigid and conform less to more tortuous vessels. Open-cell stents can have struts extending

into the lumen that can sometimes interfere with passage of catheters for use of embolic protection devices. Hybrid stents have also been developed to take advantage of the benefits of each type in separate segments, depending on the morphology of the vessel and lesion.

Tapered designs can be useful when deploying stents across the carotid bifurcation, as the common carotid artery (CCA) is typically larger than the internal carotid artery. The tapered design means that the maximum diameter at the proximal end is larger than that of the distal end, better matching the caliber of the CCA. Tapered stents can have a gradual, conical taper or a more abrupt, shouldered taper. Currently used stents are bare-metal stents (BMSs) commonly constructed of nitinol, a metal alloy of nickel and titanium. The Wallstent (Boston Scientific), which was initially approved for biliary use, is constructed of Elgiloy, a metal alloy of cobalt, chromium, iron, nickel, molybdenum, and manganese.

Vertebral Artery Stents

Posterior circulation strokes account for approximately 20% of all ischemic strokes, with approximately 9%–20% of these caused by vertebral artery stenosis (VAS).⁹ Although the natural history of VAS is not well understood, posterior circulation strokes carry a high rate of morbidity

TABLE 1. Stents used to treat carotid artery stenosis

Stent	Manufacturer	Material	Cell Type	Cell Area (mm ²)	Straight vs Tapered
Wallstent	Boston Scientific	Elgiloy	Closed	1.08	Straight
Xact	Abbott Laboratories	Nitinol	Closed	2.74	Both
NexStent	Boston Scientific	Nitinol	Closed	4.70	Tapered
Precise	Cordis Endovascular	Nitinol	Open	5.89	Straight
Protégé	ev3	Nitinol	Open	10.71	Both
Acculink	Abbott Vascular	Nitinol	Open	11.48	Both

and mortality.⁴⁶ Prospective randomized trials investigating best medical management of VAS are lacking, and patients with symptomatic disease are commonly treated with antiplatelet therapy and risk factor management. Patients who continue to have symptoms are considered eligible for either surgical or endovascular intervention for revascularization of the vertebral artery. Given the technical difficulty and morbidity of open revascularization procedures such as primary endarterectomy or transposition of the vertebral artery, endovascular intervention has become the preferred treatment modality in many centers (Fig. 2).

The CAVATAS trial failed to demonstrate any benefit of endovascular intervention with balloon angioplasty and stenting over best medical management;¹⁹ however, the study was underpowered with only 8 patients in each treatment arm and no posterior circulation strokes in either arm. Further prospective multicenter trials have also failed to demonstrate benefit of stenting over medical therapy. The Vertebral Artery Stenting Trial (VAST) was terminated early after enrolling 115 patients because funding was cut after new regulatory requirements were introduced.¹⁷ Although not adequately powered, it failed to demonstrate superiority of stenting over best medical therapy in symptomatic patients with at least 50% stenosis. The Vertebral Artery Ischemic Stenting Trial (VIST) suffered the same fate, with withdrawal of funding midway through enrollment. Results presented at the European Stroke Organization Conference in 2016 indicated a trend toward fewer strokes in the stenting group versus the medical group (hazard ratio 0.40, 95% confidence interval 0.14–1.13; $p = 0.08$).³³

Currently, no stents have been approved by the US FDA specifically for the treatment of VAS. Coronary artery stents are commonly used off-label for this purpose. The first prospective multicenter study, the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLIVIA) trial, found that 44.4% of the 18 patients who underwent stenting with BMS for symptomatic atherosclerotic lesions in the extracranial vertebral artery developed in-stent restenosis (ISR) of $> 50\%$. This is likely because the vertebral artery origin has a well-developed muscularis layer, much like other ostial segments such as coronary arteries. As a result of this finding, drug-eluting stents (DESs) were then co-opted from the cardiac world.

Early, first-generation coronary DESs were designed to release sirolimus (Cypher, Cordis Corp.) or paclitaxel (Taxus, Boston Scientific) and were found to decrease the rate of ISR in coronary arteries,^{55,59} likely by limiting macrophage accumulation and smooth muscle cell proliferation around the stent.⁶⁶ Since then, these DESs have been used off-label for VAS, with several studies comparing DESs and BMSs with regard to ISR. A large meta-analysis of 5 studies demonstrated a significantly lower ISR rate in the DES group than in the BMS group when used to treat atherosclerotic disease of the extracranial vertebral artery (15.49% vs 33.57%, odds ratio 0.388, $p = 0.001$) and a lower rate of recurrent symptoms (2.76% vs 11.26%, odds ratio 0.301, $p = 0.001$).⁶⁵ One limitation of this study, however, was the relatively short follow-up du-

FIG. 2. Images obtained in a 76-year-old woman who experienced a contralateral vertebral artery injury that required endovascular occlusion. **A:** DSA showing severe symptomatic stenosis originating from the right vertebral artery. **B:** A 3×12 -mm Resolute Integrity RX coronary stent was deployed over the area of stenosis, with follow-up angiography showing significant improvement in the area of severe stenosis.

rations—as short as a mean of 14.2 months of radiological follow-up in the DES group—which precluded the ability to evaluate for late ISR.

In the coronary literature, late and very late in-stent thrombosis is a common problem,²⁷ with the eluted drug inhibiting complete endothelialization of the stent struts. This causes increased long-term thrombogenicity of the stent, requiring prolonged antiplatelet use. As a response to these findings, second-generation coronary DESs have been developed with better vascular compatibility and less thrombogenicity. Xience V (Abbott Vascular), an everolimus-eluting stent, and Endeavor (Medtronic Vascular), a zotarolimus-eluting stent, have been found to have a lower risk of late in-stent thrombosis compared with earlier devices.² There are currently no studies investigating these newer stents and their rate of late ISR or thrombosis in the vertebral artery.

Studies evaluating the natural history of vertebral artery atherosclerotic disease are lacking, as are robust prospective randomized trials comparing stenting versus best medical therapy. Although there is some evidence from retrospective nonrandomized studies that DESs may be superior to BMSs in preventing ISR during the short term, little is known about their long-term performance. What has been demonstrated through various studies is that vertebral artery stenting has a low rate of periprocedural complications.⁶⁵ Given the neurological impact of posterior circulation strokes, endovascular treatment is likely to be warranted in a select group of patients, although further prospective randomized studies are clearly needed.

Intracranial Stents

Acute ischemic infarction from intracranial atherosclerotic disease accounts for approximately 8%–10% of strokes in the US each year.⁵⁸ The Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial demonstrated that the recurrent stroke risk of a patient with se-

FIG. 3. Angiograms from a 63-year-old man with severe atherosclerotic disease of the intracranial vertebral and basilar arteries. **A and B:** Transfacial (A) and lateral (B) DSA projections. **C and D:** Two 4 × 20-mm Wingspan stents were deployed, and follow-up angiography demonstrated improvement in vessel caliber.

vere symptomatic intracranial stenosis (70%–99%) was as high as 23% in 1 year despite best medical therapy at the time with either aspirin or warfarin,¹⁶ and subsequent trials have supported the use of dual antiplatelet therapy for improved treatment of arterial stenosis.⁴³ The poor natural history of symptomatic high-grade stenotic lesions despite best medical therapy logically presented an opportunity for endovascular intervention with balloon angioplasty and stenting to improve the caliber of the stenotic segment and perhaps improve patient outcomes (Fig. 3).

The Wingspan Stent System (Stryker Neurovascular) with the Gateway PTA Balloon Catheter is currently the only FDA-approved intracranial stent device under Humanitarian Device Exemption. The Wingspan stent is a 3.5-Fr nitinol over-the-wire, self-expanding stent available in various stent diameters (2.5, 3.0, 3.5, 4.0, and 4.5 mm) and lengths (9, 15, and 20 mm). The hydrophilic Gateway PTA balloon catheter and silicone balloon come in various diameters and lengths. The manufacturer recommends a submaximal angioplasty to achieve 80% of normal vessel diameter. The Pharos Vitesse (Micrus Endovascular Corp.) is a cobalt-chromium, open-cell, silicon carbide-coated balloon-expandable stent. Although it is Conformité Européenne (CE) Mark-approved in Europe, it is currently limited as an investigational device in the US.

The Stenting and Aggressive Medical Therapy for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) was the first multicenter, prospective, randomized controlled trial comparing angioplasty and stenting plus best medical therapy versus best medical therapy alone in patients with severe (70%–99%) symptomatic stenosis of a major intracranial artery. This study involved the only FDA-approved devices, the Gateway angioplasty balloon and the Wingspan stent. Best medical therapy included dual antiplatelet therapy with aspirin and clopidogrel, and blood pressure and cholesterol control. The study was stopped early after only 451 of the planned 764 patients had been enrolled because of futility analysis. Patients who underwent endovascular treatment had a significantly higher risk of 30-day stroke and death (14.7%) compared with patients who received best medical therapy alone (5.8%). This finding led the FDA to narrow the indications for use of the Wingspan stent to patients who had at least 2 recurrent strokes despite best medical therapy with dual antiplatelet medications and risk factor modification. Fur-

ther trials are currently underway to evaluate the efficacy of the Wingspan stent within these narrowed indications.

Similarly, the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trial, a separate multicenter, prospective, randomized controlled trial, evaluated the Pharos Vitesse balloon-expandable stent with best medical therapy versus medical therapy alone in the same high-risk patient population.⁷⁰ Again, this study was stopped early after just 112 of the planned 250 patients were enrolled because early interim analysis, in response to the SAMMPRIS results, showed higher risk in the endovascular treatment arm. Patients who underwent endovascular treatment had a higher risk of stroke or death within the first 30 days (24.1%) than patients who received medical therapy alone (9.4%).

Studies to date have failed to demonstrate the efficacy of intracranial stenting in preventing future strokes in patients with intracranial atherosclerotic disease as compared with best medical management. The SAMMPRIS trial did demonstrate the effectiveness of dual antiplatelet medications, as well as aggressive lifestyle modification and risk factor management with antihypertensive medication and statin therapy; patient outcomes in the medical arm were better than expected based on results from the WASID trial. As was the case with CAS, intracranial stenting may ultimately prove to be effective, but likely only after further technique and device refinement and better patient selection.

Cutting and Drug-Eluting Balloon Angioplasty

Many of the technical advances with balloon angioplasty are derived from the cardiology literature, where cutting balloons and drug-eluting balloons (DEBs) have been used for treating ISR as well as de-novo small vessel disease of coronary arteries.⁴⁸ The cutting balloon was designed with sharp blades to create regular longitudinal surgical cuts from the luminal surface and into the medial layer in an attempt to limit irregular intimal injury and elastic recoil.³ Likewise, the successful use of cutting balloons has been described for the treatment of carotid artery restenosis, with safety and durability.^{6,64} However, there is not yet consensus on specific management strategies for carotid ISR, with options including repeat angioplasty, repeat stent placement, and CEA with stent removal.⁶⁷

Drug-eluting balloons are covered in paclitaxel or oth-

FIG. 4. **A and B:** Angiograms from a 35-year-old woman who was involved in a motor vehicle accident and had bilateral (A, left, and B, right) vertebral artery dissections. **C and D:** Two 4 × 30-mm PEDs were deployed over the area of dissection, which resulted in increased luminal flow through the PEDs.

er antiproliferative agents such as sirolimus or zotarolimus. These balloons are kept inflated for 30–60 seconds to allow adequate transfer of the antiproliferative agent. Although initially developed and described for coronary arteries, DEB angioplasty has also been employed for treatment of ISR of the carotid artery.^{42,45} It has also been described as an adjunct treatment prior to CAS in patients with restenosis after CEA.⁵⁶ One study that described DEB angioplasty for the treatment of patients with severe refractory ISR after multiple endovascular interventions demonstrated that the treatment was durable in 6 of 9 patients; in the 3 patients who developed recurrent ISR, the time to restenosis was significantly longer than after previous interventions.³⁰

Another promising application of balloon angioplasty is for the treatment of intracranial stenosis, especially in light of the disappointing results from the SAMMPRIS trial. Restenosis risk in coronary arteries is significantly higher in smaller caliber vessels;⁷ thus, a treatment strategy that does not involve a permanent stent with risk of late ISR and further luminal caliber decrease may be superior. A study of 41 consecutive patients with atherosclerotic stenosis of intracranial vessels treated with submaximal angioplasty alone showed a 30-day event rate of 4.9% and a 1-year perioperative and ischemic event-free survival rate of 91%, both of which were better than either the medical or stenting arm of the SAMMPRIS trial.²⁴ A follow-up Phase I trial showed even better safety results with no 30-day ischemic events, and only 1 patient who had recurrent stroke at 1 year (5.55%).²⁵ Additionally, the Balloon Elution and Late Loss Optimization (BELLO) trial showed that DEB angioplasty may be superior to drug-eluting stenting for small-caliber coronary vessels.^{39,49}

Future Directions

Drug-Eluting Stents

The history of the development of cardiac stents has provided a vast fund of experience from which to draw.

Early BMSs were a step forward from balloon angioplasty but had high rates of in-stent thrombosis. This would often pose life-threatening complications, and revascularization was needed in as many as 20% of patients shortly after treatment.⁶⁰ Several solutions were attempted, including local and systemic administration of various agents to help delay or prevent in-stent thrombosis.²¹ Eventually, some of these agents were incorporated as DESs with promising initial results. Paclitaxel- or sirolimus-eluting stents were the first to be developed and demonstrated improved revascularization and reduced rates of in-stent thrombosis when compared with BMSs.^{23,63} Both of these agents work by an antiproliferative mechanism that prevents the migration and proliferation of endothelial smooth muscle cells, thus reducing rates of neointimal hyperplasia.¹⁸ DESs have proven their efficacy in preventing in-stent thrombosis compared with BMSs in the short term, but late stent thrombosis continues to be a problem.^{22,65} Some of these late stent failures were attributed to stent material design; as a result, second-generation DESs were introduced using more biocompatible materials.³⁸ Although second-generation DESs demonstrated decreased rates of late in-stent thrombosis, this complication continues to occur in as many as 1.3% of patients, an important limitation to consider if these devices are to be used for the treatment of intracranial disease.²⁹

Flow-Diverting Stents

A new class of endovascular devices that could play an important role in the treatment of ischemic stroke is the flow diverter, a stentlike device that redirects the flow of blood through the parent vessel. The Pipeline Embolization Device (PED; Covidien) is the only flow diverter approved in the US for the treatment of intracranial aneurysms; it has several important characteristics that make it a suitable candidate for such use (Fig. 4). First, the stent provides a scaffold to promote endothelial proliferation across the diseased vascular segment.⁵⁰ Second, its ability

to maintain the patency of critical perforators along both the internal carotid artery and vertebral artery make it an ideal candidate for use.^{40,44,50} Although there are no off-label reports of its use primarily for atherosclerotic disease, 1 report of its use as salvage therapy for a complication during angioplasty in a patient with severe atherosclerotic disease demonstrates its potential use for this purpose.⁶⁸

As in the case of cardiac stents, stent thrombosis remains a continual challenge. Although long-term reports are limited, stenosis rates of 10% after a median of 6 months were reported in 1 series, although there were no adverse neurological outcomes.³⁶ To mitigate this complication, a new coating technology of phosphorylcholine termed “Shield Technology” (Medtronic) has recently been developed and is in the early phases of testing, with clinical trials recruiting in Australia and Spain. Phosphorylcholine is an integral component of red blood cell membranes and has demonstrated resistance to platelet adhesion and intimal hyperplasia.^{12,14} Early animal studies have shown that a coating of phosphorylcholine reduced thrombogenicity of deployed PEDs with and without the use of adjuvant dual antiplatelet therapy.³² Additionally, this coating could potentially be used on existing stents already in use for intracranial disease.

Absorbable Stents

Although second-generation coronary DESs have been shown to have better clinical outcomes than BMSs or first-generation DESs, there are still concerns regarding long-term adverse events secondary to neoatherosclerosis and stent fracture.⁵⁴ In response to these concerns, bioresorbable vascular scaffolds (BVSs) have been developed that provide structural mechanical support and drug elution for a period of time, after which they are completely resorbed. The Absorb BVS (Abbott Vascular) consists of a 150- μ m-thick poly-L-lactide scaffold with a 7- μ m-thick poly-D,L-lactide coating that elutes everolimus. It has been extensively studied in the cardiac literature and is the only FDA-approved device of its kind for the treatment of coronary artery disease.

A large multicenter prospective randomized trial compared the Absorb BVS with the Xience DES in a noninferiority trial of 2008 patients.²⁸ The primary outcome of target-lesion failure occurred in 7.8% of patients in the Absorb group compared with 6.1% in the Xience group at 1 year ($p = 0.16$), with nonsignificant differences in the rates of cardiac death, myocardial infarction, or ischemia-driven target-lesion revascularization. The rate of device thrombosis within 1 year was 1.5% in the Absorb group compared with 0.7% in the Xience group ($p = 0.13$). Concerns regarding this study include the fact that it may be underpowered to detect differences in low-frequency events, such as device thrombosis, as well as the relatively short follow-up duration.

Cassese and colleagues¹³ published a large meta-analysis of 6 randomized clinical trials comprising data from 3738 patients randomized to receive percutaneous coronary intervention with either BVSs or second-generation DESs. Although the groups had similar risks of target lesion revascularization, target lesion failure, myocardial infarction, and death, the BVS group had double the risk

of definite or probable stent thrombosis (1.3% vs 0.5%, $p = 0.05$), with the highest risk within 30 days of implantation. This could be due to the fact that the polymer construction is inherently weaker than metal, requiring thicker bulky struts to improve tensile strength that still only provide about half the maximum radial strength of metallic DES.⁵³ In response to this, biodegradable metallic stents that have the tensile strength of metal while being fully bioabsorbable, such as zinc and magnesium alloys, are being investigated.¹⁰

These developments in cardiac BVS are likely to make their way into the neurosurgical literature, as second-generation DESs are already being used for the treatment of vertebral artery disease. With further refinement, this technology may be incorporated into stents designed for the intracranial circulation, in which long-term in-stent thrombosis poses a significant risk and traditional metal stents have already been shown to be inferior to best medical therapy.¹⁵

Biological Stents

Another approach to addressing the problem of late stent thrombosis is by improving the endothelialization of the implant and avoiding the elution of drugs that may inhibit neointimal tissue growth and delayed arterial healing in current DESs. The cobalt-chromium Genous stent (OrbusNeich) attempts to achieve accelerated endothelialization with a polysaccharide matrix coat containing anti-CD34–positive antibodies that attracts circulating endothelial progenitor cells. A single-center randomized prospective pilot study compared the Genous stent with the Taxus Liberté stent (Boston Scientific), a paclitaxel DES, in 193 patients with a high risk of restenosis.⁵ The Genous group had no cases of stent thrombosis whereas the Taxus group had 5 cases. The Genous group also had fewer episodes of target lesion revascularization (2.0% vs 5.3%).

Since that study, OrbusNeich has developed the Combo Dual Therapy stent, which combines anti-CD34–positive coating on the luminal surface with sirolimus drug elution on the abluminal surface. This would theoretically combine benefits of both types of therapy and recently received CE marking in Europe. Neither the Genous nor the Combo stent is available in the US. Currently, there are no prospective comparative studies evaluating the Combo stent.

Alternative biological coatings have been investigated in many other preclinical studies. Heparin and Type IV collagen used together were shown to enhance endothelialization on a titanium surface.⁷¹ Anti-CD34–positive antibodies combined with vascular endothelial growth factor to coat stainless-steel sheets were found to attract endothelial progenitor cells and promote differentiation.⁶² One group has proposed using oligonucleotides to promote surface endothelialization on cobalt-chromium stents,⁴ and another group proposed seeding nitinol stents with autologous endothelial cells on the stent surface.³⁵

Gene-eluting stents have become the subject of basic science and preclinical research. Several genes, such as nitric oxide synthase, vascular endothelial growth factors, and tissue inhibitor of metalloproteinases-3, have been proposed to promote endothelialization and reduce neo-

intima formation;⁵² however, there is currently no clinical applicability because a suitable vector for gene delivery has yet to be developed. Additionally, the genes may be inactivated during sterilization procedures.

Stem cells are another subject of investigation for stent biocompatibility and tissue healing. One group proposed a nanofiber stent sleeve to prevent stem cells from being washed out and to protect the cells against host immune responses while allowing the stem cells to respond to local environmental factors and release paracrine factors.³⁴ The investigators have proposed that the paracrine factors will then activate host cells and intrinsic repair mechanisms.

Systemic Therapy to Prevent Restenosis

In addition to local drug therapy to prevent IRS, systemic drug therapy with glucose- and lipid-lowering agents has shown promise. Indeed, patients with diabetes have a 2.5-fold higher risk of restenosis after percutaneous coronary intervention.¹ The exact mechanisms of restenosis are unclear but are believed to include inflammatory mediators, prothrombotic states, cytokines, adhesion molecules, and advanced glycosylation end products, the same mechanisms that are elevated in diabetes and dyslipidemia.^{41,57} Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor- γ agonists and are commonly used as insulin sensitizers in diabetic individuals. These drugs have been found to inhibit smooth muscle cell growth and migration²⁰ and to limit the production of pro-inflammatory cytokines.⁶¹ A meta-analysis of randomized controlled trials showed that TZD therapy significantly reduced the risk of ISR after percutaneous coronary intervention in both diabetic (relative risk 0.37, $p < 0.0001$) and nondiabetic patients (relative risk 0.16, $p = 0.0006$).³¹

Similarly, dyslipidemia is a major risk factor for atherosclerotic disease, and several clinical trials have shown that statins reduce the risk of coronary events. These drugs are promising agents for preventing ISR as they have been shown to have antiinflammatory and antithrombotic effects and inhibit proliferation and migration of vascular smooth muscle cells.⁵⁷ A post hoc analysis of the Treating to New Targets (TNT) study evaluated the efficacy of low- versus high-dose atorvastatin in 5407 patients with previous percutaneous coronary intervention and their rates of cardiac events and repeat revascularization.³⁷ Patients receiving high-dose atorvastatin had significantly lower rates of repeat revascularization (17.3% vs 22.9%, $p < 0.0001$).

Systemic drug therapy, including TZDs and statins, has shown promise in the cardiac literature with regard to reducing the risk of cardiac events and revascularization. It is reasonable that the same mechanisms that contribute to cardiac events and ISR in coronary stents that are ameliorated by TZDs and statins may also contribute to strokes and ISR in stents placed in the cerebral vasculature. However, clear prospective randomized trials evaluating the efficacy of these systemic drug therapies are lacking in the neurosurgical literature.

Conclusions

As a result of ongoing stent development, improvement

of endovascular techniques, and prospective clinical trials, CAS has become widely accepted as a safe and effective alternative to CEA in specific groups of patients. Although the same cannot be said about stenting of intracranial or vertebral arteries, we believe that with the same persistence, intracranial and vertebral artery stents will also find acceptance, ultimately with improvement in the outcomes of select groups of patients. Endovascular technologies are constantly evolving, with industry investing heavily in the development of new technologies as well as in the trials to demonstrate their safety and efficacy. A thorough understanding of these trials, as well as the strengths and weaknesses of each endovascular device, will be critical to providing the best individualized care for each patient.

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Disclosures

Dr. Taussky has served as a consultant to Covidien/Medtronic.

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Conception and design: Park, Yoon. Drafting the article: Yoon, Awad. Critically revising the article: Park, Kalani, Taussky. Reviewed submitted version of manuscript: Park, Yoon, Kalani, Taussky. Approved the final version of the manuscript on behalf of all authors: Park.

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