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Off-Label Use of Drugs and Devices in the Neuroendovascular Suite

M.M. Abdihalim, A.E. Hassan, and A.I. Qureshi



ABSTRACT

SUMMARY: The off-label use of drugs and devices in neuroendovascular procedures is common. Neurointerventionalists should be well aware of the level of evidence available in support of the off-label use of drugs and devices in their practice and some of the potential adverse events associated with them. These uses are categorized as I or II if they have been evaluated as primary or ancillary interventions in prospective trials/registries of neuroendovascular procedures and III if they were evaluated in case series. Category IV use is based on evaluation as primary or ancillary interventions in prospective trials/registries of non-neuroendovascular procedures. Physicians are allowed to use off-label drugs and procedures if there is strong evidence that they are beneficial for the patient. The neurointerventional professional societies agree that off-label use of drugs and devices is an important part of the specialty, but practicing providers should base their decisions on sound evidence when using such drugs and devices.

ABBREVIATIONS: GDC = Guglielmi detachable coil; IA = intra-arterial; ICH = intracerebral hemorrhage; PROACT = Prolyse in Acute Cerebral Thromboembolism; UK = urokinase

Off-label¹ use for prescription drugs, biologics, and approved medical devices is any use that is not specified in the labeling approved by the US Food and Drug Administration. Labeling includes any written material that accompanies, supplements, or explains the product. In neuroendovascular procedures practice, this use is relatively common.¹ However, the knowledge among practicing neuroradiologists, endovascular neurosurgeons, and interventional neurologists regarding the principles and consequences of using off-label products in their practice is lacking.

If physicians use a product for an indication not in the approved or cleared labeling, they have the responsibility to be well-informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain awareness of the use and effects of the product. FDA regulations allow the exchange and dissemination of scientific information on the unapproved uses of a product in response to unsolicited requests from physicians, continuing medical education programs, and peer-reviewed scientific and medical journals.¹

This Review Article provides data with the following objec-

tives: 1) allowing physicians to recognize off-label use of products within the scope of their practice, 2) identifying instances when the off-label use of medical products is recognized as a generally accepted medical standard within the physician community, 3) summarizing our experience using off-label products in our practice, and 4) providing recommendations from professional organizations on off-label use of drugs and medical devices.

OFF-LABEL USE OF DRUGS IN THE NEUROENDOVASCULAR SUITE

The following summarizes the most common drugs used off-label within the neuroendovascular suite.

Intra-Arterial Use of Thrombolytics

Approved Use of Thrombolytics. For acute ischemic stroke, intravenous administration within 3 hours of symptom onset; massive pulmonary embolus; and acute myocardial infarction.

Off-Label Use. Intra-arterial administration for acute ischemic stroke up to 9 hours after symptom onset (category I). The only FDA-approved thrombolytic for acute ischemic stroke treatment is IV alteplase (Activase; Genentech, South San Francisco, California).² Treatment should only be initiated within 3 hours after the onset of stroke symptoms and after exclusion of intracranial hemorrhage by a cranial CT scan. A subgroup of patients with ischemic stroke is treated by using intra-arterial thrombolytics with various criteria either alone or in combination with IV

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thrombolytics and/or mechanical thrombectomy.^{3,4} Intra-arterial urokinase (Abbokinase; Abbott Laboratories, Chicago, Illinois) was the most commonly used intra-arterial thrombolytic for acute ischemic stroke before 1999.⁵ However, an FDA action resulted in withdrawal of urokinase from the market for 4 years. FDA inspectors found that Abbott was not taking adequate steps to test for infection in or prevent contamination of the kidney cells used to manufacture the drug.⁶

This withdrawal led to use of other thrombolytic medications including prourokinase, reteplase, tenecteplase, and alteplase as part of endovascular treatment for acute ischemic stroke.⁵ Prourokinase was the only thrombolytic that was considered for FDA approval on the basis of the results of PROACT I and II trials.^{7,8} In both of those trials, patients were given intra-arterial (IA) prourokinase within 6 hours of symptoms onset. These trials demonstrated an increased rate of recanalization, 57.7% and 67% (treatment group) versus 14.3% and 18% (controls).^{7,8} Moreover, a recent meta-analysis of 5 randomized controlled trials of IA thrombolysis of acute ischemic stroke with 395 participants showed IA thrombolysis by using pro-UK, UK, or recombinant tissue plasminogen activator substantially increased the rates of recanalization and had excellent clinical outcomes. The increased hemorrhage frequencies were not associated with any increase in mortality.⁹ The off-label use of thrombolytics is recognized as a generally accepted medical standard within the physician community (category I). The formulation of thrombolytics (more concentrated compared with IV-use formulation) and the maximum dose used require sound principles or previous studies that have reported on these issues.¹⁰ Third-generation thrombolytics, tenecteplase (17 ± 7 minutes), and reteplase (15–18 minutes), have longer half-lives and greater penetration in the thrombus matrix than alteplase (5 minutes).¹¹

Platelet Glycoprotein IIb/IIIa Inhibitors

Approved Use. Patients with acute coronary syndrome who are treated medically only and those undergoing percutaneous coronary intervention; and patients undergoing percutaneous coronary intervention including stent placement.

Off-Label Use. Intraprocedural thrombosis and ischemic events following endovascular procedures (category III). The experience of using platelet glycoprotein IIb/IIIa inhibitors abciximab (Reopro; Johnson and Johnson, Malvern, Pennsylvania), eptifibatid (Integrillin; Merck, Whitehouse Station, New Jersey), and tirofiban (Aggrasat; Merck, West Point, Pennsylvania) in neurointerventional procedures is limited. These agents are effective in reducing ischemic complications of acute myocardial infarctions and thrombotic complications associated with percutaneous coronary interventions.^{12–14} The FDA-approved indications of glycoprotein IIb/IIIa inhibitors are in acute coronary syndromes and as an adjunct to percutaneous coronary interventions. The off-label use of glycoprotein IIb/IIIa inhibitors was evaluated in several case series and clinical trials focusing on patients undergoing endovascular treatment for acute ischemic stroke or those undergoing carotid artery stent placement.^{15–17} The use of platelet glycoprotein IIb/IIIa inhibitors in both of these applications was discontinued for the most part. The premature discontinuation of

the Abciximab in Emergency Treatment of Stroke Trial II after 808 patients with acute ischemia were enrolled due to high rates of intracranial hemorrhage associated with IV abciximab (IV bolus followed by IV infusion) limited the enthusiasm for further evaluation in ischemic stroke.¹⁸ The routine use in carotid artery stent placement was discontinued after a randomized trial, and 2 single-center comparisons with historical controls did not demonstrate any reduction in periprocedural ischemic events.^{19–21} The relatively high rate of fatal intracerebral hemorrhages (ICHs) observed in studies also reduced the enthusiasm for using these agents.²² Some local institutional review boards may require that planned use of these agents involve informing patients or relatives regarding such complications. The current use in neuroendovascular procedures is limited to intraprocedural thrombosis and ischemic events (category III).^{16,23,24} Glycoprotein IIb/IIIa inhibitors are approved only for IV administration but are usually administered by IV infusion, IA bolus followed by IV infusion, or IV bolus followed by IV infusion.¹⁵

Physicians administering these agents should be well aware of the principle of dose conversion of any agent requiring special formulation, reversal half-lives, and monitoring for thrombocytopenia. Abciximab requires filtration, while eptifibatid and tirofiban do not, before administration. Dosing of both eptifibatid and tirofiban should be adjusted in patients with renal failure (renal elimination) but this is not necessary with abciximab (eliminated by the reticuloendothelial system).²⁵ Although rare, thrombocytopenia can occur within 1–24 hours after infusion.²⁶ When these agents are infused, platelets should be monitored 1–2 hours after infusion and again 24 hours after infusion. Platelets should recover rapidly after discontinuation.²⁷ The off-label use of platelet glycoprotein IIb/IIIa inhibitors is recognized as a generally accepted medical standard within the physician community in certain situations such as intraprocedural thrombosis.

Calcium Channel Blockers

Approved Use. Cerebral vasospasm (nimodipine), hypertension, angina, atrial arrhythmia, and paroxysmal supraventricular tachycardia.

Off-Label Use. Intra-arterial administration for improving arterial luminal narrowing in patients with symptomatic cerebral vasospasm due to subarachnoid hemorrhage in native intracranial arteries (category III).

Randomized controlled trials have shown that oral nimodipine (Nimotop; Bayer, West Haven, Connecticut) is effective in reducing delayed ischemic neurologic deficits caused by cerebral vasospasm following subarachnoid hemorrhage.^{28–30} Nimodipine, 60 mg orally every 4 hours for 21 consecutive days started within 96 hours of subarachnoid hemorrhage, is FDA-approved to prevent cerebral vasospasm.³¹

Intra-arterial or intravenous use of verapamil, nimodipine (Nimotop), and nicardipine (Cardene; Baxter Healthcare, Deerfield, Illinois) have all been reported to be effective and safe in the treatment of cerebral vasospasm (category III).^{10,32–35} The off-label use of calcium channel blockers in treating cerebral vasospasm is recognized as a generally accepted medical practice within the physician community; however, the treating physician

must ensure that adequate hemodynamic monitoring is performed on patients receiving these agents. Low doses of intra-arterial calcium channel blockers were not associated with significant hemodynamic changes, but high-dose nicardipine was associated with hypotension.³⁴ The duration of monitoring must be adequate on the basis of the half-life of the agent: verapamil (4 minutes), nimodipine (7 minutes), and nicardipine (3 minutes). Physicians must also be familiar with and prepared to address commonly observed adverse events of hypotension and bradycardia. These agents are all category C medications during pregnancy.

Magnesium Sulfate

Approved Use. Atrial paroxysmal tachycardia, eclampsia, cerebral edema, barium poisoning, seizures associated with epilepsy, glomerulonephritis, or hypothyroidism.

Off-Label Use. Intra-arterial administration for improving arterial luminal narrowing in patients with symptomatic cerebral vasospasm due to subarachnoid hemorrhage in native intracranial arteries (category III).

Magnesium sulfate is a noncompetitive calcium channel blocker.³⁶ Suarez et al³⁷ reviewed 17 studies including a single phase III randomized controlled trial and 6 phase II randomized controlled trials on the effects of magnesium sulfate on cerebral vasospasm. They reported that the studies suggested either no net benefit or uncertain trade-offs.³⁷ Shah et al³⁸ reported that a combination of IA magnesium (0.25–1 g) and nicardipine (2.5–20 mg) was well-tolerated in a small case series of patients with cerebral vasospasm.

Heparin, Low-Molecular-Weight Heparin, and Direct Thrombin Inhibitors

Approved Use. Multiple indications including venous thrombosis or thromboembolism, pulmonary embolism, cardiac surgery, and heparin-induced thrombocytopenia requiring anticoagulation (direct thrombin inhibitors).

Off-Label Use. Continuous infusion or intermittent boluses during neuroendovascular procedures (category II). Heparin is primarily used in neurointerventional procedures to reduce the risk of perioperative and immediate postoperative ischemia.³⁹ Measurement of the activated coagulation time is the preferred method for evaluation of responses to heparin because the activated coagulation time demonstrates a linear heparin dose-response curve, even at the higher doses used during interventional procedures.⁵ The target activated coagulation time in neurointerventional procedures is 250–350 seconds.³⁹ Vance et al⁴⁰ found that the administration of heparin is safe during the first 24 hours after endovascular treatment of ruptured intracranial aneurysms. The measurement of the intensity of anticoagulation by activated coagulation time requires understanding of the methods and instruments used for such measurements.⁴¹

Unlike unfractionated heparin and low-molecular-weight heparin, direct thrombin inhibitors such as bivalirudin (Angio-max; The Medicines Company, Parsippany, New Jersey), lepirudin (Refludan; Bayer), or argatroban (Argatroban; GlaxoSmith-

Kline, Research Triangle Park, North Carolina) are antithrombin III-independent inhibitors of thrombin that are effective against thrombin even after it binds to fibrin. Direct thrombin inhibitors are not associated with heparin-induced thrombocytopenia.⁵ Direct thrombin inhibitors are primarily used for the anticoagulation of patients with heparin-induced thrombocytopenia or those who are at risk for heparin-induced thrombocytopenia.⁴² A recent small retrospective study showed that a bivalirudin bolus of 0.6 mg/kg followed by an infusion of 1.25 mg/kg/h until the target activated coagulation time was achieved was a safe alternative to heparin infusion for anticoagulation during neuroendovascular procedures.⁴³

Aspirin and Clopidogrel

Approved Use. Aspirin: anesthesia, antipyretic, anti-inflammatory, myocardial infarction, prophylaxis for myocardial infarction, and cerebrovascular accident. Clopidogrel: percutaneous coronary intervention for non-ST elevation myocardial infarction, prophylaxis for cerebrovascular accident, myocardial infarction, and peripheral arterial disease.

Off-Label Use. Combined aspirin and clopidogrel after intracranial or craniocervical angioplasty and/or stent placement to prevent thrombosis and ischemic complications (category II). Aspirin leads to: irreversible inhibition of platelet cyclooxygenase-1 and production of thromboxane A₂, resulting in platelet inhibition.⁵ Aspirin is commonly used in the prevention of thromboembolic events during or following neurointerventional procedures such as aneurysm embolization or carotid and intracranial stent placement.⁴⁴ van den Bergh et al⁴⁵ showed that the use of antiplatelets during or after aneurysm embolization improved outcome in patients with SAH in the International Subarachnoid Aneurysm Trial. Several retrospective case series showed that antiplatelet therapy with aspirin and/or clopidogrel reduced thromboembolic events of coil embolization for unruptured intracranial aneurysms.^{46,47} Clopidogrel (Plavix; Sanofi Aventis, Bridgewater, New Jersey) inhibits the binding of adenosine diphosphate to its platelet receptor, leading to inhibition of platelet aggregation.⁵ It is approved for the prevention of stroke in patients with recent history of stroke, myocardial infarction, or established peripheral arterial disease.^{48,49}

Dual antiplatelet therapy is routinely used after intracranial angioplasty and intracranial or extracranial stent placement. However, the duration of dual antiplatelet therapy is not well-defined.⁵⁰ Most of the data regarding periprocedural antiplatelet management are derived from the coronary interventional literature.⁵¹ A retrospective case series recently did not show increased adverse events from dual antiplatelet therapy beyond 1 month of the endovascular procedure.⁵¹ Several large prospective multicenter trials (category II) have used aspirin and clopidogrel at least 3 days before the procedure and continued to 1–3 months after carotid artery stent placement (Carotid Revascularization Endarterectomy vs. Stenting Trial [CREST]/Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy [SAPPHIRE]/International Carotid Stenting Study [ICSS]/Stent-Protected Angioplasty vs. Carotid Endarterectomy in Symptomatic Patients [SPACE]) and intracranial stent placement (Stenting vs. Aggressive Medical Management for Preventing Recur-

rent stroke in Intracranial Stenosis [SAMMPRIS]).⁵²⁻⁵⁶ The safety and tolerability of these medications for a month following the procedure has been ascertained in 3121 patients with a very low rate of ICH (1.6%).⁵²⁻⁵⁶ Two of the above trials (CREST and SAMMPRIS) permitted a bolus dose of clopidogrel (450 or 600 mg) if it could not be administered at least 3 days before the procedure.⁴⁴ Physicians should be aware of the risk of thrombotic thrombocytopenia purpura and bone marrow suppression with clopidogrel, which occurs in 1 case per 8500–26,000 patients treated with clopidogrel.

MEDICAL DEVICES

Intracranial and Extracranial Stent Placement

Drug-eluting balloon-expandable, bare-metal balloon-expandable, and self-expanding stents have all been used to treat medically refractory intracranial stenosis.^{52,57-67} These case series suggested that intracranial stent placement can be performed safely and with high technical success.

Drug-Eluting Stents

Approved Use. Improving coronary luminal narrowing in patients with symptomatic ischemic disease due to de novo lesions in native coronary arteries.

Off-Label Use. Improving arterial luminal narrowing in patients with symptomatic ischemic disease due to de novo lesions in native intracranial arteries (category III). Drug-eluting stents indicated for coronary artery disease have significantly reduced restenosis rates.⁶⁸ Common drug-eluting stents include the Taxus Express (Boston Scientific, Natick, Massachusetts), which elutes paclitaxel; Cypher (Cordis, Miami Lakes, Florida), which elutes sirolimus; and Endeavor (Medtronic, Minneapolis, Minnesota), which elutes zotarolimus. There are no large trials evaluating the safety and efficacy of drug-eluting stents in the intracranial circulation, to our knowledge. Case series report on the use of Cypher and Taxus stents for intracranial stenosis and more frequently vertebral artery–origin stenosis (category III). Intracranial application of drug-eluting stents has been limited by their inflexibility, the tortuous nature of intracranial vessels, and the high rate of late stent thrombosis requiring prolonged dual antiplatelet use.^{69,70} The benefit demonstrated in prevention of restenosis is less obvious in neurovascular applications. Fields et al⁶⁵ reported a restenosis rate of 21% with drug-eluting stents at the vertebral origin (3/14) and 38% (3/8) with intracranial use. Overall, restenosis rates were comparable with restenosis rates of bare metal stents. The off-label use must be performed with the understanding of the current guidelines for antiplatelet treatment with drug-eluting stents, which require 12 months of dual antiplatelet therapy and low-dose aspirin continued indefinitely.⁷¹

Balloon-Expandable Stents

Approved Use. Improving coronary luminal narrowing in patients with symptomatic ischemic disease due to de novo lesions in native coronary arteries.

Off-Label Use. Improving arterial luminal narrowing in patients with symptomatic ischemic disease due to de novo lesions in native intracranial arteries (category III).

The nonrandomized multicenter Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries trial, which tested the NeuroLink system (Guidant, St. Paul, Minnesota), showed 30-day and 1-year stroke rates of 7.2% and 10.9%, respectively. Recurrent stenosis occurred in 35% at 6 months.⁶⁷ The NeuroLink stent was approved on the basis of that result on a Human Device Exemption approval; however, that stent is no longer being manufactured. Cruz-Flores and Diamond⁷² reported a systematic review of 79 studies (1999 cases) on the efficacy and safety of intracranial artery angioplasty and stent placement for intracranial artery stenosis. The rate for perioperative stroke was 8%; perioperative death, 3%; perioperative stroke or death, 10%; and other perioperative complications (such as groin hematoma and arterial dissection), 10%. Additionally, in those studies with follow-up of at least 1 year, the risk of stroke or death was 6%.⁷³

Qureshi et al⁷³ reported on the complications following angioplasty and/or stent placement in 92 patients in 3 medical centers. They found a nonsignificantly higher rate of periprocedural adverse events with balloon-expandable stents. However, Kurre et al⁷⁴ analyzed the large INTRASTENT registry, a European multicenter registry, and found no statistically significant difference in complications between 254 lesions treated with balloon-expandable stents and 155 lesions treated with self-expanding stents. Some examples of balloon-expandable stents include AVE S660 (Medtronic), BX sonic (Cordis), and Multi-Link (Abbott Vascular, Redwood, California). The off-label use of balloon-expandable stents for intracranial stenosis is category III. The unique technical challenges in placement with long intracranial lesions must be recognized.

The Apollo Stent for Symptomatic Atherosclerotic Intracranial Stenosis (ASSIST) study reported that stent-delivery failure was more frequent in lesions of >10 mm compared with those of <10 mm (25% versus 3%), though no relationship could be demonstrated with periprocedural stroke and death. The presence of tortuous proximal vessels (≥ 2 acute curves requiring traversing, judged by experience or trial), limited vessel length available distal to the lesion to allow stable placement of microwire, or the inability to place a guide catheter in the distal vertebral artery or internal carotid artery resulted in a higher technical failure rate than that reported for “on-label” indications.⁷⁵ The operator must be familiar with the inflation and deployment profiles of balloon-expandable stents to avoid excessive distention of the arterial wall and difficulties with deployment in contiguous arterial segments with major differences in diameter such as the vertebral-basilar junction.

Coronary Angioplasty Balloons for Intracranial Angioplasty

Approved Use. Improving coronary luminal narrowing in patients with symptomatic ischemic disease due to de novo lesions in native coronary arteries.

Off-Label Use. Improving arterial luminal narrowing in patients with symptomatic ischemic disease due to de novo lesions in native intracranial arteries (category III).

In a systematic review of 69 studies (33 primary angioplasty studies with coronary angioplasty balloons with a total of 1027

patients and 36 stent-placement studies with a total of 1291 patients), there were 91 strokes and deaths reported in the angioplasty-treated group compared with 104 in the stent-treated group during a 1-month period ($P = .5$). The 1-year stroke and death rate in patients treated with angioplasty was 20% compared with 14% in the stent-treated patients ($P = .009$). The pooled restenosis rate was 14% in the angioplasty-treated group compared with 11% in the stent-treated group ($P = .04$). No effect of the publication year of the studies was seen on the risk of stroke and death.⁷⁶ Common balloon catheters used for intracranial angioplasty included the Maverick (Boston Scientific), Ninja (Cordis), and Gemini (Guidant). New generations of semicompliant balloon catheters such as Gateway (Boston Scientific) with hydrophilic coating designed for low-pressure inflations and high navigability have been introduced recently, specifically for intracranial use. No clear data support the superiority of such angioplasty catheters over the existing coronary angioplasty catheters.

Self-Expanding Stents for Intracranial or Extracranial Dissections

Approved Use. Intracranial stenosis (Wingspan; Boston Scientific) and stent-assisted embolization of aneurysms (Neuroform; Boston Scientific).

Off-Label Use. Improving arterial luminal narrowing and reducing irregularity in patients with symptomatic ischemic disease due to arterial dissections in native intracranial or extracranial arteries (category III).

The Wingspan self-expandable stent and Gateway balloon (Boston Scientific) are currently an FDA-approved intracranial stent and angioplasty balloon system for intracranial atherosclerotic stenosis; and the Neuroform self-expandable stent (Boston Scientific) is currently approved for stent-assisted embolization of wide-neck intracranial aneurysms that are not candidates for surgical treatment. Both stents have been used for treatment of intracranial dissections. Other self-expandable stents used in extracranial and vertebral artery dissections include the X-pert Self-Expanding Stent System (Abbott Vascular), approved for palliation of malignant strictures in the biliary system, and the Fluency Plus (Bard Peripheral Vascular, Tempe, Arizona); and carotid artery stents are approved for atherosclerotic stenosis of the ICA.⁷⁶⁻⁷⁹ Both the Wingspan and Neuroform stents have been used for treatment of extracranial dissections. There are some data that support a high technical success rate and long-term patency of these stents in intracranial or extracranial dissections (category III).⁸⁰ However, the operator must be aware that there are limited data on the comparative efficacy with medical treatment alone and long-term angiographic patency following the procedure.

Carotid Balloon Angioplasty

Approved Use. Aviator Plus and Savvy (Cordis) and Symmetry (Boston Scientific) in improving coronary or peripheral artery luminal narrowing in patients with symptomatic coronary artery or peripheral arterial disease.

Off-Label Use. Improving carotid artery luminal narrowing (category III). Carotid atherosclerotic disease is implicated in 15%–

30% of all ischemic strokes.⁸¹ Multiple studies have shown that carotid artery angioplasty and stent placement have long-term outcomes similar to those in carotid artery endarterectomy for patients with carotid artery disease.^{49,53-56} Currently, the Aviator Plus and Viatrac 14 Plus are the only 2 angioplasty balloon catheters approved for carotid angioplasty. However, many different types of angioplasty balloons with unique properties approved for coronary artery or peripheral artery angioplasty have been used off-label for carotid artery angioplasty.^{82,83} Understanding of the differences in angioplasty balloon properties is essential. Angioplasty balloon catheters can be grouped into 5 categories, as follows: standard (0.035-inch) balloon catheters (eg, Ultra-Thin Diamond; Boston Scientific), small-vessel (0.014/0.018-inch) balloon catheters (eg, Coyote, Sterling SL, and Symmetry; Boston Scientific and SLEEK and SAVVY; Cordis), high-pressure balloon catheters (eg, Mustang; Boston Scientific and Dorado and Conquest; Bard Peripheral Vascular, Tempe, Arizona), large-vessel balloon catheters (eg, XXL; Boston Scientific and Atlas; Bard Peripheral Vascular, Tempe Arizona), and special angioplasty balloon catheters (eg, Cutting Balloon and PolarCath; Boston Scientific).⁸⁴

Balloon Angioplasty for Cerebral Vasospasm

Approved Use. Improving coronary luminal narrowing in patients with symptomatic ischemic disease due to de novo lesions in native coronary arteries.

Off-Label Use. Improving arterial luminal narrowing in patients with symptomatic cerebral vasospasm due to subarachnoid hemorrhage in native intracranial arteries (category III).

Balloon angioplasty for symptomatic or angiographic cerebral vasospasm has been shown to improve clinical outcomes (category III).⁸⁵⁻⁸⁷ Angioplasty provides the most improvement in reducing vasospasm in patients with subarachnoid hemorrhage presenting with low Hunt and Hess scale SAH (I or II) and if performed within 12 hours of symptom onset.^{86,87} In a recent small series of 30 patients, no difference was noted between compliant and noncompliant balloons for the angioplasty of cerebral vasospasm.⁸⁸ This group compared compliant balloons (HyperGlide or HyperForm; ev3, Irvine, California) or noncompliant balloons (Maverick or Gateway, Boston Scientific; Sprinter, Medtronic; and Voyager, Abbott Vascular). Achieving normal or supranormal vessel-lumen diameter after the first angioplasty was associated with significant reduction in future angioplasties.⁸⁸ The main complications of balloon angioplasty are rare but include rupture or occlusion of the vessel.^{85,89-91} In addition, balloon angioplasty proximal to an unsecured aneurysm may result in aneurysmal rupture.^{90,91}

Intravascular Sonography

Approved Use. Diagnostic sonography of the peripheral and coronary vasculature.

Off-Label Use. Sonography of the carotid and intracranial vasculature (category III). Intravascular sonography has many potential applications in neurointerventional practice.⁹² It can be used in the determination of the morphology and composition of ath-

erosclerotic plaque within the extracranial and intracranial circulation, mural thrombus, plaque ulceration, and aneurysm and vessel dissection; it allows evaluation of correct stent diameter required and the amount of balloon-inflation pressure needed during angioplasty; and it enables visualization of stent apposition and expansion. Currently there are no FDA-approved intravascular sonographic devices for intracranial application. Several studies have shown that intravascular sonography is safe in the intracranial circulation.⁹³⁻⁹⁶ Clark et al⁹³ prospectively evaluated the safety of intravascular sonography in carotid stent placement in 98 patients. They had an acceptable 30-day stroke rate and combined stroke and death rates of 5% and 6%, respectively (category III).

Embolc Agents for Aneurysms, Tumors, and Epistaxis

Approved Use. Vascular malformations.

Off-Label Use. Aneurysms, tumors, and epistaxis (category III). Onyx (ev3), *n*-butyl cyanoacrylic acid (*n*-BCA) (Trufills; Cordis), and polyvinyl alcohol particles have all been approved for treating cerebral arteriovenous malformations.⁹⁷ However, they have also been used in treating intracranial aneurysms, epistaxis, tumors, and dissecting vertebral artery aneurysms.⁹⁸⁻¹⁰⁶ The FDA approved a high-viscosity type of Onyx (Onyx HD500) as a Humanitarian Use Device for wide-neck aneurysms (>4 mm or dome-neck ratio of <2) that are not amenable to surgical treatment.¹⁰⁷ Onyx HD500 is safe and effective for treating wide-neck aneurysms that are not amenable to other techniques. Piske et al¹⁰⁷ reported complete aneurysm occlusion of 65.5% (postprocedure), 84.6% (6 months), and 90.3% (18 months) in 84 aneurysms treated with Onyx HD500 with a peri-procedural mortality rate of 2.9%. Small case series have shown that *n*-BCA is safe and effective for the embolization of distal small intracranial aneurysms.^{105,106} In experimental models, polyvinyl alcohol has been shown to be effective in the embolization of aneurysms.^{108,109}

Polyvinyl alcohol, gelatin sponge pledgets (Gelfoam; Pfizer, New York, New York), and trisacryl gelatin microspheres (EmboSphere; BioSphere Medical, Rockland, Massachusetts) are used in the treatment of epistaxis (category III).^{110,111} The complication rates and success of embolization or surgical ligation are similar, though embolization is associated with more major complications when embolic agents inadvertently enter the internal carotid or ophthalmic artery.¹¹¹

Preoperative embolization of intracranial tumors with embolic agents before surgical resection is performed in selected cases. Most often these are hypervascular skull base tumors, including meningiomas, paragangliomas, and juvenile nasopharyngeal angiofibromas (category III).¹¹²⁻¹¹⁴ These procedures are associated with low complications mostly related to thromboembolic events.¹¹³

Coils for Parent Artery or Venous Sinus Occlusion

Approved Use. Embolization of intracranial aneurysms.

Off-Label Use. Embolization of the parent artery or venous sinus for achieving therapeutic occlusion (category III).

Coil embolization (HydroCoil; MicroVention Terumo, Aliso Viejo, California and GDC and Complex Helical; Boston Scientific) of intracranial aneurysms is a proved and effective treat-

ment. However, occlusion of the parent vessel may be necessary in certain situations when treating intracranial aneurysms. Most commonly, it is used when treating distal small intracranial aneurysms that cannot be accessed (category III).¹¹⁵⁻¹¹⁸ In a small series of 9 patients, Eckard et al¹¹⁸ found that parent vessel occlusion was safe and effective in treating distal aneurysms that were not amenable to surgical treatment or intra-aneurysmal coil placement. The main risk of parent vessel occlusion is brain ischemia. Temporarily inflating a balloon to occlude the parent vessel and evaluating the effects on brain function and hemodynamics can be used to predict the risk of ischemia.¹¹⁹ Ischemic sequelae may still occur even in those who tolerate a test occlusion, which has a 3.3%–10% false-negative rate.¹¹⁹

Embolization of the venous sinus is sometimes used to treat dural arteriovenous fistulas.¹²⁰⁻¹²² Kirsch et al¹²⁰ reported no complications related to transvenous coiling of the affected sinus in 21 patients with dural arteriovenous fistulas. Complete occlusion of the dural arteriovenous fistulas can be obtained in most cases with only transvenous coil placement (category III).^{120,122} In addition, the use of coils before liquid embolic agents slows and decreases flow in the fistula and provides secure anchoring to the Onyx or glue cast.¹²³

Amplatzer for Intracranial Parent Vessel Occlusion

Approved Use. Cardiopulmonary and peripheral vascular occlusions.

Off-Label Use. Parent artery deployment for achieving therapeutic occlusion of cervical arteries (category IV).

The Amplatzer Vascular Plug (St. Jude Medical, St Paul, Minnesota) is approved for vessel occlusion in the cardiopulmonary and peripheral vasculature that would have required many coils. However, experience in the intracranial vasculature is limited. Common indications for parent vessel occlusion might include treating carotid cavernous fistulas and aneurysms and preoperative embolization of skull base tumors. Several small case series have reported good technical outcome and safety when the Amplatzer Vascular Plug was used in the intracranial vasculature (category IV).^{124,125}

SINGLE-CENTER EXPERIENCE

We retrospectively reviewed the medical records and angiographic images of 100 consecutive cases of endovascular interventions at 2 institutions. The patients were identified by using local registries maintained by the cerebrovascular/endovascular programs that track all patients who undergo endovascular treatment. The patients reviewed were treated at the University of Minnesota Medical Center, Minneapolis, Minnesota, from June 2010–August 2010. The protocol for collecting data was reviewed and approved by the institutional review boards.

In the 100 cases reviewed, the indications for the procedures were the following: cerebral vasospasm following SAH (31%), coil embolization of intracranial aneurysms (16%), carotid artery stenosis (15%), IA thrombolytics for ischemic stroke (13%), intracranial angioplasty and/or stent placement for intracranial stenosis (7%), preoperative tumor embolization (8%), intracranial vascular malformation (5%), carotid or vertebral artery dissections (3%), and facial trauma/epistaxis (2%).

Principles of label use of medication and/or devices in neuroendovascular procedures

Principles

1. Identify off-label use and understand the use according to label/indications
2. Categorize the off-label use according to categories presented in the On-line Table
3. Category III requires informed consent for medication/device use with a description of adverse events observed in neurovascular procedures
4. Category IV requires informed consent for medication/device use with a description of adverse events observed in non-neurovascular procedures and acknowledgment of paucity of data from neurovascular procedures

Following the classification scheme in the On-line Table, all the procedures were performed under heparin infusion (category II); IA nicardipine or verapamil (category III) in 31 cases; dual antiplatelet therapy (category II) in 24 cases; IA thrombolytics (category I) in 13 cases; stent-assisted embolization of intracranial aneurysms (category I) in 3 cases; stent placement of intracranial stenosis (category I) in 4 cases; angioplasty alone of intracranial stenosis (category III) in 3 cases; stent placement of carotid or vertebral dissections (category III) in 5 cases; the intravascular ultrasound catheter system in 3 cases (category III); and polyvinyl alcohol embolization of the internal maxillary artery (category III) in 2 cases.

RECOMMENDATIONS FROM PROFESSIONAL SOCIETIES

The FDA states, "Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment."¹ The FDA recommends that if a physician uses an off-label drug or medical device, he or she should base judgment on sound medical evidence and should maintain a record of the products used and effects.¹ A proposed scheme to categorize the off-label use of medications and devices is summarized in the On-line Table.

The position of the Society of Interventional Radiology supports the lawful use by a physician of an FDA-approved medical device or drug product for an unlabeled indication when such use is based on sound scientific evidence and/or sound medical opinion.¹²⁶ Off-label use of drugs and devices is an important part of the specialty but practicing providers should base their decisions on sound evidence when using them.

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