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AJNR Am J Neuroradiol 2011, 32 (9) 1711-1713

doi: <https://doi.org/10.3174/ajnr.A2700>

<http://www.ajnr.org/content/32/9/1711>

This information is current as of May 30, 2025.

Stenting for Intracranial Aneurysms: How to Paint Oneself into the Proverbial Corner

Intracranial stents designed to assist coil embolization of intracranial aneurysms have been around for nearly a decade. Yet we know very little about them. The article by Hwang et al in this issue of the *American Journal of Neuroradiology*¹ is a valuable contribution to an ongoing controversy, but it raises more questions than it answers. The following important questions need to be addressed properly: When should stents be used, how effective are they, and what price must patients pay in terms of complications? This article has an air of *déjà vu*: How intracranial stents became a part of aneurysm treatment is a typical example of how we have gone about introducing new tools and techniques. We need to do this better to protect patients from our contradictions.

When the first stent was originally introduced as a Humanitarian Use Device, the application was “not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose.”² In other words, there is no need to show that the device works. “The application, however, must contain sufficient information for FDA [US Food and Drug Administration] to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.”² These are very vague statements.

Let us look at how they can be interpreted. The initial FDA application for the first coil-assist stent included the results of research on 35 rabbits. As far as we can tell, this preclinical research has never been published.³ Thirty-one patients treated in Europe were presented, 16 with asymptomatic aneurysms. The mean aneurysm size was 7.4 ± 4.3 mm. There were 12 serious adverse events in 5 patients (17% of the 29 patients who got the stent; 95% confidence interval [CI], 3%–31%). There were 21 other adverse events. The Center for Devices and Radiologic Health (CDRH) determined that the device “will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health . . . for the treatment of wide-neck, intracranial, saccular aneurysms that are not amenable to treatment with surgical clipping outweighs the risks of illness or injury,” and issued an approval order on September 11, 2002.³ Three questions immediately come to mind:

1) What would it take for the CDRH to judge that a device would need further studies to prevent “unreasonable or significant risks”?

2) How dismal must the prognosis be to justify the introduction of an experimental device, with no proof that it works and so little clinical experience? Half of the patients had asymptomatic unruptured aneurysms, a disease that may not justify such a blind leap of faith in new technology.

3) Finally, how could the CDRH judge that patients in-

cluded in the application and future patients in whom the device would be implanted would not be amenable to surgical clipping, a more standard approach?

One of the very first reports in 2005 should have tempered the rate of adoption of stents by the endovascular community: Stent placement led to adverse events in 8 of 32 treated patients (25%), resulting in a permanent neurologic deficit or death in 4 patients (12.5%; 95% CI, 2%–25%).⁴

However, you cannot stop progress. By September 2009, at least 1 such stent had been used in more than 45,000 patients. The quarterly report of the company in 2010 mentions that “our . . . adjunctive stent in both Europe and the US continues to receive positive feedback from physicians. In the third quarter [of 2010] . . . sales in US and Europe were up 34% compared with the third quarter last year and 24% versus the second quarter of this year.”⁵

What has sparked such enthusiasm within our community? There must be evidence showing that patients have greatly benefited from the use of this device. Many case series have been published. Looking at the abstracts of these articles, one cannot miss the enthusiasm or doubt the reality of publication bias. Some even sound like advertisements: “The aim of this study was to re-enforce the use of this stent for EVT [endovascular treatment] of wide-necked cerebral aneurysms.” “The . . . is very useful for EVT of wide-necked intracranial aneurysms because it is easy to navigate and to deploy accurately.”⁶ “In treating complex intracranial aneurysms, the . . . stent-assisted coiling is a secure and effective technique.”⁷ “For complex unruptured middle cerebral artery aneurysms, EVT by using a self-expandable intracranial stent was feasible, safe, and durable and could be considered as the first-option treatment.”⁸

Multiple other devices have since taken the same path, with equally positivistic case series.⁹

Perhaps case series in our literature should be followed by the same kind of notice that can be found at the end of industry press releases: “This press release contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934. Forward-looking statements may be identified by words like ‘anticipate,’ ‘expect,’ ‘project,’ ‘believe,’ ‘plan,’ ‘estimate,’ ‘intend,’ and similar words. These forward-looking statements are based on our beliefs, assumptions, and estimates by using information available to us at the time and are not intended to be guarantees of future events or performance.”⁵

Not a single one of these series, no matter how enthusiastic, has been convincing. One large experience, published last year,¹⁰ clearly shows the dilemma as well as the drift. It seems that follow-up angiographic recurrences of aneurysms treated with stent-assisted coiling, as far as they can be compared with those treated with coiling alone, were improved from 33.5% to 15%, while procedure-related morbidity and mortality were much higher with stent placement (7.4% versus 3.8%; $P = .0001$). However, groups may not be comparable, with aneurysms chosen for stent placement more often being unruptured sidewall aneurysms, as opposed to bifurcation aneurysms. Stented aneurysms were not followed up as long (a mean of 14 months compared with 22 months in coil-only patients). All these are factors that would tend to decrease recurrence rates for stented aneurysms. Most interesting, in

more than half of the patients, stents were implanted after coiling, rendering absurd the claim that stents are mainly used to treat patients untreatable by other means. Encouraged by countless “forward-looking” presentations by physicians and engineers, the reason for stent use has shifted away from being only for otherwise uncoilable lesions. The rationale for stent use in addition to coils is now (supposedly) because it decreases the risk of recurrences. This hypothesis has never been formally tested, much less proved, to our knowledge.

Following publication of this large series, a letter to the editor commented, “This is an alarmingly high rate of serious complications, especially in a population harboring mostly unruptured aneurysms (with benign natural history) located on sites that are easily accessible for surgery.”¹¹

Another article in favor of moderation appears in this issue. There are 3 strengths to the article by Hwang et al,¹ which directly addresses our hopes for decreasing recurrences: First, the authors, during the years, have mastered alternative techniques to manage wide-neck aneurysms (multiple-catheter technique, balloon-assistance) and are thus capable of offering a comparison between groups that are similarly challenging. Second, while many reports of new devices tend to compare recurrences occurring years after simple coiling with 6-month recurrence rates for the new device, the authors have fixed the time period for angiographic follow-up at 2 years for all patients to allow a fairer comparison of recurrence rates. Finally, the article emphasizes the common pitfall of finding that a new device can lead to an improved result at follow-up. As the authors have shown, most of time, this phenomenon simply reflects more frequent incomplete occlusions immediately, which have then a higher chance of showing improved results in a delayed fashion, especially relevant when we remember that the baseline images are usually obtained with the patient under procedural doses of heparin. When simple platinum coiling was assessed in a similar fashion, there was no difference in the number of patients who had “improved”.¹

Nevertheless, the methodology used in all reports, so far, is weak, and by all acceptable standards, the results cannot be used to guide clinical decisions. A decade has passed, and an amazing number (at least 45 000) of patients have been treated with stents. What happened to them? What can we learn from this? Nobody can tell.

Painting Oneself into the Proverbial Corner

We want access to the novelty, and we want it fast. If we justify the use of a device without evidence that it works by claiming that the patient cannot be treated otherwise, a valid comparison with any other treatment alternative becomes impossible without falling into a contradiction. How will the device ever be judged useful or harmful? This is a recurring problem with new devices introduced in this fashion. This principle of non-contradiction can even become part of a regulation: In Canada, the Humanitarian Device Exemption process allows the use of new thrombectomy devices, embolic material that is supposed to replace coils, or flow-diverters for any patient that we claim needs them, but we cannot obtain authorization for devices if our intention is to do a trial comparing the new approach with standard treatment. Either I am a clinician and I care for patients and my personal judgment that the patient needs the device remains unquestioned or I design and pro-

pose a trial; but then I am a scientist doing research, who does not truly care for patients. Needless to say, this dichotomy is absurd. When offering novel and promising treatment strategies, we have the responsibility to protect patients from enthusiasm, wishful thinking, fashion, marketing, conflict of interest, and false promises. Hence in this context, there is no better care than to offer the novelty only within the context of a randomized clinical trial (RCT). We have a collective duty to remember that medicine does not always work and that we have been disappointed (and wrong) before; when we offer promising treatment, we must protect the patients who blindly put their faith in us.

Let us be honest: The claim that patients cannot be treated without the new device is rarely, strictly speaking, true. Intracranial stents are not used solely in patients in whom other options are impossible. Another less novel option nearly always exists. Most of the time, another endovascular option is possible. If not, surgical clipping or even conservative management remain real and valuable, though perhaps less “enthusiastic” options. Once more we have demonstrated our failure to introduce a new device in a safe effective manner. There is no need to lament about misplaced regulatory pathways or to wait for industry to propose the necessary trials. This can only be within the competence and the responsibility of clinicians.¹²

The problem is that we have artificially separated care and research. We pretend to know what is best, and make important decisions on behalf of patients, hiding from them that our convictions are only beliefs, or, in other words, hypotheses that need testing and confirmation. Once more we are using retrospective case series, doing biased research after the fact, and using patients who consented for care but not as uncontrolled research subjects. The path required to do a better job and now to come out of this mess is clear: RCTs. All these case series and 10 years of use only tell us that there is a hope of improving long-term results in certain patients, but this could come at the cost of increased immediate complications. The balance between hopes and fears and positive and negative perspectives with novelty will continue to remain unknown, continue to be the object of expert speculations, until formally tested in a trial. We insist that the emphasis is not to produce research data to answer scientific questions, but rather, properly conducted research (read randomized trials) is the way to offer the best possible treatment, now, before any scientific answer arrives. Patients would then be told the truth: that we remain uncertain about what is best and that the new device may offer some benefit, but at an as-of-yet unknown cost.

A prudent physician who cares for patients should only use devices that have been proven beneficial. When proof does not exist, the physician can offer the new device, but only within the context of a trial. In this way, the patient has a chance to benefit from the new promising device but, most important, an equal chance to escape false promises, new complications, or other undesirable-but-unknown aspects of the novel device use. The multiple forces acting on those providing clinical care are simply too strong; the risks of being wrong are too high to continue to care for patients the way we currently do. The patient must no longer be deprived of the protection that only proper scientific methods can provide. RCTs have become increasingly difficult, time-consuming, and costly.¹³ How-

ever, what could be more time-consuming and costly than forever adopting new devices that can never be proven beneficial or harmful?

We submit that 2 types of trials are possible: 1) For those who believe that stent placement is a way to replace surgical clipping in difficult cases, they have the burden of the proof, and they should offer participation in a trial comparing clipping and stent-assisted coiling (in the spirit of the Canadian Unruptured Aneurysm Endovascular vs. Surgery [CURES] trial¹⁴). 2) For those who believe that stent placement is a promising option for patients who can undergo coiling without stents, they should offer a randomized comparison between coiling with or without stent placement (like the Stenting in the Treatment of Aneurysms trial, constructed in the spirit of the Patients Prone to Recurrence after Endovascular Treatment trial^{15,16}).

We have repeatedly demonstrated the failure of the current way of doing things. It is now time to provide care under the protection of scientific methods. As clinicians, our patients should either receive care that is guided by evidence or be treated with as-yet-unproven therapies under the protection of a well-designed RCT.

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<http://dx.doi.org/10.3174/ajnr.A2700>