

HydroCoils Are Associated with Lower Angiographic Recurrence Rates Than Are Bare Platinum Coils in Treatment of “Difficult-to-Treat” Aneurysms: A Post Hoc Subgroup Analysis of the HELPS Trial

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ABSTRACT

BACKGROUND AND PURPOSE: The HydroCoil Endovascular Aneurysm Occlusion and Packing Study was a randomized controlled trial that compared HydroCoils to bare platinum coils. Using data from this trial, we performed a subgroup analysis of angiographic and clinical outcomes of patients with “difficult-to-treat” aneurysms, defined as irregularly shaped and/or having a dome-to-neck ratio of <1.5 .

MATERIALS AND METHODS: Separate subgroup analyses comparing outcomes of treatment with HydroCoils to that of bare platinum coils were performed for the following: 1) irregularly shaped aneurysms, 2) regularly shaped aneurysms, 3) aneurysms with a dome-to-neck ratio of <1.5 , and 4) aneurysms with a dome-to-neck ratio of ≥ 1.5 . For each subgroup analysis, the following outcomes were studied at the last follow-up (3–18 months): 1) any recurrence, 2) major recurrence, 3) re-treatment, and 4) an mRS score of ≤ 2 . Multivariate logistic regression analysis was performed to determine if the HydroCoil was independently associated with improved outcomes in these subgroups.

RESULTS: Among the patients with an irregularly shaped aneurysm, the HydroCoil was associated with lower major recurrence rates than the bare platinum coils (17 of 66 [26%] vs 30 of 69 [44%], respectively; $P = .046$). Among the patients with an aneurysm with a small dome-to-neck ratio, the HydroCoil was associated with lower major recurrence rates than the bare platinum coils (18 of 73 [24.7%] vs 32 of 76 [42.1%], respectively; $P = .02$). No difference in major recurrence was seen between HydroCoils and bare platinum coils for regularly shaped aneurysms (42 of 152 [27.6%] vs 52 of 162 [32.1%], respectively; $P = .39$) or aneurysms with a large dome-to-neck ratio (41 of 145 [28.3%] vs 50 of 155 [32.3%], respectively; $P = .53$).

CONCLUSIONS: This unplanned post hoc subgroup analysis found that HydroCoils are associated with improved angiographic outcomes in the treatment of irregularly shaped aneurysms and aneurysms with a dome-to-neck ratio of <1.5 . Because this was a post hoc analysis, these results are not reliable and absolutely should not alter clinical practice but, rather, may inform the design of future randomized controlled trials.

ABBREVIATIONS: D/N = dome-to-neck ratio; HELPS = HydroCoil Endovascular Aneurysm Occlusion and Packing Study

The HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS) was a randomized controlled trial that compared the rate of clinical and angiographic outcomes in patients treated with the HydroCoil Embolic System (MicroVention, Tustin, California) and those treated with bare platinum coils.¹ This study found a statistically significant lower rate of major recurrence among aneurysms treated with the HydroCoil

(a secondary trial outcome) but found no difference in the rates of trial primary composite outcome, which was a composite measure of adverse outcomes including major aneurysm recurrence at 18 months after treatment and procedure-related deaths and morbidity that resulted in the patients not having follow-up angiography.

Hydrogel coils are manufactured with an expansile hydrogel that has been shown to result in improved aneurysm filling when compared with bare platinum coils.² Experimental models have suggested that hydrogel-coated coils are more effective in filling areas of potential aneurysm growth, such as aneurysm rupture points, lobulations, and daughter sacs, and along the aneurysm neck.^{3–5} Aneurysms with a small dome-to-neck ratio (D/N) (<1.5) and lobulated/irregularly shaped aneurysms have been identified as difficult to coil and at high risk of recanalization after

Received November 13, 2014; accepted after revision January 30, 2015.

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<http://dx.doi.org/10.3174/ajnr.A4349>

coil embolization with bare platinum coils.⁶ On the basis of findings from experimental models, we hypothesized that HydroCoils would result in a significantly lower rate of aneurysm recurrence than would bare platinum coils in “difficult-to-treat” aneurysms, defined as irregularly shaped aneurysms and aneurysms with a D/N of <1.5. We evaluated this hypothesis by using data from the HELPS trial and performing the following subgroup analyses: 1) analysis of angiographic and clinical outcomes in treatment groups of patients with an irregularly or regularly shaped aneurysm treated with the HydroCoil versus those treated with a bare platinum coil and 2) analysis of angiographic and clinical outcomes of patients with a small D/N (<1.5) aneurysm or large D/N (≥ 1.5) aneurysm treated with the HydroCoil versus those treated with a bare platinum coil. Because this was not a prespecified subgroup analysis, it is important to mention that the results of this study should not be used to alter clinical management but, rather, to inform the design of future clinical trials.

MATERIALS AND METHODS

Patient Population

The HELPS trial enrolled patients from 24 centers in 7 countries. Enrolled were patients 1) with a previously untreated intracranial aneurysm of 2–25 mm in maximum diameter, 2) aged 18–75 years, 3) determined by a neurovascular team to benefit from coiling, 4) who were not pregnant, 5) who had anatomy such that endovascular occlusion was deemed possible, 6) who had not been previously enrolled in another trial, and 7) whom the neurointerventionist performing the surgery was content or willing to randomly assign to bare platinum or HydroCoil Embolic System coils. Patients who had more than one aneurysm that required treatment in one procedure were excluded. Details regarding informed consent, ethics approval, the coiling procedures, randomization techniques, baseline demographics, and data handling are shown elsewhere.^{1,7}

For the purposes of this analysis, we identified the following subgroups of patients: 1) patients with an irregularly shaped aneurysm, 2) patients with a regularly shaped aneurysm, 3) patients with an aneurysm with a small D/N (<1.5), and 4) patients with an aneurysm with a large D/N (≥ 1.5). Analysis of outcomes in these subgroups was not prespecified in the design of the HELPS trial. An aneurysm was considered irregularly shaped if it was multilobulated (ie, bilobed or multilobular). These features were recorded at the time of randomization, and trial arms were matched on them as part of the minimization algorithm (also minimized on aneurysm size, rupture status intention to use a coil assist device, and randomized in the United States versus anywhere else in the world).⁷

Outcomes

For each subgroup of patients, the following baseline and procedural characteristics were obtained: sex, age, D/N, rupture status, use of assist device, aneurysm shape, and baseline World Federation of Neurosurgical Societies score. For the purposes of this subgroup analysis, we studied the following individual outcomes: 1) any recurrence, 2) major recurrence, 3) modified Rankin Scale of ≤ 2 , and 4) re-treatment. The presence of aneurysm recurrence

was defined as increased contrast filling of an aneurysm by using a revised 3-point Montreal scale (complete, near-complete, or incomplete occlusion). A major recurrence was defined as a recurrence sufficiently large enough to technically allow placement of further coils as defined by the core laboratory blind assessment of angiograms.⁸ Re-treatment was classified as any further treatment of the target aneurysm. The mRS assessment was performed by a postal questionnaire completed by each patient or by his or her main caretaker and was independent of the interventional team. The outcomes listed above were studied at the last clinical or angiographic follow-up. For each subgroup, we compared the rate of these outcomes between patients randomly assigned to the HydroCoil group and those randomly assigned to the bare platinum group.

Statistical Analysis

All means are presented with their corresponding standard deviations. Comparisons between groups of these categorical outcomes were performed by using the Fisher exact test or ANOVA. Multivariate logistic regression analyses were performed to determine if differences between the HydroCoil and control groups existed for the following outcomes: 1) any recurrence at last follow-up, 2) major recurrence at last follow-up, 3) an mRS score of ≤ 2 at last follow-up, and 4) re-treatment at last follow-up. Multivariate logistic regression analyses were performed to determine if coil type was independently associated with any of the outcomes listed above for each subgroup. When performing subgroup analysis according to aneurysm shape, we adjusted for aneurysm size, D/N, rupture status, and use of an assist device. When performing the subgroup analysis according to aneurysm D/N, we adjusted for aneurysm size, shape, rupture status, and use of an assist device. Statistical analysis was performed by using JMP 10.0 Pro (www.jmp.com; SAS Institute, Cary, North Carolina).

Role of Funding Source

The study sponsor (MicroVention) had no part in trial design, data collection, analysis, or reporting, which were organized by the steering committee. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

RESULTS

Patient and Aneurysm Characteristics

Details of baseline patient characteristics for all patients and aneurysms treated in the HELPS trial were described previously.¹ One hundred fifty-three aneurysms (30.7%) were irregular in shape, and 346 aneurysms (69.3%) were regular in shape. When comparing patient characteristics according to aneurysm shape, there was no difference in the proportion of aneurysms in each group that had recently ruptured; 56.9% of the irregularly shaped aneurysms (87 of 153) and 51.6% of the regularly shaped aneurysms (179 of 346) had recently ruptured ($P = .29$). There was a higher proportion of small aneurysms in the irregularly shaped aneurysm group (36.6% [56 of 153]) than in the regularly shaped aneurysm group (20.8% [72 of 346]) and, correspondingly, a higher proportion of large aneurysms in the regularly shaped aneurysm group (19.3% [67 of 346]) than in the irregularly shaped

aneurysm group (10.5% [16 of 153]) ($P = .0003$). However, the overall mean maximum aneurysm dimension was higher in the irregularly shaped aneurysm group than in the regularly shaped aneurysm group (8.9 ± 3.7 vs 7.5 ± 3.2 mm, respectively; $P < .0001$). These data are summarized in Table 1.

One hundred sixty-four aneurysms had a D/N of <1.5 (32.9%), and 335 aneurysms (67.1%) had a D/N of ≥ 1.5 . The proportions of recently ruptured aneurysms were similar in the small D/N group (51.2% [84 of 164]) and the large D/N group

(54.2% [182 of 335]; $P = .57$). As expected, patients in the small D/N group were more likely to have had an assist device used than those in the large D/N group (55.6% [90 of 164] vs 40.4% [133 of 335], respectively; $P = .002$). The distributions of aneurysm sizes were similar between groups ($P = .05$); however, the overall mean aneurysm size was lower in the small D/N group than in the large D/N group (7.2 ± 3.1 vs 8.2 ± 3.5 mm, respectively; $P = .001$). These data are summarized in Table 2.

Table 1: Characteristics of patients with an irregularly or regularly shaped aneurysm

Characteristic	Irregularly Shaped	Regularly Shaped	P
No. (%)	153 (30.7)	346 (69.3)	
Mean (SD) age, y	52.3 (11.8)	52.1 (11.6)	.86
Female, no. (%)	108 (70.6)	243 (70.0)	.92
Recently ruptured, no. (%)	87 (56.9)	179 (51.6)	.29
Assist device used, no. (%)	79 (52.3)	144 (42.4)	.05
Small D/N ratio, no. (%)	43 (28.1)	121 (34.9)	.15
Aneurysm size, no. (%)			
Small	56 (36.6)	72 (20.8)	.0003
Medium	81 (52.9)	208 (59.9)	
Large	16 (10.5)	67 (19.3)	
Mean (SD) size, mm	8.9 (3.7)	7.5 (3.2)	$<.0001$
WFNS score, no. (%)			
0	62 (40.5)	156 (45.0)	.38
I	73 (47.7)	161 (46.4)	
II	16 (10.5)	26 (7.5)	
III	1 (0.7)	4 (1.2)	
VI	1 (0.7)	0 (0.0)	

Note:—D/N indicates dome-to-neck ratio; WFNS, World Federation of Neurological Societies.

Table 2: Characteristics of patients with a small D/N aneurysm versus those with a large D/N aneurysm

Characteristic	D/N		P
	Small	Large	
Total patients, no. (%)	164 (32.9)	335 (67.1)	
Mean (SD) age, y	52.5 (11.4)	51.9 (11.7)	.64
Female, no. (%)	118 (72.0)	233 (69.4)	.6
Recently ruptured, no. (%)	84 (51.2)	182 (54.2)	.57
Assist device used, no. (%)	90 (55.6)	133 (40.4)	.002
Irregular shape, no. (%)	121 (73.8)	226 (67.3)	.15
Aneurysm size, no. (%)			
Small	36 (22.0)	47 (14.0)	.05
Medium	93 (56.7)	196 (58.3)	
Large	35 (21.3)	93 (27.7)	
Mean (SD) size, mm	7.2 (3.1)	8.2 (3.5)	.001
WFNS, no. (%)			
0	76 (46.3)	142 (42.3)	.51
I	71 (43.3)	163 (48.5)	
II	14 (8.5)	28 (8.3)	
III	3 (1.8)	2 (0.6)	
VI	0 (0.0)	1 (0.3)	

Table 3: Univariate outcomes according to aneurysm shape

Outcome	Irregularly Shaped			Regularly Shaped		
	HydroCoil, n/N (%)	Bare Platinum, n/N (%)	P	HydroCoil, n/N (%)	Bare Platinum, n/N (%)	P
Good neurologic outcome	63/70 (90.0)	63/73 (86.3)	.61	141/162 (87.0)	146/164 (89.0)	.58
Any recurrence	23/66 (34.9)	41/69 (59.4)	.004	65/151 (43.0)	75/162 (46.3)	.57
Major recurrence	17/66 (25.8)	30/69 (43.5)	.046	42/152 (27.6)	52/162 (32.1)	.39
Re-treatment	2/76 (2.6)	3/77 (3.9)	.66	4/173 (2.3)	8/173 (4.6)	.26

Univariate Outcomes According to Aneurysm Shape

For irregularly shaped aneurysms, HydroCoil treatment was associated with significantly lower rates of any angiographic recurrence than treatment with a bare platinum coil (34.9% [23 of 66] vs 59.4% [41 of 69], respectively; $P = .004$) and a significantly lower rate of major recurrence (25.8% [17 of 66] vs 43.5% [30 of 69], respectively; $P = .046$). There was no difference in re-treatment rates between the HydroCoil and bare platinum groups (2.6% [2 of 76] vs 3.9% [3 of 77], respectively; $P = .66$). The rates of good neurologic outcome were similar in the HydroCoil and bare platinum groups (90.0% [63 of 70] vs 86.3% [63 of 73], respectively; $P = .61$).

For regularly shaped aneurysms, there was no difference in the rates of any recurrence between the HydroCoil and bare platinum groups (43.0% [65 of 151] vs 46.3% [75 of 162], respectively; $P = .57$) or in the rates of major recurrence (27.6% [42 of 152] vs 32.1% [52 of 162], respectively; $P = .39$). There was no difference in re-treatment rates between the HydroCoil and bare platinum groups (2.3% [4 of 173] vs 4.6% [8 of 173], respectively; $P = .26$). The rates of good neurologic outcome were similar in the HydroCoil and bare platinum groups (87.0% [141 of 162] vs 89.0% [146 of 164], respectively; $P = .58$). These data are summarized in Table 3.

Univariate Outcomes According to Aneurysm Dome-to-Neck Ratio

For aneurysms with a small D/N, HydroCoil treatment was associated with significantly lower rates of any angiographic recurrence than treatment with a bare platinum coil (35.6% [26 of 73] vs 55.3% [42 of 76], respectively; $P = .02$) and a significantly lower rate of major recurrence (24.7% [18 of 73] vs 42.1% [32 of 76], respectively; $P = .02$). There was no difference in re-treatment rates between the HydroCoil and bare platinum groups (1.2% [1 of 83] vs 3.7% [3 of 81], respectively; $P = .36$). The rates of good neurologic outcome were similar in the HydroCoil and bare platinum groups (88.3% [68 of 77] vs 89.7% [70 of 78], respectively; $P = .80$).

For aneurysms with a large D/N, there was no difference in the rates of any recurrence between the HydroCoil and bare platinum groups (43.1% [62 of 144] vs 47.7% [74 of 155], respectively; $P = .49$) or the rates of major recurrence (28.3% [41 of 145] vs 32.3%

Table 4: Univariate outcomes according to aneurysm D/N

Outcome	Small D/N			Large D/N		
	HydroCoil, n/N (%)	Bare Platinum, n/N (%)	P	HydroCoil, n/N (%)	Bare Platinum, n/N (%)	P
Good neurologic outcome	68/77 (88.3)	70/78 (89.7)	.80	136/155 (87.7)	139/159 (87.4)	1.00
Any recurrence	26/73 (35.6)	42/76 (55.3)	.02	62/144 (43.1)	74/155 (47.7)	.49
Major recurrence	18/73 (24.7)	32/76 (42.1)	.02	41/145 (28.3)	50/155 (32.3)	.53
Re-treatment	1/83 (1.2)	3/81 (3.7)	.36	5/166 (3.0)	8/169 (4.7)	.57

[50 of 155], respectively; $P = .53$). There was no difference in re-treatment rates between the HydroCoil and bare platinum groups (3.0% [5 of 166] vs 4.7% [8 of 169], respectively; $P = .57$). The rates of good neurologic outcome were similar in the HydroCoil and bare platinum groups (87.7% [136 of 155] vs 87.4% [139 of 159], respectively; $P = 1.00$). These data are summarized in Table 4.

Multivariate Analysis

When we adjusted for aneurysm size, D/N, rupture status, and use of an assist device in the irregularly shaped aneurysm subgroup, use of the HydroCoil was associated with decreased odds of any recurrence (OR, 0.34 [95% CI, 0.19–0.89]; $P = .003$) and decreased odds of major recurrence (OR, 0.42 [95% CI, 0.19–0.89]; $P = .02$). There was no difference in the odds of good neurologic outcome (OR, 1.56 [95% CI, 0.55–4.69]; $P = .40$) or re-treatment (OR, 0.57 [95% CI, 0.07–3.76]; $P = .56$).

In the regularly shaped aneurysm subgroup, HydroCoils were not associated with any improvement in the odds of any recurrence (OR, 0.87 [95% CI, 0.54–1.39]; $P = .55$), major recurrence (OR, 0.79 [95% CI, 0.47–1.32]; $P = .36$), good neurologic outcome (OR, 0.81 [95% CI, 0.41–1.59]; $P = .54$), or re-treatment (OR, 0.45 [95% CI, 0.11–1.49]; $P = .19$) when we compared HydroCoils with bare platinum coils. These data are summarized in Table 3.

When we adjusted for aneurysm size and shape, rupture status, and use of an assist device in the small D/N aneurysm subgroup, the use of HydroCoils was associated with decreased odds of any recurrence (OR, 0.44 [95% CI, 0.22–0.87]; $P = .02$) and major recurrence (OR, 0.42 [95% CI, 0.19–0.89]; $P = .02$) in the treatment of aneurysms with a small D/N. There was no difference in good neurologic outcomes (OR, 0.81 [95% CI, 0.29–2.28]; $P = .69$) or re-treatment rates (OR, 0.26 [95% CI, 0.01–2.16]; $P = .22$).

For the large D/N aneurysm subgroup, HydroCoils were not associated with any significant improvement in the odds of any recurrence (OR, 0.78 [95% CI, 0.48–1.26]; $P = .32$), major recurrence (OR, 0.79 [95% CI, 0.47–1.33]; $P = .38$), good neurologic outcome (OR, 1.04 [95% CI, 0.53–2.06]; $P = .91$), or re-treatment (OR, 0.61 [95% CI, 0.18–1.87]; $P = .38$). These data are summarized in Table 4.

DISCUSSION

In this unplanned post hoc subgroup analysis of patients in the HELPS trial, we found that embolization with the HydroCoil, compared with a bare platinum coil, was associated with significantly lower rates of any recurrence and major recurrence in aneurysms with a small D/N and irregularly shaped aneurysms. This improvement was seen on the univariate analysis and when we

adjusted for confounding variables such as aneurysm size, use of adjunctive devices, and aneurysm rupture status, all of which are independently associated with propensity for aneurysm recurrence. No difference was seen between HydroCoils and bare platinum coils in the treatment of aneurysms with a large D/N and regularly shaped aneurysms. These findings are important, because patients with irregularly shaped aneurysms and aneurysms with a small D/N are generally at a higher risk of recurrence; thus, identifying safe and effective endovascular treatments for such aneurysms is of utmost importance.

A number of previous studies have found that aneurysms with a small D/N and irregularly shaped aneurysms are more difficult to treat and at higher risk of recurrence after endovascular coiling with bare platinum coils than aneurysms with a large D/N and regularly shaped aneurysms, respectively.^{6,9–12} This analysis on the HELPS control arm confirms these as risk factors for recurrence. Aneurysms with a small D/N are prone to have neck remnants after coiling, which can result in recanalization of the aneurysm, because they are exposed to high wall shear stress and blood-flow velocities.^{13,14} Irregular aneurysm geometries also present a challenge in endovascular coiling. Aneurysms with daughter sacs or multilobular configurations are prone to higher rates of growth and rupture.^{15,16} Because of this tendency, achieving high packing attenuations in such aneurysms may be important for sufficiently reducing intra-aneurysmal blood-flow velocity and wall shear stress to prevent further growth of such weak points within the aneurysm.¹⁷

There are a number of potential reasons why HydroCoils were independently associated with reduced recurrence rates in the treatment of wide-neck and irregularly shaped aneurysms. As mentioned previously, irregularly shaped aneurysms with multilobular configurations or daughter sacs have been shown to be more likely to grow and rupture. Because HydroCoils are designed with an expansile hydrogel that fills more of the aneurysmal lumen than platinum coils, they provide higher rates of aneurysm packing.^{18,19} By expanding and achieving higher packing attenuations, HydroCoils may allow for increased conformation to geometric irregularities of intracranial aneurysms, such as aneurysm rupture points.³ The expansile property of these coils likely explains why the recurrence rates for aneurysms with a small D/N treated with HydroCoils were lower than for those treated with bare platinum coils. Histologic studies in humans and rabbits have shown that HydroCoils are more effective at sealing the aneurysm neck.^{4,20} Killer et al²¹ found that HydroCoils resulted in higher rates of angiographic and histologic occlusion at both the aneurysm neck and the dome, which increased over time.

Bare platinum and modified coils have been compared in a number of studies. One meta-analysis of 82 studies found no dif-

ference in angiographic outcomes between bare platinum coils, HydroCoils, and Cerecyte coils (Codman Neurovascular, Raynham, Massachusetts).²² However, no subgroup analyses were performed to examine the relative benefits of modified coils in easily identified difficult-to-treat subgroups, such as wide-neck or irregularly shaped aneurysms. Single-center studies have found that, when compared with bare platinum coils, HydroCoils are associated with decreased recurrence rates; however, none was a randomized controlled trial, and many were too small for subgroup analyses to define which patients may benefit most from HydroCoil treatment.^{23,24} The HELPS trial found 8.6% fewer major angiographic recurrences for HydroCoil- versus bare platinum-treated aneurysms ($P = .049$).¹ Clinical trials for other modified coils, such as the Matrix (Stryker, Kalamazoo, Michigan) and Cerecyte coils, failed to show any significant benefit for polyglycolic acid/polyglycolic/polylactic acid–modified versus bare platinum coils.^{11,25} Our data suggest that hydrogel-modified coils are more beneficial in certain subsets of patients and aneurysms; recurrence rates were reduced 17%–18% in patients with an aneurysm with a small D/N or an irregularly shaped aneurysm.

Our study had several limitations. First, because this was not a prespecified subgroup analysis for the HELPS trial, these data should not necessarily alter clinical practice but, rather, serve as a guide for the design of future trials comparing modified with bare platinum coils in reducing aneurysm recurrence rates. No follow-up data on aneurysm recurrence and re-treatment were available beyond 18 months. Given this significantly higher rate of major recurrence in the small D/N and irregularly shaped aneurysm control groups, it is conceivable that more of these patients would go on to re-treatment during the long-term follow-up period. However, this suggestion is purely speculative. The combination of low power and lack of consistent follow-up beyond 18 months may have contributed to the lack of statistical significance in aneurysm re-treatment rates between the groups, despite the higher rates of major recurrence in the control group. Another limitation is the fact that there is wide interobserver and intraobserver variability in assessments of aneurysm geometric irregularities such as dome-to-neck ratio, lobularity, and the presence of daughter sacs.²⁶ The core laboratory in this study assessed angiographic recurrence but did not assess aneurysm morphology. Last, we did not study differences in packing attenuation between groups.

CONCLUSIONS

Our subgroup analysis of the HELPS trial found that treatment of irregularly shaped and relatively wide-neck aneurysms with HydroCoils was associated with significantly lower major and minor recurrence rates than treatment with bare platinum coils during the study period. Because this was not a prespecified analysis, these results are not reliable enough to alter clinical practice and should in no way alter the way in which these patients with an irregularly shaped aneurysm or an aneurysm with a small dome-to-neck ratio are treated. Rather, these results should guide the development and design of future randomized controlled trials on the use of modified coils in the treatment of intracranial aneurysms, because these findings suggest that inclusion of such difficult-to-treat aneurysms in future clinical trials may help to dem-

onstrate the benefits that modified coils have compared to conventional bare platinum coils.

Disclosures: Waleed Brinjikji—UNRELATED: Grants/Grants Pending: Brain Aneurysm Foundation Research Grant.* Philip M. White—RELATED: Grant: HELPS trial (Chief Investigator, P.M.W.) was funded by MicroVention*; Consulting Fee or Honorarium: MicroVention; Support for Travel to Meetings for the Study or Other Purposes: MicroVention, Comments: Support for travel to present HELPS results at international congresses; UNRELATED: Grants/Grants Pending: Codman* and Covidien,* Comments: Limited support for PISTE trial (Chief Investigator, P.M.W.) start-up phase; Payment for Lectures (including service on speakers bureaus): Codman and Covidien, Hans Nahser—RELATED: Grant: HELPS Trial,* Comments: Sponsored by Lothian National Health service; Support for Travel to Meetings for the Study or Other Purposes: Travel for steering committee meetings in Edinburgh (HELPS Trial); UNRELATED: Consultancy: Stryker*; Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: Stryker, Covidien, Surpass, WEB, and MicroVention, Comments: Travel and registration fees for conferences, training courses, and scientific meetings. Joanna Wardlaw—RELATED: Grant: Covidien,* Comments: Provided funding for the trial and catheters (grant holder, P.M.W.). Anil Gholkar—UNRELATED: Consultancy: I have a consultant agreement with MicroVention, through which I organize and teach a course called Brainstorm; Payment for Lectures (including service on speakers bureaus): as stated above. David F. Kallmes—UNRELATED: Board Membership: GE Healthcare, Comments: Cost-effectiveness advisory board; Consultancy: ev3, Comments: Planning and implementing clinical trials; Grants/Grants Pending: MicroVention,* Sequent Medical,* Codman,* SurModics,* and NeuroSigma,* Comments: Preclinical and clinical research; Royalties: UVA Patent Foundation, Comments: spinal fusion. *Money paid to institution.

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