AJNR

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AJNR Am J Neuroradiol 2015, 36 (6) 1136-1141
doi: https://doi.org/10.3174/ajnr.A4266
http://www.ajnr.org/content/36/6/1136

HydroCoils Reduce Recurrence Rates in Recently Ruptured Medium-Sized Intracranial Aneurysms: A Subgroup Analysis of the HELPS Trial

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ABSTRACT

BACKGROUND AND PURPOSE: The HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS) was a randomized, controlled trial comparing HydroCoils with bare-platinum coils. The purpose of this study was to perform a subgroup analysis of angiographic and clinical outcomes of medium-sized aneurysms in the HELPS trial.

MATERIALS AND METHODS: Patients with medium-sized aneurysms (5–9.9 mm) were selected from the HELPS trial. Outcomes compared between the HydroCoil and bare-platinum groups included the following: 1) any recurrence, 2) major recurrence, 3) retreatment, and 4) mRS score of ≤2. Subgroup analysis by rupture status was performed. Multivariate logistic regression analysis adjusting for aneurysm neck size, shape, use of adjunctive device, and rupture status was performed.

RESULTS: Two hundred eighty-eight patients with medium-sized aneurysms were randomized (144 in each group). At 15–18 months posttreatment, the major recurrence rate was significantly lower in the HydroCoil group than in controls (18.6% versus 30.8%, $P = .03$, respectively). For patients with recently ruptured aneurysms, the major recurrence rate was significantly lower for the HydroCoil group than for controls (20.3% versus 47.5%, $P = .003$), while rates were similar between groups for unruptured aneurysms (16.7% versus 14.8%, $P = .80$). Multivariate analysis of patients with recently ruptured aneurysms demonstrated a lower odds of major recurrence with HydroCoils (OR = 0.27; 95% CI, 0.12–0.58; $P = .0007$). No difference in retreatment rates or mRS of ≤2 was seen between groups.

CONCLUSIONS: HydroCoils were associated with statistically significant and clinically relevant lower rates of major recurrence for recently ruptured, medium-sized aneurysms in the HELPS trial. Because this was not a prespecified subgroup analysis, these results should not alter clinical practice but, rather, provide insight into the design of future clinical trials comparing bare platinum with second-generation coils.

ABBREVIATION: HELPS = HydroCoil Endovascular Aneurysm Occlusion and Packing Study

Coil embolization of intracranial aneurysms is prone to recurrence rates of up to 20% within 18 months of treatment.[1] Up to 10% of coiled aneurysms require retreatment, usually with additional coil embolization. The costs and risks of monitoring aneurysms for recurrences and retreating them, when necessary, are not negligible.[2] Many modified coils have been developed aimed at decreasing aneurysm recurrence and retreatment rates. Hydrogel coils (HydroCoil; MicroVention, Tustin, California) are designed with an expansile hydrogel that fills more of the aneurysm lumen than standard platinum coils.[3] By doing so, these coils are thought to achieve increased packing density thus accelerating aneurysm healing and decreasing recurrence and retreatment rates.[4]

The HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS) was a randomized, controlled trial comparing HydroCoils with bare platinum coils.[5] This study compared the rate of a composite primary outcome, which included both angiographic and clinical outcomes, between groups. The trial demonstrated a 7.0% reduction in the proportion of adverse composite primary outcomes with HydroCoils ($P = .13$), with significantly higher rates of adverse outcomes in the control group when only ruptured aneurysms were considered. In addition, the investigators found a statistically significant, but not clinically meaningful, difference in major angiographic recurrences between the HydroCoil and bare platinum groups.

While the HELPS trial represents level 1 evidence, the clinical

Received September 22, 2014; accepted after revision December 11.

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http://dx.doi.org/10.3174/ajnr.A4266

applicability of the findings of the trial may be difficult to apply in clinical practice.[6] While the composite analysis has definite benefits over exclusive focus on recurrence and treatment rates, this composite end point has not been the usual metric used to evaluate the efficacy of aneurysm treatment. In addition, small aneurysms have very low recurrence rates, and large aneurysms have high recanalization rates, regardless of the device used.[7] As such, inclusion of small or large aneurysms may mask benefits isolated to medium-sized aneurysms.[8,9] Furthermore, ruptured aneurysms have a different biology from unruptured ones as evidenced by elevated recurrence rates in many series.[10] To fully characterize potential differences in "usual" outcomes between HydroCoil and bare platinum coils, we performed a subgroup analysis of angiographic and clinical outcomes of medium-sized aneurysms in the HELPS trial, stratifying outcomes by rupture status. We hypothesized that treatment with the HydroCoil would result in significantly improved recurrence rates among medium-sized aneurysms.

MATERIALS AND METHODS

Patient Population

Patients were enrolled in the HELPS trial from 24 centers in 7 countries. Patients were eligible for inclusion if they presented with a previously untreated cerebral aneurysm measuring 2–25 mm in maximum diameter, were 18–75 years of age, were deemed by the neurovascular team to need coiling, were not pregnant, had a World Federation of Neurosurgical Societies grade between 0 and III, had anatomy in which endovascular occlusion was judged possible, had not previously been enrolled in the trial, and the neurointerventionalist who would perform the procedure was content to randomize to bare platinum coils or HydroCoils. Patients were excluded if they had >1 aneurysm requiring treatment at 1 procedure. For the purposes of this subgroup analysis, only the subset of patients with medium-sized (5.0–9.9 mm) aneurysms were included. All patients gave written informed consent. If they could not give consent, then informed consent was provided by a surrogate or legally authorized representative. This trial had UK Multicenter Research Ethics Committee approval, and all centers had local ethics approval. Detailed information about the coiling procedure, randomization techniques, baseline demographics, data handing, and coiling is shown elsewhere.[5,11]

Outcomes

The following baseline characteristics were compared between the HydroCoil and control groups: sex, age, dome-to-neck ratio, rupture status, use of assist device, aneurysm shape, aneurysm location (anterior versus posterior), and baseline World Federation of Neurosurgical Societies score. For the purposes of this subgroup analysis, we studied the following individual outcomes: any recurrence, major recurrence, mRS of ≤2, and retreatment. A major recurrence was defined as a recurrence sufficiently large enough to technically allow placement of further coils as defined by the core laboratory assessing the angiograms.[12] Retreatment was classified as any further treatment on the target aneurysm. mRS assessment was performed by a postal questionnaire completed by the patients or by their main caretaker and was independent of the interventional team. The above outcomes were studied at 2 separate periods: 3–6 months postcoiling and 15–18 months postcoiling. Analyses were performed comparing the rate of these outcomes between patients randomized to the HydroCoil group and those randomized to the control group (bare platinum coils). The analyses included the following patient subgroups: 1) all patients with medium aneurysms, 2) all patients with recently ruptured aneurysms, and 3) all patients with non-recently ruptured/unruptured aneurysms. Recently ruptured aneurysms were defined as those that had ruptured within 30 days of treatment.

Statistical Analysis

All means are presented with their corresponding SDs. Comparison between groups of these categoric outcomes was performed by using the Fisher exact test. Multivariate logistic regression analyses were performed to determine whether 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) mRS of ≤2 at last follow-up, and 4) retreatment at last follow-up. Multivariate logistic regression analyses, including all patients with medium-sized aneurysms, were adjusted for neck size, rupture status, aneurysm shape, and the use of an assist device. When we performed subgroup analyses by rupture status, the above-mentioned variables were included with the exception of rupture status. Statistical analysis was performed by using JMP 10.0 Pro (www.jmp.com; SAS Institute, Cary, North Carolina).

Role of Funding Source

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

RESULTS

Patient and Aneurysm Characteristics

A total of 288 patients with medium-sized aneurysms were randomized. There were no significant differences in any of the baseline characteristics studied between groups. Of 144 patients in the HydroCoil group, 74 (51.4%) had recently ruptured aneurysms; and of the 144 patients in the control group, 75 (52.1%) had recently ruptured aneurysms ($P = 1.00$). Sixty-six aneurysms in the HydroCoil group were treated with assist devices (46.2%) versus 63 patients in the control group (44.4%) ($P = .81$). There were no differences in the usage rate of balloon assistance ($P = .50$) or stent assistance ($P = .63$) between groups. Aneurysm shape did not differ between groups because 43 patients (29.9%) in the HydroCoil group had irregular-shaped aneurysms compared with 38 patients (26.4%) in the control group ($P = .60$). There was no difference in aneurysm location ($P = .13$). These data are summarized in Table 1.

Outcomes: All Patients with Medium-Sized Aneurysms

At 3–6 months posttreatment, 114 patients (79.2%) in the HydroCoil group and 115 patients (79.9%) in the control group had angiographic follow-up. There was a lower rate of any recurrence in the HydroCoil group compared with the control group (23 patients, 20.2%, versus 35 patients, 33.3%; $P = .03$). Major recur-

rence rates did not differ between groups, however, as 11 patients (9.6%) in the HydroCoil group had major recurrences versus 17 patients (16.2%) in the control group ($P = .16$). At 15–18 months posttreatment, 113 patients (78.5%) in the HydroCoil group and 120 patients (83.3%) in the control group had angiographic follow-up. There was a similar rate of any recurrence between groups (40 patients, 35.4%, versus 55 patients, 45.8%; $P = .11$). However, the rate of major recurrence was significantly lower in the HydroCoil group than in the control group (21 patients, 18.6%, versus 37 patients, 30.8%; $P = .03$). No difference in retreatment rates or mRS of ≤2 was seen between groups at either time point. These data are summarized in Table 2.

Twelve patients in the medium aneurysm cohort died during follow-up (6 in the bare platinum group and 6 in the HydroCoil group). Of these, 8 died within 1 month of the procedure. Four died because of subarachnoid hemorrhage; 1 death was due to cardiac arrest and multiorgan failure; 1, due to bleeding of a treated unruptured aneurysm; and 2, from ischemic complications secondary to vasospasm or intracranial hypertension. Of the other 4 deaths, 1 was from gastric cancer, 1 was from bacterial meningitis, 1 was due to a post-SAH stroke that resulted in the patient being in a vegetative state, and 1 was from rebleed of a treated ruptured aneurysm.

Table 1: Baseline characteristics of medium-sized aneurysms

	HydroCoil	Control	*P*
Total patients (No.)	144	144	–
Sex			
Female	100 (69.4)	102 (70.8)	.90
Male	44 (30.6)	42 (29.2)	
Age (yr)			
45 or younger	42 (29.2)	49 (34.0)	.57
46–55	43 (29.9)	44 (30.6)	
Older than 55	59 (41.0)	51 (35.4)	
Dome-to-neck ratio			
<1.5	43 (29.9)	50 (34.7)	.45
>1.5	101 (70.1)	94 (65.3)	
Rupture status			
Recently ruptured	74 (51.4)	75 (52.1)	1.0
Unruptured/not recently ruptured	70 (48.6)	69 (47.9)	
Use of assist device[a]			
Yes	66 (46.2)	63 (44.4)	.81
No	77 (53.9)	79 (55.6)	
Balloon	39 (27.1)	33 (22.9)	.50
Stent	27 (18.8)	31 (21.5)	.66
Aneurysm shape			
Irregular (multilobulated)	43 (29.9)	38 (26.4)	.60
Not multilobulated	101 (70.1)	106 (73.6)	
Aneurysm location			
Anterior circulation	119 (82.6)	127 (88.2)	.13
Posterior circulation	25 (17.4)	17 (11.8)	
Baseline WFNS			
0	67 (46.5)	64 (44.4)	.76
I	66 (45.8)	64 (44.4)	
II	9 (6.3)	14 (9.7)	
III	2 (1.4)	2 (1.4)	

Note:—WFNS indicates World Federation of Neurosurgical Societies.
[a] Data on assist device use were not available for 1 patient in the HydroCoil group and 2 patients in the control group.

Outcomes: Patients with Recently Ruptured, Medium-Sized Aneurysms

Among patients with recently ruptured aneurysms, at 3–6 months posttreatment, 56 patients in the HydroCoil group and 50 patients in the control group had angiographic follow-up. The rate of any recurrence was lower in the HydroCoil group (14 patients, 25.0%, versus 24 patients, 38.0%; $P = .02$), as was the rate of major recurrence (4 patients, 7.1%, versus 13 patients, 26.0%; $P = .02$). At 15–18 months posttreatment, 59 patients in each group had angiographic follow-up. The rate of any recurrence was significantly lower in the HydroCoil group (22 patients, 37.3%, versus 38 patients, 64.4%; $P = .006$), as was the rate of major recurrence (12 patients, 20.3%, versus 28 patients, 47.5%; $P = .003$). There was no difference in retreatment or mRS of ≤2 at either time point. These data are summarized in Table 3.

Table 2: Angiographic and clinical results of all patients with medium-sized aneurysms

	3–6 Months			15–18 Months		
	HydroCoil (No.) (%)	Bare Platinum (No.) (%)	*P*	HydroCoil (No.) (%)	Bare Platinum (No.) (%)	*P*
No. of patients with angiographic follow-up	114	115	–	113	120	–
No. of patients with clinical follow-up	124	119	–	128	129	–
Any recurrence	23 (20.2)	35 (33.3)	.03[a]	40 (35.4)	55 (45.8)	.11
Major recurrence	11 (9.6)	17 (16.2)	0.16	21 (18.6)	37 (30.8)	.03[a]
Retreatment	1 (0.9)	2 (1.7)	1.0	3 (2.7)	5 (4.2)	.72
mRS ≤ 2	107 (86.3)	106 (89.1)	.56	113 (88.3)	116 (89.9)	.69

[a] Significant.

Table 3: Angiographic and clinical results of patients with recently ruptured medium-sized aneurysms

	3–6 Months			15–18 Months		
	HydroCoil (No.) (%)	Bare Platinum (No.) (%)	*P*	HydroCoil (No.) (%)	Bare Platinum (No.) (%)	*P*
No. of patients with angiographic follow-up	56	50	–	59	59	–
No. of patients clinical follow-up	63	64	–	65	65	–
Any recurrence	14 (25.0)	24 (48.0)	.02[a]	22 (37.3)	38 (64.4)	.006[a]
Major recurrence	4 (7.1)	13 (26.0)	.02[a]	12 (20.3)	28 (47.5)	.003[a]
Retreatment	0 (0.0)	0 (0.0)	1.0	0 (0.0)	2 (3.4)	.50
mRS ≤ 2	54 (85.7)	56 (87.5)	.80	56 (86.2)	59 (90.8)	.58

[a] Significant.

Table 4: Angiographic and clinical results of patients with non-recently ruptured medium-sized aneurysms

	3–6 Months			15–18 Months		
	HydroCoil (No.) (%)	Bare Platinum (No.) (%)	*P*	HydroCoil (No.) (%)	Bare Platinum (No.) (%)	*P*
No. of patients with angiographic follow-up	58	55	–	54	61	–
No. of patients with clinical follow-up	61	55	–	63	64	–
Any recurrence	9 (15.5)	11 (20.0)	.62	18 (33.3)	17 (27.9)	.55
Major recurrence	7 (12.1)	4 (7.3)	.53	9 (16.7)	9 (14.8)	.80
Retreatment	1 (1.7)	2 (3.6)	.61	3 (5.6)	3 (4.9)	1.0
mRS ≤ 2	53 (86.9)	50 (90.9)	.57	57 (90.5)	57 (89.1)	1.0

Table 5: Multivariate logistic regression analysis[a]

	All Patients (OR) (95% CI)[b]	*P*	Recently Ruptured (OR) (95% CI)[c]	*P*	Non-Recently Ruptured (OR) (95% CI)[c]	*P*
Any recurrence	0.72 (0.43–1.20)	.21	0.37 (0.18–0.76)	.006	1.58 (0.73–3.47)	.25
Major recurrence	0.54 (0.30–0.98)	.04	0.27 (0.12–0.58)	.0007	1.55 (0.58–4.29)	.38
mRS ≤ 2	1.08 (0.51–2.32)	.83	0.96 (0.35–2.68)	.94	1.23 (0.38–4.06)	.73
Retreatment	0.51 (0.07–2.78)	.44	0.00 (0.00–2.01)	.12	0.97 (0.11–8.81)	.98

[a] Odds of HydroCoil versus the control group.
[b] Adjusted for neck size, use of adjunctive device, aneurysm shape, and rupture status.
[c] Adjusted for neck size, use of adjunctive device, and aneurysm shape.

Outcomes: Patients with Non-Recently Ruptured Aneurysms

Fifty-eight patients in the HydroCoil group and 55 patients in the control group had angiographic follow-up at 3–6 months. The rate of any recurrence was similar between groups as 15.5% of patients treated with HydroCoil (9 patients) and 20.0% of controls (11 patients) had a recurrence ($P = .62$). The same was true for major recurrences (7 patients, 12.1%, versus 4 patients, 7.3%, respectively; $P = .53$). At 15–18 months, 54 patients treated with HydroCoils and 61 control patients had follow-up angiograms. The recurrence rate was 33.3% for patients treated with HydroCoils (18 patients) and 27.9% for controls (17 patients) ($P = .55$). No difference in major recurrence rates was seen between groups (16.7%, 9 patients, versus 14.8%, 9 patients, respectively; $P = .80$). These data are summarized in Table 4.

Multivariate Analysis

On multivariate logistic regression analysis, when considering the aneurysms of all patients (unruptured/non-recently ruptured and recently ruptured), HydroCoil was associated with lower odds of major recurrence (OR = 0.54; 95% CI, 0.30–0.98; $P = .04$). For patients with recently ruptured aneurysms, HydroCoil was associated with lower odds of any recurrence (OR = 0.37; 95% CI, 0.18–0.76; $P = .006$) and major recurrence (OR = 0.27; 95% CI, 0.12–0.58; $P = .0007$). There was a trend toward lower retreatment rates in the recently ruptured group treated with HydroCoils (OR = 0.00; 95% CI, 0.00–2.01; $P = .12$). No difference in recurrence rates was seen between coil types in the non-recently ruptured/unruptured group. There were no differences in mRS of ≤2 between groups. These data are summarized in Table 5.

DISCUSSION

This subgroup analysis of patients in the HELPS trial found that HydroCoil is associated with statistically significant and clinically relevant lower rates of recurrence compared with bare platinum, specifically for major recurrence, among patients with medium-sized, recently ruptured aneurysms. In addition, multivariate analysis found lower rates of major recurrence with the HydroCoil group for all aneurysms, even when adjusting for rupture status. Subgroup analyses of patients with non-recently ruptured/unruptured aneurysms found no difference in recurrence rates between the HydroCoil and control groups. Overall, these data strongly suggest that hydrogel coils, such as the HydroCoil, are superior to bare platinum coils in the treatment of ruptured medium-sized aneurysms. These findings could have substantial therapeutic implications if validated in future trials because medium-sized aneurysms accounted for nearly half of the patients with ruptured aneurysms treated in the International Subarachnoid Aneurysm Trial.[13] This was not a prespecified subgroup analysis; thus, these results should not serve to alter clinical practice at this time and need to be validated in future studies.

There are a few potential explanations for the association of HydroCoils with superior occlusion rates compared with bare platinum coils, specifically in ruptured aneurysms. The biology of ruptured aneurysms differs substantially from that of unruptured aneurysms. Ruptured aneurysms are, by definition, unstable and more prone to growth and recurrence than unruptured aneurysms.[10] Hydrogel coils are designed with an expansile hydrogel that fills more of the aneurysm lumen than standard platinum coils. HydroCoils provide substantially improved volumetric packing of the aneurysm lumen compared with standard bare platinum coils.[4,14] By expanding to fill the aneurysm lumen, these coils may be more effective at sealing the aneurysm rupture point, a point of growth within the aneurysm. Furthermore, in an in vitro study, Watanabe et al[15] found that HydroCoils were more effective than bare platinum coils in stopping outflow from the rupture point of experimental aneurysms. These coils may also be more effective at sealing the aneurysm neck as supported by histologic studies in both rabbits and humans.[16,17] In a study comparing the efficacy of HydroCoil, HydroSoft (MicroVention), platinum, and Cerecyte coils (Codman Neurovascular, Raynham, Massachusetts) in angiographic and histologic occlusion of aneurysms in a rabbit model, Killer et al[18] found that hydrogel devices (ie, HydroCoil and HydroSoft) had significantly

higher rates of histologic and angiographic occlusion, which increased with time. Increased healing was seen at both the aneurysm neck and dome.

A number of previously published studies have compared the efficacy of bare platinum and modified coils. In a meta-analysis of 82 studies, Rezek et al[19] compared the efficacy of bare platinum coils with Matrix (Stryker, Kalamazoo, Michigan), HydroCoil, and Cerecyte coils. They found no difference in the rate of unfavorable angiographic outcomes among groups. This study was limited in that they did not perform subgroup analyses by aneurysm size and rupture status. Furthermore, a vast majority of the included studies were noncontrolled case series, thus limiting the level of evidence of these findings. Several single-center studies have demonstrated that HydroCoils are associated with decreased recurrence rates compared with bare platinum coils; however, none were randomized, controlled trials, and many were too small for subgroup analyses to define which patients may benefit the most from HydroCoil treatment.[20,21] A number of single-arm studies have demonstrated high aneurysm-occlusion rates with HydroCoils.[22-24] The largest of these, the HydroCoil for Endovascular Aneurysm Occlusion study, found high rates of initial and long-term occlusion in a series of 191 aneurysms treated with HydroCoils.[25] The authors found relatively low rates of minor and major recurrences among aneurysms of <10 mm, similar to the findings of our study.[26] Our subgroup analysis of patients in HELPS is the largest comparative analysis to date examining clinical and angiographic results of medium-sized aneurysms, to our knowledge.

Limitations

Our study has limitations. Subgroup analyses can be misleading for a number of reasons.[27] For example, if the overall result of a trial is significant, then on the basis of chance, some subgroups will have a positive result and some will have a negative result. Also, if the overall result of a study is negative, on the basis of chance alone, some subgroups may have a larger treatment effect. Subgroup analyses should be based on hypotheses that make sense biologically.[27] On the basis of prior preclinical studies, we thought that it was biologically plausible that HydroCoils would be more effective in the treatment of ruptured aneurysms. Ultimately, subgroup analyses are most helpful when they are prespecified in the trial design. Ours was not a prespecified subgroup analysis for the HELPS trial; therefore, these data should not necessarily alter clinical practice but rather serve as a guide for the design of future trials comparing second-generation coils with bare platinum coils. Another major flaw in subgroup analyses in general is overemphasis of *P* values rather than the treatment effect. Therefore, readers should examine the results of subgroup analyses closely to determine whether the differences between groups are clinically meaningful.[28]

No follow-up data on aneurysm recurrence and retreatment were available beyond 18 months. Given the significantly higher rate of major recurrence in the control group with medium-sized ruptured aneurysms, it is conceivable that more of these patients would go on to retreatment during the long-term follow-up. The combination of low power and lack of consistent follow-up beyond 18 months likely contributes to the lack of statistical significance in the aneurysm retreatment rates between groups, despite the higher rates of major recurrence in the control group. Not all patients received angiographic and clinical follow-up. Of the 288 initially randomized patients with medium-sized aneurysms, only 229 had angiographic follow-up at 3–6 months and 233 had angiographic follow-up at 15–18 months. Last, we did not study differences in packing attenuation between groups. Baseline factors, such as hypertension, which may be associated with aneurysm recurrence, were not assessed in our analysis. In addition, we did not study the types of recurrence (recurrence due to recanalization, regrowth, coil compaction, or coil migration through the aneurysm wall).

The aneurysm recanalization rate in our study was much higher than that reported in other clinical studies and meta-analyses studying postcoiling recanalization rates.[9] The most likely reason is that we used a core laboratory in the assessment of unfavorable outcome, whereas in most clinical studies, clinical and angiographic outcomes are not assessed by an independent core laboratory. For example, in the Cerecyte Coil Trial, unfavorable angiographic outcomes were noted twice as frequently by the independent core laboratory compared with the operators that performed the procedure.[29] In addition, in a meta-analysis of >15,000 treated aneurysms in 104 studies, Rezek et al[30] found that core laboratory studies reported statistically significant and clinically meaningful higher rates of unfavorable outcomes than self-reported studies.

CONCLUSIONS

Our subgroup analysis of patients with medium-sized aneurysms in the HELPS trial found that treatment with HydroCoils resulted in significantly lower rates of major recanalization in this population. The benefits of HydroCoils were most marked in the medium-sized, recently ruptured population. Because this was not a prespecified subgroup analysis, these results should not serve to alter clinical practice but, rather, provide insight into the design of future clinical trials comparing bare platinum with second-generation coils.

Disclosures: Waleed Brinjikji—*UNRELATED*: *Grants/Grants Pending*: Brain Aneurysm Foundation.* Philip M. White—*RELATED*: *Grant*: MicroVention,* *Comments*: HELPS trial was funded by MicroVention; *Consulting Fee or Honorarium*: Codman, MicroVention, *Comments*: for educational Stroke and Institute for Natural Resources meetings organized by me but funded by industry support; *Support for Travel to Meetings for the Study or Other Purposes*: MicroVention, *Comments*: standard class airfare only. Hans Nahser—*RELATED*: *Support for Travel to Meetings for the Study or Other Purposes*: Lothian National Health Service, *Comments*: mainly for being present at the steering committee meetings; *Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed*: Stryker Target, ev3, Covidien, Codman, NeuroLogic, *Comments*: infrequently, by various companies. Joanna Wardlaw—*RELATED*: *Grant*: MicroVention,* *Comments*: funded the HELPS trial; *UNRELATED*: *Consultancy*: ReNeuron,* *Comments*: expenses for work on Data Monitoring Committee of PISCES (Pilot Investigation of Stem Cells in Stroke) and PISCES 2 trials. Harry J. Cloft—*UNRELATED*: *Grants/Grants Pending*: Cordis Endovascular,* *Comments*: Site Principal Investigator at enrolling site for Stenting and Angioplasty with Protection in Patients and HIgh Risk for Endarterectomy registry sponsored by Cordis Endovascular. David F. Kallmes—*UNRELATED*: *Board Membership*: GE Healthcare, *Comments*: Cost-Effectiveness Board; *Consultancy*: ev3,* Medtronic,* *Comments*: planning and implementing clinical trials; *Grants/Grants Pending*: MicroVention,* SurModics,* Sequent,* NeuroSigma,* ev3,* Codman,* *Comments*: preclinical research and clinical trials; *Royalties*: University of Virginia Patent Foundation, *Comments*: Spine Fusion. *Money paid to the institution.

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