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February 14, 2012

Louis Jacques, M.D.
Director
Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Re: Formal Request for Reconsideration of the National Coverage Determination for PTA and Intracranial Stenting (Section Number 20.7 (B)(5))

Dear Dr. Jacques:

Public Citizen, a consumer advocacy group representing more than 250,000 members and supporters nationwide, many of whom are beneficiaries of the Medicare program, formally requests revocation of the National Coverage Determination (NCD) for reimbursement of percutaneous transluminal angioplasty and stenting (PTAS) of intracranial arteries for the treatment of cerebral artery stenosis.[1] This procedure is currently covered by the Centers for Medicare and Medicaid Services (CMS) for treatment of cerebral artery stenosis ≥50% in patients with intracranial atherosclerotic disease when furnished in accordance with the Food and Drug Administration (FDA)-approved protocols governing Category B investigational device exemption (IDE) clinical trials. We urge CMS to issue a revised NCD excluding all coverage of PTAS of intracranial arteries for the treatment of cerebral artery stenosis on the basis of new medical evidence concerning its dangers — evidence that was not known or considered during the initial NCD review or subsequent reconsiderations.

In a randomized, controlled trial funded by the National Institute of Neurological Disorders and Stroke (NINDS), the Stenting Versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, the 30-day rate of stroke or death was more than twice as high in subjects receiving PTAS plus aggressive medical management, compared with subjects receiving aggressive medical management alone (14.7% versus 5.8%, P=0.002).[2] The one-year rate of stroke or death was also significantly higher in subjects receiving PTAS (20.0% versus 12.2%, P=0.009). This study presents convincing evidence that PTAS offers no health benefit but instead poses substantial safety risks to patients. Continued Medicare coverage for PTAS is neither supportable nor justifiable in light of this new evidence. We therefore urge you to conclude that the procedure is not reasonable or necessary to treat cerebral artery stenosis and to exclude PTAS from coverage.

I. Regulatory Background

Each year in the U.S., approximately 700,000 patients experience a stroke, and 240,000 have a transient ischemic attack (TIA). [3,4] Atherosclerotic intracranial arterial stenosis (narrowing of the blood vessel supplying blood to the brain) is a common cause of these events, accounting for approximately 8% of ischemic strokes and TIAs.[5,6] Patients with 70-99% stenosis are at particularly high risk for recurrent stroke.[7] Medical therapy (combination antiplatelet therapy, blood pressure-lowering medication, and management of risk factors) has long been available as a standard treatment for this condition and has improved over time.[8,9] Over the past three decades, clinicians in the U.S. and other countries have also experimented with intracranial angioplasty with and without stent placement as an alternative or supplement to medical therapy.[10,11,12] For many years, these procedures were performed using balloon catheters and stents that were unapproved by the FDA for intracranial use.[13] They were also performed without any published evidence from randomized, controlled clinical trials comparing intracranial angioplasty and stenting to standard medical therapy without the use of such devices. During this time, CMS maintained a national non-coverage policy excluding coverage for PTAS of intracranial arteries for the treatment of cerebral artery stenosis, based on lack of evidence of effectiveness.[14]

In 2005, Boston Scientific Corporation applied for and quickly received FDA approval for the Wingspan Stent System with Gateway PTA Balloon Catheter (hereafter referred to as "the Wingspan Stent System") under a humanitarian device exemption (HDE).[15] The HDE provides an exemption from the ordinary approval requirements for medical devices, meaning the sponsor need not submit a premarket approval application demonstrating effectiveness through scientifically valid clinical investigations (or gain approval by demonstrating substantial equivalence to a previously approved product).[16,17] By utilizing the HDE process, Boston Scientific was able to gain marketing approval for the Wingspan Stent System based on a single, uncontrolled, 45-subject trial that was not designed to demonstrate whether treatment with the device was safer or more effective than medical therapy alone.[18]

Although the FDA approved the Wingspan Stent System via the HDE route, the FDA approval itself did not affect reimbursement by CMS, because CMS does not have a national policy that addresses coverage of Humanitarian Use Devices.[19,20] Boston Scientific sought a change in CMS's national non-coverage policy by making a formal request to CMS to reconsider its existing non-coverage policy.[21] In a decision memo issued November 6, 2006, the CMS Coverage and Analysis Group, Division of Medical and Surgical Services, noted that it could not identify any clinical trial (randomized or nonrandomized) that compared angioplasty and stenting to medical therapy.[22] Instead, CMS was forced to base its determination on case series and single-center experiences, most of which involved stent systems other than the Wingspan Stent System.

In 2006, the only data available to CMS on intracranial angioplasty and stenting using the Wingspan Stent System came from the small, uncontrolled, prospective , multicenter, single-arm study of 45 subjects conducted in 12 academic medical centers in Europe and Asia and submitted

to the FDA as part of the HDE application (the Wingspan safety study).[23,a] Enrollment criteria included recurrent stroke, refractory to medical therapy, and symptomatic intracranial stenosis ≥50%. Forty-four subjects underwent intervention with the Wingspan Stent System and were considered evaluable at 30 days post-stent placement; 42 subjects were evaluated at six months post-stent placement. The composite ipsilateral stroke (a stroke occurring on the side of the brain supplied by the stented intracranial artery) or death rate at 30 days post-procedure, the primary safety end point of the study, was 4.5% (two subjects had ipsilateral strokes, one of whom died). The composite ipsilateral stroke or death rate at six months post-procedure was 7.1% (three subjects had ipsilateral strokes, one of whom died).[b]

In its 2006 analysis, CMS compared data from the Wingspan safety study to outcomes in subjects enrolled in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial[24] who had a TIA or nondisabling stroke within 90 days prior to enrollment that was attributable to a ≥50% stenosis of a major intracranial artery. The study, in which subjects were randomly assigned to receive aspirin or warfarin, did not involve an assessment of stents. The WASID trial subjects who received aspirin had a 15% one-year probability of death, ischemic stroke, or brain hemorrhage.[25] Subjects who received warfarin had a 17% one-year probability of death, ischemic stroke, or brain hemorrhage.

In examining the data on intracranial angioplasty and stenting using the Wingspan Stent System, CMS noted that "[i]n addition to the small sample sizes, short term follow-up and weak study design, the death and stroke rate for patients who underwent intracranial angioplasty and stenting using the Wingspan [Stent System] was high." CMS concluded that

> [T]here is not sufficient information … : (1) [to] predict the effect of generalized use of intracranial artery stenting; (2) to evaluate the long-term outcomes of this therapy; and, (3) to determine the appropriate patient groups that may benefit.[26]

Nevertheless, because weak evidence from case series and single-center experiences "suggest[ed] a potential benefit to some patients," CMS determined to allow restricted coverage of treatment with PTAS only in a clinical study setting, where patients could be more closely monitored. Accordingly, CMS revised its previous decision for non-coverage in its NCD to now cover PTAS when furnished in accordance with FDA-approved protocols governing Category B IDE clinical trials.[27]

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[a] CMS also considered a 15-case series studying the Wingspan Stent System. Henkes H, Miloslavski E, Lowens S, et al. Treatment of intracranial atherosclerotic stenoses with balloon dilatation and self-expanding stent deployment (WingSpan). Neuroradiol. 2005; 47:222-8. The CMS decision memo noted that "it is unclear if there is overlap of the patients in [the] Henkes study and the data presented to the FDA." Centers for Medicare and Medicaid Services. Decision memo for intracranial stenting and angioplasty (CAG-00085R2), November 6, 2006. *Available at* http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=177&ver=23&NcaName=Intracranial+Stenting+and+Angioplasty&DocID=CAG-00085R2&bc=gAAAAAgAIBAA& (last accessed January 30, 2012). Personal communications by Public Citizen's Health Research Group with Arani Bose, M.D., and Hans Henkes, M.D., confirmed that these 15 cases were a subset of the 45 subjects enrolled in the Wingspan safety study.

[b] In its November 2006 decision memo, CMS appears to have incorrectly reported that the composite ipsilateral stroke or death rates at 30 days and six months post-procedure were 6.7% and 11%, respectively.

Of note, while the CMS Decision Memorandum for Intracranial Stenting and Angioplasty (CAG-00085R2) focused on "angioplasty and stenting using the Wingspan Stent System or other stents used in off label indications for intracranial artery stenosis ≥ 50%, *refractory to medical therapy*," (emphasis added)[28] its ultimate coverage determination dropped the "refractory to medical therapy" requirement.

An approved IDE permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting clinical investigations of that device.[29] The trials do not require premarket approval and are generally conducted in order to gather data for a premarket approval application or a premarket notification (510[k]) submission to the FDA.[30]

In the past, Medicare coverage was denied for devices that were under an IDE and had not yet received premarket notification clearance or premarket approval because the treatments were considered experimental. On September 8, 1995, the FDA entered into an agreement with the administrator of the Medicare program (then called the Health Care Finance Administration now CMS). Under this agreement, certain un-approved and un-cleared devices can be viewed as "reasonable and necessary" by Medicare (and treatments can therefore be covered if all other applicable Medicare coverage requirements are met). Specifically, the FDA will place all IDEs it approves in one of two categories: "Category A," (experimental), involving innovative devices in which "absolute risk" has not been established (i.e., initial questions of safety and effectiveness have not been resolved, and thus the FDA is unsure whether the device type can be safe and effective); and "Category B," (investigational, non-experimental), involving device types believed to be in Class I or II or device types believed to be in Class III where the incremental risk is the primary risk in question (i.e., underlying questions of safety and effectiveness have been resolved). Category B includes device types that can be safe and effective because, for example, other manufacturers have obtained FDA approval for that device type. The FDA provides the category determination on the IDE approval letter to the sponsor and also forwards this information to the CMS administrator. [31,32]

PTAS involves a Class III device for which only one stent system, the Wingspan Stent System, has obtained FDA approval. Thus, while Medicare coverage is not limited to the Wingspan Stent System, CMS evidently contemplated covering IDE clinical trials using the Wingspan Stent System and similar stent systems where incremental risk over the approved Wingspan stent was the primary risk in question.

All other indications for PTAS to treat obstructive lesions of the vertebral and cerebral arteries, as well as percutaneous transluminal angioplasty without stenting, remained uncovered.[33]

In August 2007, Boston Scientific formally requested that CMS reconsider its 2006 NCD to permit broader coverage for PTAS with the Wingspan Stent System, including coverage for patients not enrolled in clinical trials.[34] In a decision memo issued May 12, 2008, addressing the reconsideration request, CMS analyzed studies and evidence relating to the Wingspan Stent System published after the 2006 NCD.[35] This evidence included three studies presenting data from two registries including 78 patients and 129 patients,[36,37,38] one single case study,[39] and a

published paper presenting the data from the uncontrolled Wingspan safety study of 45 subjects previously submitted to the FDA with Boston Scientific's HDE application for the Wingspan Stent System.[40] The CMS decision memo cited methodological concerns with all of the studies presented, noting that "the lack of control groups and long term follow-up add to the uncertainty of clinical benefit."[41]

CMS ultimately determined not to expand coverage for PTAS treatment, stating that "[g]iven the invasive nature of this treatment and the severe risks, ... a well designed, well conducted randomized controlled trial is needed."[42]

II. Standard for Review of National Coverage Determinations

In order to be covered by Medicare, an item or service must fall within one or more benefit categories,[43] must not otherwise be excluded from coverage, and must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[44] In making the "reasonable and necessary" determination, CMS reviews and critically appraises scientific evidence from multiple sources and determines 1) to what degree the specific clinical questions relevant to the coverage request can be answered conclusively and 2) whether the intervention will improve the patients' health outcomes.[45]

In assessing the clinical evidence, CMS will consider 1) the quality of the individual studies, 2) the generalizability of findings from individual studies to the Medicare population, and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

III. New Clinical Evidence Since the May 12, 2008, Reconsideration Determination Decision

a. The SAMMPRIS trial[46]

i. Methods

The SAMMPRIS trial was an investigator-initiated, randomized, controlled clinical trial funded by the NINDS, part of the National Institutes of Health, and conducted at 50 sites in the U.S. Patients were eligible if they had a TIA or nondisabling stroke within 30 days before enrollment, attributable to angiographically verified stenosis of 70-99% of the diameter of a major intracranial artery.

Patients were randomly assigned to receive aggressive medical management alone (medical-management group) or aggressive medical management plus PTAS with the Wingspan Stent System (PTAS group). Aggressive medical management consisted of aspirin (325 milligrams [mg] per day) and clopidogrel (75 mg per day) for 90 days after enrollment, as well as management of primary and secondary risk factors (elevated systolic blood pressure, elevated low-density lipoprotein and non-high-density lipoprotein cholesterol levels, diabetes, smoking, excess weight, and insufficient exercise). In addition to aspirin and clopidogrel, one drug from

each major class of antihypertensive agents, rosuvastatin, and a lifestyle program were also provided to manage primary and secondary risk factors.

The PTAS was performed by neurointerventionists selected by a committee of experienced neurointerventionists on the basis of procedure notes and outcomes of the 20 most recent consecutive cases of intracranial stenting or angioplasty performed by the neurointerventionists under consideration. Subjects who were randomly assigned to PTAS were required to undergo the procedure within three business days after randomization.

Subjects were evaluated at the time of study entry, at four days, and at 30 days, and have continued to be evaluated every four months. Subjects were to undergo assessment until 90 days after a primary end point occurs, the subject dies, three years of follow-up are completed, or the close-out visit for the trial — occurring when the last subject enrolled has been followed for one year — is held. At follow-up visits, subjects were examined by study neurologists who also managed the subjects' vascular risk factors. If a stroke was suspected during the follow-up period, the subject was examined by the study neurologist, and magnetic resonance imaging (MRI) or computed tomography (CT) of the brain was typically performed. Because study group assignment was known to the study neurologist, there was a protocol requirement for a second site neurologist who was not aware of the study group assignment to evaluate any subject who had a hard-to-classify event (a TIA lasting more than one hour or mild ischemic stroke).

The primary end point was stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period (i.e., angioplasty for symptomatic restenosis in a subject in the PTAS group or placement of a stent in a subject in the aggressive medical-management alone group) or ischemic stroke in the vicinity of the qualifying artery beyond 30 days. Ischemic stroke was defined as a new focal neurological deficit of sudden onset, lasting at least 24 hours, that was not associated with hemorrhage on CT or MRI of the brain. All end points were adjudicated by an independent panel of neurologists and cardiologists who were not informed of study group assignments.

ii. Results

Enrollment in the SAMMPRIS trial began in November 2008 and ended in April 2011, after the trial's independent data and safety monitoring board recommended that enrollment be stopped because of safety concerns regarding the increased risk of periprocedural stroke or death in the PTAS group and because the futility analysis indicated that there was virtually no chance that a benefit from PTAS would be shown by the end of the follow-up period if enrollment continued.

A total of 451 subjects underwent randomization (medical-management group N=227, PTAS group N=224). Data published by the SAMMPRIS trial investigators included all adverse events as of the date when the last subject enrolled had completed the 30-day evaluation. There were no significant differences between the two study groups with respect to any of the baseline characteristics of the subjects.

Regarding primary end points within 30 days after enrollment, the 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke, 12.5%; fatal stroke, 2.2%) and 5.8% in the

medical-management group (nonfatal stroke, 5.3%; non-stroke-related death,[c] 0.4%) (P=0.002), constituting a more than 2.5-fold increase in the rate of stroke or death caused by the PTAS. The number needed to harm for PTAS, based on the difference in the rate of stroke or death within 30 days of intervention, was only 11 (i.e., for every 11 subjects treated with the Wingspan Stent System and medical therapy, one additional subject died or suffered a stroke within 30 days in comparison to subjects treated with medical therapy alone).

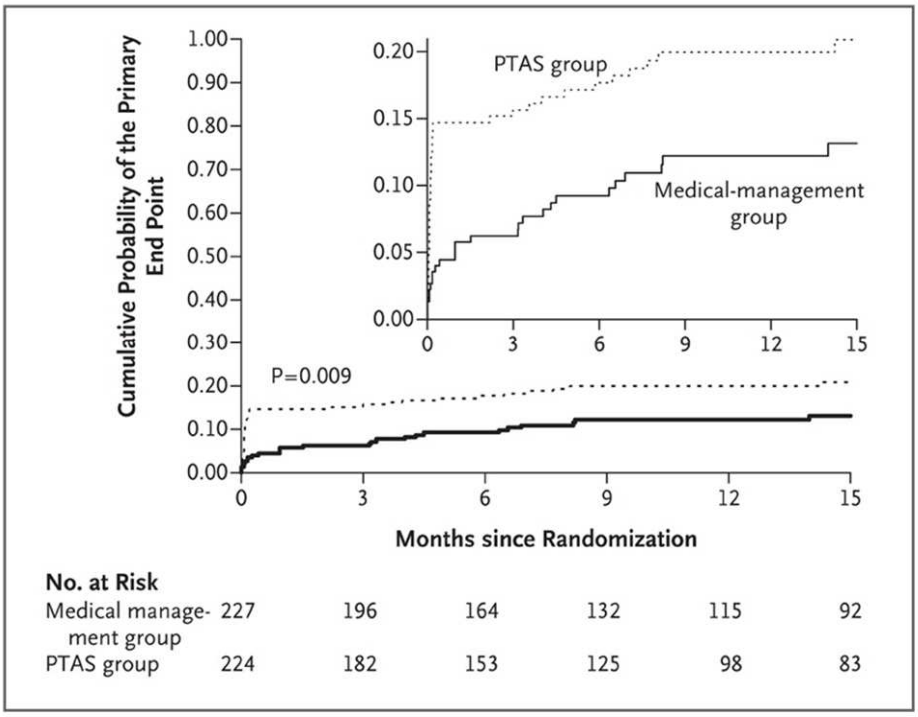
Ten of the 33 strokes in the PTAS group (30.3%), but none of the 12 in the medical-management group (0%), that occurred within 30 days of enrollment were symptomatic brain hemorrhages (P=0.04).

Of the 33 strokes in the PTAS group that occurred within 30 days after enrollment, 25 occurred within one day after the procedure, and eight occurred within two to six days later. The 33 strokes occurred at 25 investigational sites. Of the six sites at which more than one periprocedural stroke occurred, five were among the highest enrolling sites (i.e., at the 12 sites enrolling half the subjects). The 30-day stroke rate in PTAS group subjects was 13.5% at the highest-enrolling study sites and 14.7% at the other sites (the 38 sites that enrolled the other half) (P=0.77). The risk of periprocedural stroke did not diminish over the course of the enrollment period.

Regarding primary end points beyond 30 days, nonfatal ischemic strokes in the territory of the qualifying artery occurred in 13 subjects in each group. The probability of the occurrence of a primary end point over the entire follow-up period after enrollment also differed significantly between the two study groups, with one-year rates of the primary end point at 20.0% in the PTAS group and 12.2% in the medical-management group (P=0.009) (see Figure 1).

[c] Here, “fatal stroke” is compared to “non-stroke-related death” to highlight the fact that in the PTAS group, all five deaths were related to stroke. In the medical management group, there was only one death, and it was unrelated to stroke. Hence the statements here compare the total fatality rates in each group. .

Figure 1: Kaplan–Meier Curves for the Cumulative Probability of the Primary End Point, According to Treatment Assignment.



Chimowitz MI et al. N Engl J Med 2011;365:993-1003.

An as-treated analysis that excluded the 11 subjects in the PTAS group who did not undergo angioplasty or have a stent placed (three of whom had a stroke) and the nine subjects in the medical-management group who underwent PTAS after a TIA during the follow-up period (three of whom had a stroke after PTAS) showed the same result (P=0.009)

iii. Conclusions and comments by SAMMPRIS trial investigators

In discussing the dramatic results of their study, the SAMMPRIS trial investigators noted the following:

> Contrary to what we hypothesized, the results of this trial showed that aggressive medical therapy was superior to PTAS with the use of the Wingspan system in high-risk patients with intracranial stenosis, because the rate of periprocedural stroke after PTAS was higher than expected and the rate of stroke in the medical-management group was lower than estimated. The 30-day rate of stroke or death in the PTAS group (14.7%) is substantially higher than the rates previously reported with the use of the Wingspan stent in the phase I trial and in two registries (rates ranging from 4.4% to 9.6%). The higher rate in the current study does not reflect inexperience of the operators, because most of the interventionists who participated in the registries also participated in this trial, and all the interventionists in this trial were credentialed to participate on the basis of evidence of

> their experience. In addition, the rates of periprocedural stroke did not decline over the course of the enrollment period and did not differ significantly between high-enrolling sites and low-enrolling sites in this trial. …
>
> The rate of stroke in the medical-management group was much lower than expected. … Although we expected the rate of stroke to be reduced with intensive management of risk factors — on the basis of post hoc analyses from the WASID trial that suggested that lowering LDL cholesterol and systolic blood pressure could reduce the risk of stroke — we were surprised at the extent and rapidity of the reduction. It is also possible that the combination of aspirin and clopidogrel played an important role in lowering the early risk of stroke. This is supported by the results of a study of transcranial Doppler ultrasonography involving patients with recently symptomatic intracranial stenosis, which showed that aspirin and clopidogrel, as compared with aspirin alone, reduced the frequency of ipsilateral distal microemboli. The effect of the lifestyle modification program on the outcome can be determined only at the end of the follow-up period, but it is unlikely that it contributed to a reduction in the risk of stroke in the medical-management group within 30 days after enrollment. …
>
> The difference between the treatment groups in the rate of the primary end point is driven by the early events, since the rates of the primary end point beyond 30 days are currently similar in the two groups.

b. Other new evidence

The U.S. Wingspan Registry: a prospective, uncontrolled, multicenter, single-arm registry study, Fiorella et al[47]

The U.S. Wingspan Registry was one of two registries referenced in CMS's May 12, 2008, NCD memo. The most recent report of this multicenter registry study provided 12-month follow-up results on 158 patients who underwent treatment of 168 intracranial artery stenoses ≥50% with the Wingspan Stent System at five academic medical centers in the U.S. The average degree of pre-treatment stenosis was 75.2%, and 115 of the treated lesions (68.5%) were ≥70%. The primary end point was any stroke or death within 30 days of the stenting procedure or any ipsilateral stroke after 30 days. The average duration of follow-up was 14.2 months, with 143 patients followed for at least three months, and 110 for at least 12 months. Periprocedural strokes occurred in nine patients (5.7%), and four patients (2.5%) died from these strokes. The cumulative rate for the primary end point was 15.7% for all patients, and 13.9% for patients with high-grade (≥70%) stenosis. Of 13 ipsilateral strokes occurring after 30 days, three resulted in death.

In commenting on the limitations of their study, the investigators noted that 13% of patients were lost to follow-up at the 12-month time period. This may have resulted in bias with respect to the reported one-year event rates. This study also did not include a control group of patients who received medical therapy only, making it impossible to draw conclusions about the relative efficacy or safety of PTAS as a treatment in relation to medical therapy.

Prospective, single-center, uncontrolled case series study, Lanfranconi et al[48]

This study presented outcome data for 16 patients who underwent treatment of 17 severe (>70%) atherosclerotic intracranial artery stenoses with the Wingspan Stent System at a single academic medical center in Italy between March 2006 and July 2008. Nearly all of the patients had neurologic symptoms in the distribution of the stenotic artery prior to treatment. Within one day of the procedure, three patients had periprocedural complications, including two strokes and one intracerebral hemorrhage (17.6% post-procedural complication rate).

Like the Fiorella et al study, the Lanfranconi et al study failed to include a control group of patients who received medical therapy only.

Prospective, single-center, uncontrolled case series study, Yu SC et al[49]

This was a prospective case series study involving 60 patients with either symptomatic ≥70% intracranial stenosis or symptomatic ≥50% intracranial stenosis with recurrent ischemia despite medical therapy who underwent angioplasty and stent placement using the Wingspan Stent System at a single academic medical center in Hong Kong, China, between February 2006 and November 2008. Major outcomes for this series included the following:

- Periprocedural complications: two patients (3.3%)
- Ipsilateral stroke at 30 days: three patients (5.0%)
- Any stroke or death at 30 days: five patients (8.3%)
- Ipsilateral stroke at one year: six patients (10%)
- Any stroke or death at one year: eight patients (13.3%)
- In-stent restenosis at one year: five patients (8.3%)

Again, the Yu SC et al study lacked a control group of patients who received medical therapy alone.

Prospective, randomized, single-center study comparing two sizes of Wingspan Gateway PTA Balloon Catheters, without a medical-therapy alone control group, Yu J et al[50]

This was a prospective, randomized study comparing two different sizes of Gateway PTA Balloon Catheters in 72 subjects with symptomatic 50-99% intracranial stenosis documented by angiographies, who were undergoing intervention with the Wingspan Stent System at a single university hospital in China between April 2007 and September 2009. Thirty-four subjects underwent angioplasty of 36 stenoses prior to stent placement with a catheter that had a balloon diameter sized to 80% of the normal parent vessel diameter, which is the recommended balloon size in the operating manual for the Wingspan Stent System (standard group). Thirty-eight subjects underwent balloon angioplasty of 41 stenoses prior to stent placement with a catheter that had a balloon diameter sized to 100% of the normal parent vessel diameter (experimental group). The in-stent restenosis rate was significantly lower in the experimental group than in the standard group (22.0% versus 33.3%, $P<0.05$). Periprocedural complications included three stenosis-related ischemic strokes (two in the experimental group and one in the standard group),

one parent vessel dissection (experimental group), one arterial perforation (experimental group), and one stent migration (standard group). No deaths were reported in the perioperative phase.

Once again, in this study there was no control group that received medical therapy alone.

Retrospective, single-center case series, Zhao et al[51]

This was a retrospective review of medical records for 27 patients with ≥50% intracranial artery stenosis who underwent treatment of 29 stenotic lesions with the Wingspan Stent System from May to October 2007 at a single university hospital in China. Patients presented with TIAs (N=14), recent acute stroke (N=9), or transient or persistent dizziness (N=4). The mean degree of stenosis was 72% (range 56-88%) at baseline and 25% (range 0-45%) immediately post-stenting. Four patients (14.8%) suffered periprocedural strokes, three of which were ipsilateral.

In this study, just as in the preceding studies, there was no control group that received medical therapy alone.

Prospective, historically controlled cohort study, Jiang et al[52]

This prospective case series study included 100 subjects with 105 angiographically verified ≥70% stenoses of a major intracranial artery who underwent treatment with the Wingspan Stent System within 90 days of a TIA or minor ischemic stroke at a single academic medical center in China between January 2007 and February 2009. All patients were treated with aggressive medical therapy, including dual antiplatelet agents and management of modifiable atherosclerotic risk factors. The primary end point was stroke or death within 30 days or ipsilateral ischemic stroke after 30 days. Data from the ≥70% stenosis subgroup in the WASID trial (discussed previously) were used as a historical control. The cumulative probability of a primary end point in the prospective case series was 7.3% (95% CI 2.0% to 12.5%) at one year, which was lower than the 18% (95% CI 13% to 24%) risk of ipsilateral stroke at one year in the historical control group from the WASID study ($P<0.05$).[d]

The Jiang et al study failed to randomize patients, introducing potential for bias, and relied on a single center, limiting generalizability. The study also failed to involve a contemporaneous control group assigned to medical therapy alone, relying instead on historical data from the WASID study. Such a control is inadequate as a comparator, as noted by Jiang et al, because "medical treatment ... in our days is not the same as it was in the WASID trial, especially regarding the use of antiplatelets, statins, and blood pressure control."[53]

[d] The WASID study enrolled patients with angiographically verified stenosis of 50-99% of a major intracranial artery (carotid, middle cerebral, vertebral, or basilar), a modified Rankin score of 3 or less, and age ≥40 years. The primary end point was a composite of ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke. The study investigators determined that the one-year probability of a primary end point was 15% for patients receiving aspirin. Post hoc subgroup analysis revealed a higher rate of stroke among patients with 70-99% stenosis (23% at one year, 25% at two years). Kasner SE, Chimowitz MI, Lynn MJ, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation. 2006;113:555-563.

Retrospective comparison of medical therapy versus PTAS, Samaniego et al[54]

This retrospective, single-center study reviewed charts of patients treated for symptomatic intracranial atherosclerotic disease at an academic medical center in the U.S. from July 2004 to September 2007. Patients were treated with either "best medical therapy" (undefined, N=58) or PTAS plus antiplatelet agents (N=53). PTAS was performed on 31 lesions using the Wingspan Stent System, and the remaining 26 lesions were treated with other stent devices.[e] The occurrence of transient ischemic attack, stroke, and vascular death following treatment was higher in the PTAS group, with 28.3% events in the PTAS group versus 24.0% events in the medical-therapy group (time frame unspecified).

The Samaniego et al study, like the Jiang et al study, also failed to randomize patients and relied on a single center. Also, the study was small, showed no statistically significant difference between groups, and failed to demonstrate that it was adequately powered to detect such a difference.

IV. Discussion

The evidence from the SAMMPRIS trial conclusively demonstrated that treatment of high-risk patients with intracranial artery stenosis with the Wingspan Stent System provides substantially less benefit and causes significantly more harm in comparison to aggressive medical treatment alone and will not improve outcomes for Medicare patients with intracranial artery stenosis. We therefore urge CMS to conclude that PTAS is not reasonable or necessary for the treatment of cerebral artery stenosis >50% in patients with intracranial atherosclerotic disease, even when furnished in accordance with FDA-approved protocols governing Category B IDE clinical trials.

a. The SAMMPRIS trial provides strong, reliable scientific evidence from which definitive conclusions may be drawn regarding the superiority of medical therapy to PTAS in treating cerebral artery stenosis >50% in patients with intracranial atherosclerotic disease.

The evidence from the SAMMPRIS trial conclusively demonstrated that treatment of high-risk patients with intracranial artery stenosis with the Wingspan Stent System provides substantially less benefit and causes significantly more harm in comparison to aggressive medical treatment alone.

In particular, the SAMMPRIS trial showed that the rates of stroke or death after treatment with PTAS in combination with aggressive medical therapy were more than twice as high compared to treatment with aggressive medical therapy alone. Shockingly, out of every 11 patients treated with the Wingspan Stent System and medical therapy, one additional subject died or suffered a stroke within 30 days in comparison to subjects treated with medical therapy alone. After 30 days, the Kaplan-Meier curves for the cumulative probability of stroke or death for each study group were parallel, meaning that after undergoing a dangerous procedure with a high 30-day complication rate, patients received no additional benefit from stenting in terms of decreased

[e] The authors report performing stenting on 57 lesions in the 53 patients who enrolled in the PTAS group. Samaniego EA, Hetzel S, Thirunarayanan S, et al. Outcome of symptomatic intracranial atherosclerotic disease. Stroke. 2009; 40:2983-87.

long-term risk of stroke or death These dramatic results led the SAMMPRIS investigators to terminate enrollment early based on safety concerns (and because a futility analysis indicated that there was virtually no chance that a benefit from the stenting procedure would be shown if enrollment continued). These results were achieved even though the PTAS procedures were performed by neurointerventionists in the U.S. who were highly trained and experienced in intracranial artery stenting procedures.

The message from the trial could not be clearer: The risks of this intervention substantially outweigh any potential benefit to patients. The study also had strong internal validity: it is the only study of the Wingspan Stent System that possesses all of the attributes associated with best scientific evidence, including the following:

- Use of randomization, clear definition of end points, and adjudication of all end points by an independent panel of neurologists and cardiologists who were not informed of study group assignments (to minimize bias)
- Use of contemporaneous controls to ensure comparability between groups and to minimize bias
- Use of prospective design to ensure thorough and systematic assessment of factors related to outcomes
- Use of sample sizes large enough to rule out chance as a possible explanation to ensure statistically and clinically significant outcomes
- Use of multiple centers to ensure generalizability to the broader population.

b. All of the other existing evidence fails to refute the SAMMPRIS trial results, because no study conducted in *any* group of patients has ever shown that PTAS is superior to medical therapy using a contemporaneous control group

Other than the SAMMPRIS trial, no prospective, randomized, controlled clinical trial has ever compared PTAS to other treatments or optimal medical therapy. CMS has repeatedly noted the weaknesses in information from previously submitted case series and prospective registries, including non-randomization, inherent biases, small sample sizes, short-term follow-up, lack of control groups, and ambiguous results. The more recent studies not yet reviewed by CMS (referred to above), suffer from similar infirmities. These studies reveal important data regarding the risks of the Wingspan Stent System (i.e., use of the device can cause strokes and death) but fail to provide any valid data regarding the relative safety and efficacy of treatment with this device compared to medical therapy alone.

The only study relying on a contemporaneous control group (Samaniego, et al) showed the occurrence of TIA, stroke, and vascular death at 28.3% in the PTAS group and 24.0% in the medical-therapy group. These figures suggest that PTAS is actually *more* dangerous than medical therapy, supporting the results of the SAMMPRIS trial.[55] (However, if this study were presented in isolation, no meaningful conclusions regarding treatment with the Wingspan Stent System in comparison to treatment with medical therapy alone could be drawn, because the differences between groups were not statistically significant and the study was not powered to detect any difference. Also, the study was a retrospective case study and not randomized, there were large imbalances between the two patient groups with respect to many important clinical

variables,[f] the outcomes for all PTAS-treated patients — including patients undergoing PTAS with other devices — were pooled together, and outcome data for the subset of patients treated with the Wingspan Stent System were not presented.)

On the other hand, these studies all demonstrated that treatment with the Wingspan Stent System carries substantial risk of grave harm, especially in the short term, including the risk of death and stroke. Of particular concern is the significant number of periprocedural adverse events that can be caused by placement of the Wingspan Stent System, including the following:

- Ischemic or hemorrhagic stroke (periprocedural stroke rates ranged from 5.7% to 17.6%)
- Death (periprocedural mortality rates ranged from 0% to 2.5%)
- TIAs
- Intracranial artery dissection
- Intracranial artery perforation
- Stent thrombosis

In addition, the risk of any stroke or death within 30 days post-stenting ranged from 5% to 9.6%.

It is also important to recognize that neurological morbidity in patients across these studies was likely underestimated for a variety of reasons, including a lack of independent neurological adjudication of events, inadequately defined study end points, and incomplete patient follow-up.

Such outcomes establish that stenting offers no benefit over currently available medical therapy and poses grave safety risks.

c. Results from the SAMMPRIS trial are generalizable to the Medicare population currently covered under the PTAS NCD.

The subjects who enrolled in the SAMMPRIS trial are representative of the Medicare population who would be exposed to PTAS under the current NCD (cerebral artery stenosis $\geq$50%), because they represent a subset of patients within that category long understood to be at particularly high risk for future stroke and death (i.e., angiographically verified stenosis of 70-99% of the diameter of a major intracranial artery).[56] While future IDE studies might enroll a subject population with a different clinical characteristics profile than that of the subjects in the SAMMPRIS trial, there is no evidence at this time that relative outcomes would be any better for that hypothetical population than they were for the SAMMPRIS subjects. Furthermore, given the results of the SAMMPRIS trial, it is highly improbable that treatment with the Wingspan Stent System would provide benefits that outweigh the known risk of serious harm caused by the device for any segment of the Medicare population. Therefore, it would be arbitrary for CMS to speculate that PTAS could be reasonable and necessary for patients enrolled in such a trial when it was unsafe, ineffective, and entirely unnecessary for SAMMPRIS subjects.

[f] These include prior TIAs, presence of diffuse intracranial atherosclerosis, stroke or TIA as the presenting condition, and severity score for stroke at presentation.

d. CMS should not fund future Category B IDEs because it would be a mistake for the FDA to categorize any future IDE as Category B.

CMS should not have determined initially to cover treatment with the Wingspan Stent System in the context of a Category B IDE because evidence on its safety and effectiveness has always been so weak that investigations involving the Wingspan and other similar stent systems could not reasonably have fallen into Category B. (The Wingspan Stent System is in Class III, and underlying questions about the safety and effectiveness have not been resolved). The decision to cover PTAS in the context of such investigations is even less reasonable given the present information. The results of the SAMMPRIS trial have conclusively shown that the device is *not* safe or effective. FDA would be wrong to categorize any IDE involving this device type as a Category B IDE, and CMS should not compound FDA's mistake by covering the costs of using the device in such a trial.

e. Further IDE trials of the Wingspan Stent System would be unethical.

Based on the data from the SAMMPRIS study, enrollment of Medicare beneficiaries in future clinical trials involving PTAS with the Wingspan Stent System would be unethical, as the procedure demonstrates no likelihood of benefit to the subjects and would expose them to significant, unnecessary risks when compared to medical therapy alone.

V. Conclusion

- The results from the SAMMPRIS trial make it clear that the Wingspan Stent System (and by extension, similar systems) is unreasonably dangerous, exposing patients to a more than two-fold increase in risk of stroke or death.
- There is no evidence reasonably supporting the safety and efficacy of the Wingspan Stent System in *any* population.
- The results of the SAMMPRIS trial are generalizable to the Medicare population that would be eligible for coverage under the current NCD because the subjects enrolled in the SAMMPRIS trial population represent a subset of the patients potentially covered under the NCD, and there is no evidence than any other subset of patients would respond differently.
- CMS should not fund the Wingspan Stent System or similar systems in the context of any future Category B IDEs because it would be unreasonable for the FDA to categorize any future IDEs involving the Wingspan Stent System or similar systems as Category B. The device is in Class III, and underlying questions of safety and effectiveness have not been resolved (or more accurately, the device has been conclusively shown to be unsafe and ineffective).
- Further IDE studies of the Wingspan Stent System would be unethical.

The current CMS policy regarding PTAS reimbursement exposes Medicare beneficiaries to risk by facilitating their enrollment in dangerous and unethical clinical trials. Only by irrational, unsupported, and dangerous speculation could future investigators hope to achieve better outcomes in some subset of the Medicare population. Such a future investigation would expose patients to an invasive and inherently dangerous PTAS procedure with the knowledge that even

successful stent placement will more than double the patient's chance of death or stroke. Such a trial should not be conducted at all, let alone funded by CMS. It is not reasonable or necessary, and it is, in fact, unethical for CMS to continue to fund such experiments. We therefore urge CMS to revoke the existing NCD on PTAS and exclude Medicare coverage of this service.

Sincerely,

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