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Second-Generation Hydrogel Coils for the Endovascular Treatment of Intracranial Aneurysms

A Randomized Controlled Trial

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Background and Purpose—Endovascular embolization of intracranial aneurysms with hydrogel-coated coils lowers the risk of major recurrence, but technical limitations (coil stiffness and time restriction for placement) have prevented their wider clinical use. We aimed to assess the efficacy of softer, second-generation hydrogel coils.

Methods—A randomized controlled trial was conducted at 22 centers in France and Germany. Patients aged 18 to 75 years with untreated ruptured or unruptured intracranial aneurysms measuring 4 to 12 mm in diameter were eligible and randomized (1:1 using a web-based system, stratified by rupture status) to coiling with either second-generation hydrogel coils or bare platinum coils. Assist devices were allowed as clinically required. Independent imaging core laboratory was masked to allocation. Primary end point was a composite outcome measure including major aneurysm recurrence, aneurysm retreatment, morbidity that prevented angiographic controls, and any death during treatment and follow-up. Data were analyzed as randomized.

Results—Randomization began on October 15, 2009, and stopped on January 31, 2014, after 513 patients (hydrogel, n=256; bare platinum, n=257); 20 patients were excluded for missing informed consent and 9 for treatment-related criteria. Four hundred eighty-four patients (hydrogel, n=243; bare platinum, n=241) were included in the analysis; 208 (43%) were treated for ruptured aneurysms. Final end point data were available for 456 patients. Forty-five out of 226 (19.9%) patients in the hydrogel group and 66/230 (28.7%) in the control group had an unfavorable composite primary outcome, giving a statistically significant reduction in the proportion of an unfavorable composite primary outcome with hydrogel coils—adjusted for rupture status—of 8.4% (95% confidence interval, 0.5–16.2; P=0.036). Adverse and serious adverse events were evenly distributed between groups.

Conclusions—Our results suggest that endovascular coil embolization with second-generation hydrogel coils may reduce the rate of unfavorable outcome events in patients with small- and medium-sized intracranial aneurysms.

Clinical Trial Registration—URL: https://www.drks.de/drks_web/. Unique identifier: DRKS00003132.

(*Stroke*. 2018;49:667-674. DOI: 10.1161/STROKEAHA.117.018707.)

Key Words: aneurysm, ruptured ■ embolization, therapeutic ■ hydrogel, polyethylene glycol dimethacrylate ■ intracranial aneurysm ■ randomized controlled trial

Received July 13, 2017; final revision received November 29, 2017; accepted December 7, 2017.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.018707/-/DC1.

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Endovascular coil embolization is the preferred treatment modality for many patients with intracranial aneurysms because the results of the ISAT (International Subarachnoid Aneurysm Trial) showed better clinical outcomes with endovascular coiling than neurosurgical clipping in patients with ruptured aneurysms.[1] Nevertheless, incomplete aneurysm occlusion or recanalization of completely occluded aneurysms may occur after endovascular coiling. In aneurysms treated with bare platinum coils, the recanalization rates reported in the literature ranged from 4.7% to 28%,[2] and the rehemorrhage rates ranged from 0.12% to 0.4% per year.[3,4]

Earlier studies on aneurysm recanalization suggested a correlation between packing density—the percentage of the aneurysmal volume occluded with coils—and the recanalization rate.[5] To enhance the durability of endovascular coiling, coated coils were brought to clinical practice. Platinum coils coated with polymers including polyglycolic acid/polylactic acid were meant to enhance the inflammatory response at the neck of the aneurysm, to promote organization of clot in the aneurysm and the formation of neointima at the neck, but the concept did not prove effective in 2 randomized controlled trials.[6,7]

A different approach consists of platinum coils coupled with hydrogel, which expands once in contact with liquids, resulting in increased packing density. The results of the HELPS (Hydrocoil Endovascular Aneurysm Occlusion and Packing Study) that assessed the efficacy and safety of a corresponding hybrid hydrogel-coated platinum detachable coil (HydroCoil; MicroVention, Inc, Tustin, CA) indicate that their use lowers major recurrence,[8] but technical limitations of the HydroCoil (coil stiffness and time restriction for placement) have prevented its wider clinical use. To circumvent these limitations, softer hydrogel coils (HydroSoft, HydroFrame [3D]; MicroVention, Inc) containing less hydrogel and expanding more slowly than the HydroCoil have been developed.

In GREAT (German-French Randomized Endovascular Aneurysm Trial), we aimed to establish whether the use of softer, second-generation hydrogel coils for the treatment of intracranial aneurysms improves clinical and angiographic outcomes compared with the use of bare platinum coils.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

GREAT was an investigator-initiated, pragmatic, postmarket, multicenter clinical trial with randomized parallel treatment group assignments, open-label treatment, and blinded end point evaluation for angiographic data. The study was conducted in 15 centers in France and 7 in Germany. The study protocol was approved by the leading ethics committee (Faculty of Medicine, University of Freiburg, 077/09) and the local ethics committees and was authorized by the competent French and German authorities. Members of the trial steering committee and the local investigators designed the study, collected and analyzed the data, wrote the article, and made the decision to submit the article for publication.

Patients

Patients were eligible for enrolment if they were 18 to 75 years of age and had untreated ruptured (World Federation of Neurosurgical Societies [WFNS] grade 0–3) or unruptured aneurysms measuring 4 to 12 mm in diameter with an anatomy such that endovascular occlusion with either bare platinum or hydrogel coils was considered possible. We chose to restrict the aneurysm size because the largest second-generation hydrogel coil available when the trial started measured 12 mm. Detailed inclusion and exclusion criteria are listed in the study protocol.[9] We did not keep a log of patients screened for eligibility. All patients or their legal representatives provided written informed consent. In Germany, the ethics committee approved randomization without prior informed consent, with the option to obtain consent at a later stage, but patients with missing informed consent were excluded from further analysis.

Randomization and Masking

Endovascular embolization of intracranial aneurysms with second-generation hydrogel coils was compared with endovascular embolization with bare platinum coils. Randomization occurred immediately before the study intervention. The randomization procedure was web based (Randoulette; Institute for Medical Informatics, Biometry, and Epidemiology, Ludwig-Maximilians-University, Munich, Germany). Allocation to a coil group was by block randomization in a 1:1 ratio, stratified by rupture status (ruptured versus unruptured aneurysm); block sizes were 2, 4, and 6. Centers were not informed about the block sizes. Masking of the interventional team to the randomly allocated treatment was not possible. Masking of patients was not mandatory; however, investigators were encouraged to refrain from unnecessary disclosure of treatment allocation.

Procedures

Participants in the intervention group underwent endovascular embolization with second-generation hydrogel coils (HydroSoft, HydroFrame; MicroVention, Inc). Standard local procedures for the coiling of aneurysms were followed. All procedures were performed under general anesthesia. Within the hydrogel arm of the study, second-generation hydrogel coils had to constitute >50% of the total coil length deployed. Any bare platinum coils were permitted, as were assist devices such as remodeling balloons or endovascular stents. Only devices that had received Conformité Européenne marking were used in the trial. The antiplatelet and anticoagulation regimens were left to the discretion of the individual operator as part of the standard operation procedure at each center. Detailed information about the coiling procedure was reported elsewhere.[10]

Clinical and Radiological Assessments

All patients underwent clinical examination and angiographic assessment of the underlying aneurysm. At the time of randomization, the following parameters were collected: sex, age, and rupture status (unruptured versus recently ruptured [<30 days]). Baseline data collected included number of aneurysms, aneurysm size (in mm), aneurysm neck size (in mm), dome-to-neck ratio, and aneurysm location. In patients with ruptured aneurysms, the WFNS grade was determined. After the coiling procedure, data were obtained on coils used, use of assist devices, disease- and procedure-related complications, and the initial angiographic outcome.[10] Study data were entered locally by the treating physician or a dedicated study nurse into the trial database via web-based electronic case report forms. Digital copies of angiographic images of the aneurysm before treatment, immediately after treatment, at 6-month follow-up, and at 18-month follow-up were sent to the trials office. Digital subtraction angiography was preferred to magnetic resonance angiography, but magnetic resonance angiography was considered acceptable for centers where angiographic controls routinely are performed with magnetic resonance angiography. Imaging data were entered into the picture archiving and communication system in a pseudonymised way and reviewed by the core laboratory (H.D. and J.F.), who were masked to both treatment allocation and treatment received. The core laboratory reviewed imaging data together and were asked to assess the degree of aneurysm occlusion according to the 3-class Raymond scale (complete occlusion, neck

remnant, and residual aneurysm).[11] A major recurrence was defined as any change from complete aneurysm occlusion or neck remnant at the end of the index procedure to residual aneurysm at angiographic follow-up. In patients with residual aneurysms at the end of the index procedure, major recurrence was defined as any increase in size of the residual aneurysm as judged by the independent core laboratory. The modified Rankin Scale (mRS) score was assessed by the team treating the patient during follow-up. The formulas used to calculate the total aneurysm volume, the volume of 1 coil, the total coil volume, and packing density have previously been published.[10]

Study End Points

Primary end point was a composite outcome of predefined unfavorable angiographic and clinical events. The composite primary end point included major aneurysm recurrence on follow-up angiography within 18 months after treatment (judged by a blinded core laboratory), any aneurysm retreatment, morbidity that prevented patients from having angiographic controls (mRS score, 3–5), and any death during treatment and follow-up. When angiographic results at 18 months were not available, angiographic results at 6 months were used. In patients subject to >1 of the predefined unfavorable outcome events, only 1 was considered for the primary end point. In patients with retreatment or death during follow-up, the result of angiographic follow-up was disregarded for the composite primary end point. A composite angiographic and clinical end point was used rather than an angiographic end point alone because some patients die or are left so disabled after coiling or subarachnoid hemorrhage that they do not have follow-up angiographies. Secondary outcomes included clinical outcomes at 18 months using the mRS score, total coil length deployed, and coil packing density obtained. We did not compare the ease of use of second-generation hydrogel coils with that of bare platinum coils.

Statistical Analysis

The initially planned study size was 306 patients, but the target sample size was amended after the publication of the results of the HELPS, based on the assumption that unfavorable outcomes occur in 10% (hydrogel) versus 20% (bare platinum).[8] Two hundred eighteen patients per group were needed to detect this difference between hydrogel and bare platinum coils with a power of 80% using Fisher exact test at a 2-sided significance level of 5%. With expected noncompliance or drop-out of patients after randomization in the order of 10%, 486 patients had to be randomized to observe the desired amount of compliant patients. The Trial Steering Committee decided to increase the target sample size to 500 patients in July 2012. This decision was driven exclusively by the external HELPS data.

Randomized patients without informed consent, patients who received flow-diverting stents or intrasaccular flow diverters, and patients in whom the intervention was stopped after the initial digital subtraction angiography were excluded. The lead investigator (C.A.T.) determined these treatment-based patient exclusions after final data cleaning of the database with respect to procedural data blinded for treatment allocation. Corresponding exclusions are indicated in Figure 1 (aneurysm not accessible, no aneurysm found, received flow diverters, and received web devices). The remaining patients formed the analysis population in which nonmissing data were analyzed as randomized.

For binary outcomes, the absolute difference of the proportion of outcome events between the 2 arms, expressed as percentages, was calculated along with a 2-sided Newcombe 95% confidence interval (CI) and *P* value with Cochran–Mantel–Haenszel weights, stratified by rupture status.[12] A preplanned sensitivity analysis of the primary end point explored the worst-case scenario in the analysis population where all missing outcomes for patients randomized to the hydrogel arm were evaluated as unfavorable and all those in the bare platinum arm as favorable. For post hoc analyses, we calculated Newcombe CI for the absolute difference in the proportion of unfavorable outcomes between treatments within subgroups, and we examined odds ratios (±the interaction with treatment) by Wald tests from logistic regression. Ordinal and continuous data were compared using van Elteren Wilcoxon rank-sum test stratified for rupture status.[13] Adverse events (AE) were evaluated by received treatment in the analysis population. Periprocedural AE and specific items requested in the electronic case report form describing treatment were evaluated jointly. AE with onset >14 days from initial aneurysm treatment were coded using the medical dictionary for regulatory activities. *P* values were 2 sided and considered statistically significant if <0.05 and exploratory except for the primary analysis. All analyses were performed using version 9.2 of the Statistical Analysis System (SAS; SAS Institute, Cary, NC). The statistical analysis plan has been described in detail[9] (online-only Data Supplement).

Two interim analyses were undertaken, after randomization of 100 and 300 patients, which included assessment of trial data on procedure-related complications, postoperative degree of aneurysm occlusion, AE, and mortality. Results of these analyses were reviewed by an independent data safety monitoring board in strict confidentiality, and relevant information from other sources was considered. The data safety monitoring board advised the lead investigator (C.A.T.) both times to continue with the trial. The primary end point had not been evaluated in the interim analyses.

Results

Baseline Results

From October 15, 2009, to January 31, 2014, 513 patients underwent randomization in 15 centers in France and 7 centers in Germany. Recruitment was stopped after the predetermined sample size was reached. Twenty-nine patients were excluded from the analysis population (Figure 1). The mean age of the 484 patients in the analysis population was 52.4 years (range, 21–82); 151 (31%) patients were men. Two hundred eight patients (43%) were treated for ruptured aneurysms. Two hundred forty-three patients (50.2%) in the analysis population were assigned to the hydrogel group, and 241 (49.8%) were assigned to the bare platinum group. Among patients allocated to hydrogel, 5 were treated with bare platinum coils alone; among patients allocated to the control group, 6 received additional hydrogel coils. The use of assist devices (balloon remodeling and stent-assisted coiling) was balanced between the 2 arms of the study (Table 1). Potential risk factors for unfavorable angiographic and clinical outcomes (age, rupture status, WFNS grade ≥3, aneurysm dome-to-neck ratio <1.5, target aneurysm size, and target aneurysm neck size) were evenly distributed between the 2 treatment groups (Table 1).

AE and serious AE (SAE) collected during treatment and through to discharge included perforation, dissection or occlusion of the parent vessel, procedure-related aneurysm rupture, thromboembolic events, stroke, coil migration, or procedure-related AE with outcome death. AE and SAE with onset >14 days from coiling were also collected.

Primary end point data were available in 456 patients (Figure 1).

Hydrogel Arm

Among patients allocated to the hydrogel group (n=243), 103 (42%) were treated for ruptured aneurysms. Ninety-six patients (40%) were treated without the use of assist devices. Balloon remodeling alone was used in 88 patients (36%), stent-assisted coiling alone in 18 patients (7%), and both balloon remodeling and stent-assisted coiling in 41 patients (17%). On core laboratory–assessed final angiographic

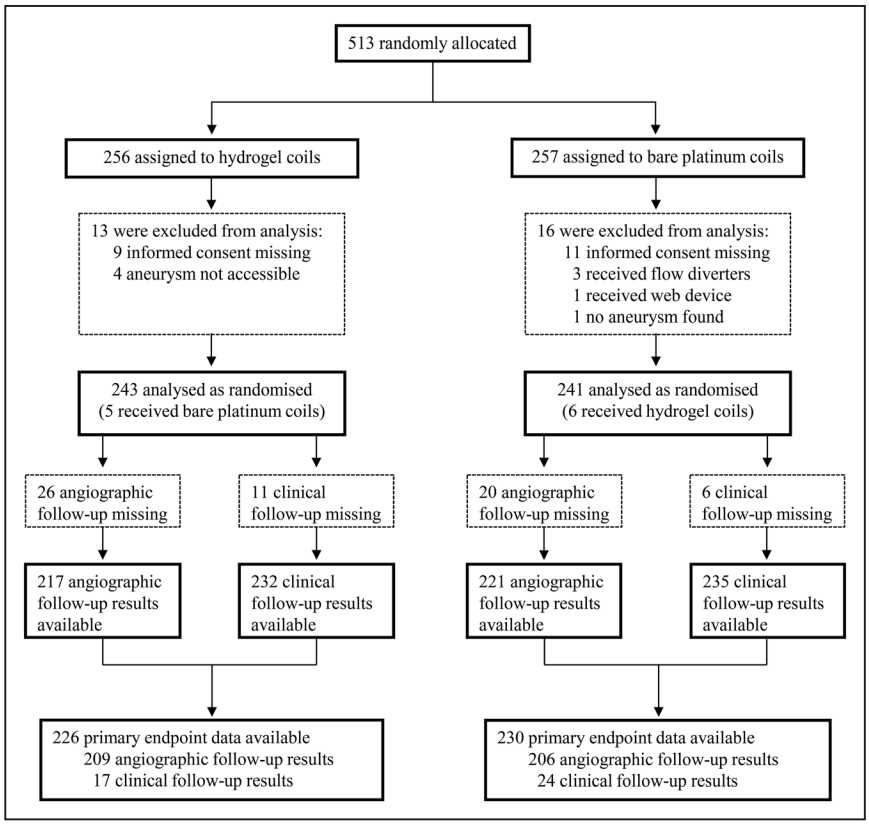

Figure 1. Trial profile. Centers did not keep comprehensive eligibility logs.

controls (n=239), 130 (54%) aneurysms were completely occluded, 47 (20%) showed a neck remnant, and 62 (26%) were residual aneurysms.

Primary end point data for the analysis population were available in 226 of 243 patients. Of 226 patients, 28 (12%) had major aneurysm recurrences, 7 (3%) had aneurysm retreatment, 3 (1%) had morbidity that prevented them from having angiographic follow-up, and 7 (3%) died. AE and SAE occurring during treatment through to discharge were reported in 31 patients. AE and SAE with onset >14 days from coiling were reported in 20 patients. Hydrocephalus was reported in 2 patients (Tables I and II in the online-only Data Supplement).

Bare Platinum Arm

Among patients allocated to the bare platinum arm (n=241), 105 (44%) were treated for recently ruptured aneurysms. One hundred and ten patients (46%) were treated without the use of assist devices. Balloon remodeling alone was used in 81 patients (34%), stent-assisted coiling alone was performed in 21 patients (9%), and both balloon remodeling and stent-assisted coiling in 29 patients (12%). On core laboratory–assessed final angiographic controls (n=237), 124 (52%) aneurysms were completely occluded, 55 (23%) showed a neck remnant, and 58 (24%) were residual aneurysms. These results did not differ significantly from those in the hydrogel arm (P=0.80).

Primary end point data for the analysis population were available in 230 of 241 patients allocated to the bare platinum arm of the study. Of 230 patients, 42 (18%) had major aneurysm recurrences, 14 (6%) had aneurysm retreatment, and 10 (4%) died. AE and SAE occurring during treatment through to discharge were reported in 27 patients. AE and SAE with onset >14 days from coiling were reported in 17 patients. Hydrocephalus was reported in 1 patient (Tables I and II in the online-only Data Supplement).

Six-month instead of 18-month angiographic controls were used for 31 (14.3%) of 217 patients in the hydrogel arm with available angiographic results and 50 (22.6%) of 221 patients in the control group.

Primary and Secondary End Point Results

There was a shift in the distribution of the unfavorable composite primary outcome toward the control group (Table 2). This difference was statistically significant: among patients with recently ruptured aneurysms, 27 (28.7%) of 94 in the hydrogel group versus 38 (37.6%) of 101 in the control group experienced unfavorable composite primary outcome, yielding an absolute increase in the risk of unfavorable composite primary outcome in the control group of 8.9% (95% CI, −4.3 to 21.6; P=0.19). Among patients with unruptured aneurysms, 18 (13.6%) of 132 in the hydrogel group versus 28 (21.7%) of 129 in the control group experienced unfavorable composite primary outcome, yielding an absolute increase in the risk of unfavorable composite primary outcome in the control group of 8.1% (95% CI, −1.2 to 17.3; P=0.089).

Adjusted for rupture status by stratified analysis, the absolute increase in the risk of unfavorable composite primary outcome for the control arm was 8.4% (95% CI, 0.5–16.2; P=0.036; number needed to treat, 12; relative increase, odds ratio, 1.61; 95% CI, 1.04–2.50; P=0.034).

Subgroup analysis stratifying for rupture status (ruptured versus unruptured) and aneurysm size (aneurysm size <10

Table 1. Demographic and Baseline Characteristics by Randomized Treatment

	Randomized Treatment	
	Hydrogel Coils, n (%)	Bare Platinum Coils, n (%)
Total no. of patients	243	241
Sex		
Female	172 (71)	161 (67)
Male	71 (29)	80 (33)
Age, y		
Mean±SD, range	52.9±12.6 (24–79)	54.1±11.8 (21–82)
Baseline rupture status		
Yes, in previous 30 d	103 (42)	105 (44)
No	140 (58)	136 (56)
WFNS scores in patients with previously ruptured aneurysms		
WFNS 1	65 (64)	74 (71)
WFNS 2	21 (21)	15 (14)
WFNS 3	11 (11)	11 (11)
WFNS 4	4 (4)	3 (3)
WFNS 5	1 (1)	1 (1)
Missing	n=1	n=1
Aneurysm location		
Anterior	177 (74)	182 (76)
Posterior/other	62 (26)	56 (24)
Missing	n=4	n=3
Target aneurysm size, mm		
Median, range	7 (2–15)	7 (2–18)
Mean±SD, range	6.8±2.1 (2–15)	7.1±2.5 (2–18)
Missing	n=1	n=0
Size aneurysm neck, mm		
Mean±SD, range	3.5±1.3 (1–8)	3.6±1.3 (2–9)
Missing	n=5	n=4
Dome-to-neck ratio		
<1.5	90 (38)	90 (38)
≥1.5	147 (62)	150 (63)
Missing	n=6	n=1
Aneurysm shape		
Regular	136 (56)	133 (55)
Irregular/lobulated	107 (44)	107 (45)
Missing	n=0	n=1
Assist device used		
None	96 (40)	110 (46)
Balloon, no stent	88 (36)	81 (34)
Stent, no balloon	18 (7)	21 (9)
Balloon+stent	41 (17)	29 (12)

WFNS indicates World Federation of Neurosurgical Societies.

Table 2. Composite Angiographic and Clinical Outcomes

	Hydrogel, n=226	Control, n=230
Good, n (%)		
No major aneurysm recurrence on angiographic follow-up	181 (80)	164 (71)
Unfavorable, n (%)		
Major aneurysm recurrence on angiographic follow-up without retreatment	28 (12)	42 (18)
Retreatment	7 (3)	14 (6)
No angiographic follow-up because of morbidity, mRS, 3–5	3 (1)	0
Any death, mRS score 6	7 (3)	10 (4)
Refused or lost to angiographic follow-up	17	11

Data are represented as n (%). In 81 (18%) patients, 31 (14.3%) from the hydrogel arm and 50 (22.6%) from the control arm), 6-month angiographic results were used because 18-month angiography was not done or available. In patients with retreatment or death during follow-up, the result of any angiographic follow-up was disregarded for the composite primary end point. mRS indicates modified Rankin Scale.

versus ≥10 mm) showed that the effect of second-generation hydrogel coils seemed more pronounced in unruptured aneurysms and in aneurysms <10 mm (Figure 2).

A sensitivity analysis was performed under a worst-case scenario: for additional 28 patients of the analysis population with missing primary outcome data, we assumed an unfavorable composite primary outcome for patients in the hydrogel group and a favorable outcome for patients in the control group. The sensitivity analysis failed to show a statistically significant increase in the risk of unfavorable composite primary outcome in the control group (1.7%; 95% CI, −9.5 to 6.2; P=0.67).

Angiographic outcomes at follow-up are displayed in Table III in the online-only Data Supplement. The test for between-group differences in the 7-level mRS score for the clinical status at 18 months was not statistically significant (P=0.76; Table IV in the online-only Data Supplement). Greater aneurysm packing density was achieved in the hydrogel group (median, 39%; range, 8–152) than in controls (median, 31%; range, 6–95). This difference was statistically significant (P<0.001). The analysis of administered coil lengths showed a nonsignificant trend that less total coil length was administered in the hydrogel arm (median, 38 cm; range, 2–259) than in the control arm (median, 41 cm; range, 3–352; P=0.065).

Procedural complications occurred in 31 (12.7%) patients treated with hydrogel coils and 30 (12.4%) who received platinum coils (rate difference, 1.6%; 95% CI, −4.2 to 7.5; P=0.59). Procedure-related stroke or death occurred in 9 patients (3.7%) treated with hydrogel coils and 7 patients (2.9%) who had received bare platinum coils (Table I in the online-only Data Supplement). The 14-day mortality rates were comparable in both arms of the study: 5 patients per arm (2.0% versus 2.1%; rate difference, 0.1%; 95% CI, −3.2 to 3.1; P=0.96). There was no significant between-group difference in the occurrence

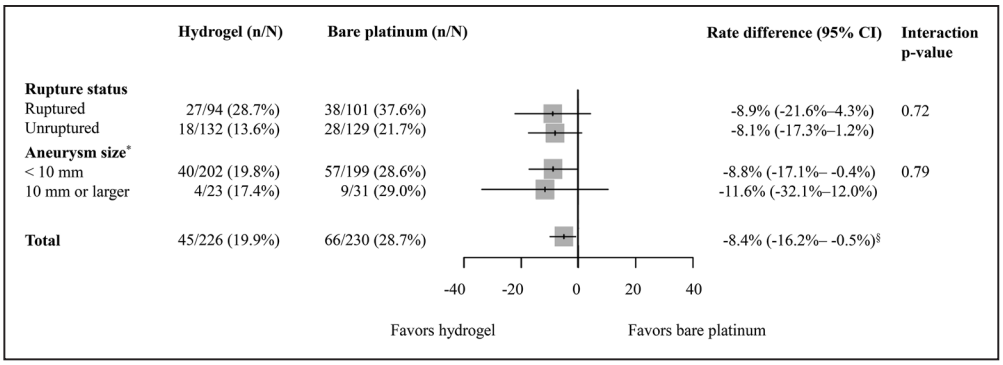

Figure 2. Subgroup analysis of composite primary end point (differences in unfavorable outcome rates in percentage). *Aneurysm size missing in 1 patient assigned to hydrogel. §Adjusted for rupture status. CI indicates confidence interval.

of AE and SAE during the 18-month follow-up period (Table II in the online-only Data Supplement).

Twelve deaths (5 in the hydrogel group and 7 in the control group) occurred in the subgroup of patients with recently ruptured aneurysms and available clinical follow-up (n=195). Seven additional patients with recently ruptured aneurysms had poor clinical outcomes (mRS score, 3–5; 5 in the hydrogel group and 2 in the control group). In the subgroup of patients with incidental aneurysms and available clinical follow-up (n=270), 5 deaths (2 in the hydrogel group and 3 in the control group) occurred. Three additional patients with incidental aneurysms (2 in the hydrogel arm and 1 in the control group) had poor clinical outcomes (mRS score, 3–5). This results in a morbidity and mortality rate (mRS score ≥3) of 9.6% for patients with recently ruptured aneurysms and 3.0% for patients with incidental aneurysms.

Discussion

In this study, the risk of meeting the unfavorable composite primary end point of major angiographic recurrence and poor clinical outcome at 18 months after treatment was significantly lower in patients treated with second-generation hydrogel coils than in the control group of patients treated with bare platinum coils.

Our findings stand in clear distinction to those of recent randomized controlled trials on embolization with polyglycolic acid/polylactic acid-coated coils for the treatment of intracranial aneurysms that failed to show a benefit when compared with bare platinum coils.[6,7] The results of 2 other randomized controlled trials on embolization with hydrogel coils showed variable results.[8,14] HELPS, which investigated the effectiveness of first-generation hydrogel coils (HydroCoils; MicroVention, Inc), failed to show significant differences for the composite primary end point of the trial. Analysis of a secondary end point showed an 8.6% reduction in major recurrences for aneurysms treated with hydrogel coils when compared with aneurysms treated with bare platinum coils.[8] The PRET trial (Patients Prone to Recurrence After Endovascular Treatment) analyzed the potential effect of first- and second-generation hydrogel coils on 2 different cohorts: patients with large aneurysms (PRET 1) and patients with aneurysms that had previously recurred after coiling (PRET 2). The PRET trial did not show any benefit of hydrogel coils over bare platinum coils with respect to an unfavorable composite primary end point of residual/recurrent aneurysm, retreatment, intracranial bleeding, or mass effect during an 18-month follow-up period in both cohorts.[14]

Differences in inclusion criteria and primary end points among these randomized controlled trials make a head-to-head comparison difficult (Table V in the online-only Data Supplement). The inclusion criteria in HELPS and PRET did not restrict aneurysm size, a factor known to have a major influence on the recurrence rate of coiled aneurysms. In GREAT, enrolment was restricted to patients with aneurysms 4 to 12 mm in diameter. This might explain the better results obtained in GREAT and corroborates findings from a recent post hoc subgroup analysis of data from patients with medium-sized (5–9.9 mm) ruptured aneurysms in the HELPS that showed a significantly lower major recurrence rate in the hydrogel group than in the control group (18.6% versus 30.8%; P=0.03) at 15 to 18 months after treatment.[15]

The primary end points for HELPS, PRET, and GREAT seem comparable. All 3 were measured at 18 months after the index aneurysm procedure and combined angiographic and clinical measures. The MAPS trial (Matrix and Platinum Science) used target aneurysm recurrence as a measure of clinical effectiveness after aneurysm treatment. Target aneurysm recurrence composed of target aneurysm rupture, sudden unexplained death, and target aneurysm retreatment and is meant to capture the clinical events that are most important to patients after aneurysm treatment.[7] In GREAT, we used a comparable composite end point but added angiographic measures (recurrent aneurysm).

Comparison of clinical outcomes between studies seems difficult because we excluded per-protocol patients with WFNS grade >3 from randomization into the trial. The rate of death or disability (mRS score ≤3) at 18 months in the overall group of patients treated for ruptured aneurysms was 9.6% (19/197), which is comparable with the reported rate of 10.5% (30/287) death or disability at 3 to 6 months follow-up in a subgroup of patients presenting with WFNS grades 1 to 3 (n=287) and treated with bare platinum coils in the CLARITY study (Clinical and Anatomical Results in the Treatment of Ruptured Intracranial Aneurysms), a prospective registry conducted in France that included 405 patients with ruptured aneurysms.[16] In HELPS (WFNS grades 1–3 in patients with ruptured aneurysms) and MAPS (WFNS grades in patients with ruptured aneurysms not indicated), the death or disability

rate for patients treated for ruptured aneurysms were 17.7% and 9.6%, respectively.[7,8] The authors of the Cerecyte Coil Trial unfortunately did not provide corresponding data.[6]

In our study, the death or disability rate (mRS score ≥3) at 18 months was 3.0% (8/270) for patients treated for unruptured aneurysms, which compares favorably with the 3.1% rate reported at 1-month follow-up in the ATENA study (Analysis of Treatment by Endovascular approach of Nonruptured Aneurysms), a prospective registry conducted in France that included 649 patients treated for unruptured aneurysms.[17] In HELPS and MAPS, the death or disability rate for patients treated for unruptured aneurysms was 11.1% and 4.2%, respectively.[7,8] These favorable comparisons might be explained by improved materials and increased experience among neurointerventionalists. Another factor playing a certain role is the restriction of GREAT to aneurysms measuring 4 to 12 mm, thereby excluding small and large aneurysms—both known to have higher procedural complication rates. In addition, the inclusion of patients with ruptured aneurysms in GREAT was limited to WFNS grades 1 to 3, potentially influencing the overall clinical outcome of the study cohort.

The inclusion of a broad international panel of treatment teams increased representativeness of the cohort because 12 of 22 participating centers randomized ≥10 patients per center (range, 1–85).

The median packing density was significantly higher in the hydrogel group and seems to have translated into better long-term angiographic results and lower retreatment rates in our study. This observation corroborates findings from PRET that showed a correlation between packing density and angiographic recurrences for both the hydrogel and the control arms of that study.[14]

GREAT had several limitations. The generalizability of our findings is limited because of the restrictions in aneurysm size. There were more patients missing primary end point data in the hydrogel group (n=17) than in the control group (n=11). In irregularly shaped aneurysms and in aneurysms carrying multiple blebs, the ellipsoid model used for the calculation of the total aneurysm volume may result in inaccurately small aneurysm volumes potentially exaggerating the packing density.[10]

The worst-case scenario analysis showed no statistically significant reduction in the composite end point for the second-generation hydrogel arm compared with the bare platinum arm. Although some of these outcomes were missing for reasons unrelated to treatment, the reasons are not known for all patients. The clinical end point (mRS score) was self-assessed. Because the composite outcome included morbidity that prevented angiographic controls, the primary end point is not complexity blinded to the allocated arm. The study was designed in December 2008; at that time, flow-diverting stents and intrasaccular flow disruptors had not been introduced to standard interventional neuroradiology practice. We decided during the course of the trial to exclude patients treated with these novel devices from further analyses. The option practiced in Germany, to obtain informed consent in patients with WFNS grades 2 and 3 at a later stage, may have led to under-reporting of treatment or disease-related mortality, because patients with missing informed consent were excluded from analysis. The follow-up period of 18 months was not completed by all patients; we used 6-month follow-up for 18% of patients.

Conclusions

Our results suggest that endovascular coil embolization with second-generation hydrogel coils may reduce the rate of unfavorable outcome events, composed of major aneurysm recurrence, aneurysm retreatment, morbidity that prevented angiographic controls, and any death during treatment and follow-up in patients with small- and medium-sized intracranial aneurysms.

Acknowledgments

We are grateful to all the investigators and coordinators for their support and hard work in enrolling patients, completing data collection forms, and participating in the study. Trial Steering Committee members are as follows: Christian Taschner (chair), Alain Bonafé (coordinator French centers), Martin Schumacher, Matthias Reinhard, and Vera van Velthoven. Data Monitoring and Safety Committee members are as follows: Daniel Rüfenacht (chair), Werner Hacke, and Meinhard Kieser (statistician). Scientific Advisor: Philip M. White. We would like to show our gratitude to Marinette Moynier and Ulrike Bergmann at the coordinating centers in Montpellier, France, and Freiburg, Germany, for their great work and outstanding commitment. We would also like to thank Dagmar Schnau for her invaluable assistance in editing and reviewing this article.

Sources of Funding

The funder of the study (MicroVention, Inc) had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. MicroVention, Inc contributed the electronic case report form but was not granted access to the trial database. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Disclosures

Dr Taschner reports grants and nonfinancial support from MicroVention, Inc, during the conduct of the study. Dr Herbreteau reports consultant relationship with Sequent Medical during the conduct of the study. The other authors report no conflicts.

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