GREAT—a randomized controlled trial comparing HydroSoft/HydroFrame and bare platinum coils for endovascular aneurysm treatment: procedural safety and core-lab-assessedangiographic…

Article *in* Neuroradiology · August 2016

DOI: 10.1007/s00234-016-1693-y

CITATIONS
35

READS
393

23 authors, including:

Christian Taschner
University of Freiburg
194 PUBLICATIONS **3,426** CITATIONS
SEE PROFILE

René Chapot
Alfried Krupp Krankenhaus
286 PUBLICATIONS **8,681** CITATIONS
SEE PROFILE

Vincent Costalat
Centre Hospitalier Universitaire de Montpellier
333 PUBLICATIONS **13,770** CITATIONS
SEE PROFILE

Paolo Machi
Hôpitaux Universitaires de Genève
154 PUBLICATIONS **3,411** CITATIONS
SEE PROFILE

Neuroradiology
DOI 10.1007/s00234-016-1693-y

INTERVENTIONAL NEURORADIOLOGY

GREAT—a randomized controlled trial comparing HydroSoft/HydroFrame and bare platinum coils for endovascular aneurysm treatment: procedural safety and core-lab-assessed angiographic results

Christian A. Taschner[1] · René Chapot[2] · Vincent Costalat[3] · Paolo Machi[3] · Patrick Courthéoux[4] · Xavier Barreau[5] · Jérôme Berge[5] · Laurent Pierot[6] · Kryzsztof Kadziolka[6] · Betty Jean[7] · Raphaël Blanc[8] · Alessandra Biondi[9] · Hervé Brunel[10] · Sophie Gallas[11] · Ansgar Berlis[12] · Denis Herbreteau[13] · Joachim Berkefeld[14] · Horst Urbach[1] · Samer El Shikh[1] · Jens Fiehler[15] · Hubert Desal[16] · Erika Graf[17] · Alain Bonafé[3]

Received: 18 March 2016 / Accepted: 25 April 2016

Abstract

Introduction Hybrid hydrogel-platinum coils (HydroCoil) have proven effective for endovascular aneurysm treatment. To overcome technical limitations (coil stiffness, time restriction for placement), a second generation of softer hydrogel coils has been brought to clinical practice (HydroSoft, HydroFrame). We report

Preliminary data from this study was presented at the WIN ABC meeting, Val d'Isère, France, in January 2015, and the Annual Meeting of the American Society of Neuroradiology, Chicago, IL, in April 2015.

GREAT investigators France
C Barbier. Department of Neuroradiology, CHU Caen, Caen
Jean Gabrillargues, Emanuel Chabert, A Fischer. Department of Neuroradiologie, Hôpital Gabriel-Montpied, CHU Clermont-Ferrand, Clermont-Ferrand
Frédéric Ricolfi. Department of Neuroradiology, CHU Dijon, Dijon
Charbel Mounayer. Department of Neuroradiology, CHU Limoges, Limoges
Marinette Moynier. Department of Neuroradiology, CHU Montpellier, Montpellier
Michel Piotin, Bruno Bartolini. Department of Interventional Neuroradiology, Fondation Rothschild Hospital, Paris
Nader Sourour. Department of Neuroradiology, Hôpital Salpétrière, AP-HP, Paris
Jean-Yves Gauvrit. Department of Neuroradiology, CHU Rennes, Rennes
Eléonore Tollard. Department of Neuroradiology, CHU Rouen, Rouen
C Papgiannaki, Richard Bibi. Department of Neuroradiology, CHU Tours, Tours
Germany
Paul Stracke. Department of Intracranial Endovascular Therapy, Alfried-Krupp Krankenhaus Hospital, Essen
Marc Schlamann, Sophia Göricke, Claudia Möller-Hartmann, Isabell Wanke. Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Essen
Richard du Mesnil de Rochemont. Institute of Neuroradiology, University Hospital Frankfurt, Frankfurt am Main
Stephan Meckel, Ulrike Bergmann. Department of Neuroradiology, Medical Centre-University of Freiburg, Freiburg
Elke Gizewski, Thorsten Schmidt. Department of Neuroradiology, University Hospital Giessen, Giessen
Christoph Groden. Department of Neuroradiology, Universitätsmedizin Mannheim, University of Heidelberg, Mannheim

✉ Christian A. Taschner
christian.taschner@uniklinik-freiburg.de

1 Department of Neuroradiology, Medical Centre - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
2 Department of Intracranial Endovascular Therapy, Alfried-Krupp Krankenhaus Hospital, Essen, Germany
3 Department of Neuroradiology, CHU Montpellier, Montpellier, France
4 Department of Neuroradiology, CHU Caen, Caen, France
5 Department of Neuroradiology, CHU Bordeaux, Bordeaux, France
6 Department of Neuroradiology, CHU Reims, Reims, France
7 Department of Neuroradiology, Hôpital Gabriel-Montpied, CHU Clermont-Ferrand, Clermont-Ferrand, France
8 Department of Interventional Neuroradiology, Fondation Rothschild Hospital, Paris, France
9 Department of Neuroradiology, CHU Besançon, Besançon, France
10 Department of Neuroradiology, Hôpital La Timone, CHU Marseille, Marseille, France
11 Department of Neuroradiology, Hôpital Henri-Mondor, AP-HP, Créteil, France
12 Department of Radiology and Neuroradiology, Augsburg Hospital, Augsburg, Germany

Published online: 30 April 2016

on procedural safety and core-lab-assessed angiographic results from an open-label multicenter randomized controlled trial.
Methods Web-based randomization occurred in 15 medical centers in France and seven in Germany between coil embolization with second-generation hydrogel coils and treatment with any bare platinum coil. Assist devices could be used as clinically required. Primary endpoint is a composite outcome including major aneurysm recurrence and poor clinical outcome at 18 months follow-up.
Results Five hundred thirteen patients were randomized (hydrogel $n=256$, bare platinum $n=257$). Twenty patients were excluded for missing informed consent and nine patients for treatment related criteria. Four hundred eighty-four patients were analyzed as randomized (hydrogel $n=243$, bare platinum $n=241$). Two hundred eight had ruptured aneurysms (43 %). Prespecified procedural complications occurred in 58 subjects (hydrogel $n=28$, bare platinum $n=30$, $p=0.77$). The 14-day mortality rate was 2.1 % in both arms of the study. The median calculated packing densities for aneurysms assigned to hydrogel and bare platinum were 39 and 31 % respectively ($p<0.001$). No statistically significant differences were found between arms in the post procedural angiographic occlusion rate ($p=0.8$).
Conclusion Second-generation hydrogel coils can be used in a wide spectrum of aneurysms with a risk profile equivalent to bare platinum. Packing density was significantly higher in aneurysms treated with hydrogel coils.
Trial registration http://www.germanctr.de, DRKS00003132

Keywords Intracranial aneurysm · Hydrogel coils · Randomized controlled trial

Introduction

Endovascular coil embolization for treatment of intracranial aneurysms is widely accepted [1]. Incomplete aneurysm occlusions or recanalization of completely occluded aneurysm may occur. The recanalization rate for aneurysm treatment with bare platinum coils reported in the literature varies between 4.7 and 28 % [2]. The re-hemorrhage rates described in these patient series including between 141 and 960 patients ranged from 0 to 2.8 % [2]. Early studies on aneurysm recanalization suggested a correlation between packing density—the percentage of the aneurysmal volume occluded with coils—and the recanalization rate [3].

Various modifications of bare platinum have been suggested and were brought to clinical practice. Incorporation or coverage of platinum coils with polymers including polyglycolic/polylactic acid was 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. This concept was subject to two randomized controlled trials. There were no significant differences in the angiographic outcomes between this class of modified coils and bare platinum coils [4, 5].

A different approach consists of the inclusion of a hydrogel filament into platinum coils. This hydrogel, once in contact with liquids, amplifies its volume resulting in an increased packing density. The effectiveness of a corresponding hybrid hydrogel platinum detachable coil (HydroCoil, MicroVention Inc., Tustin, CA) was shown in a randomized controlled trial [6]. Several limitations of these first-generation hybrid hydrogel platinum detachable coils (coil stiffness, time restriction for placement) led to the development of new, supposedly softer coils containing less hydrogel and swelling more slowly than the HydroCoil (HydroSoft, HydroFrame [3D], MicroVention Inc., Tustin, CA) [7–12]—referred to as hydrogel or hydrogel coil in this article.

The effectiveness of this new class of hydrogel coils has been subject to a retrospective multicentre analysis comparing endovascular coil embolization with hydrogel coils with a control group of patients that underwent coil embolization with bare platinum coils [11, 12]. The authors concluded that coil embolization using hydrogel coils achieved higher volumetric packing density. Twelve-month follow-up data favored hydrogel coils, with lower retreatment rates.

In 2009, with support from MicroVention Inc. (Tustin, CA), funding was obtained to conduct an investigator-initiated trial with independent blinded angiographic outcome assessment comparing aneurysmal repair with hydrogel coils to coil embolization with bare platinum coils in a randomized controlled study. As primary objective, the trial aims to clarify whether hydrogel coils are superior to bare platinum in terms of recurrence, retreatment, and clinical outcome after 18 months [13]. Here, we report procedural safety and core-lab-assessed post-surgical angiographic results.

Methods

Patients and techniques

GREAT is a French-German multicenter, open-label, randomized controlled trial comparing a new class of hydrogel coils

[13] Department of Neuroradiology, CHU Tours, Tours, France

[14] Institute of Neuroradiology, University Hospital Frankfurt, Frankfurt/Main, Germany

[15] Department of Neuroradiology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

[16] Department of Neuroradiology, Hôpital G et R Laënnec, CHU Nantes, Nantes, France

[17] Clinical Trials Unit, Medical Centre - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

(HydroSoft, HydroFrame [3D], MicroVention Inc., Tustin, CA) and bare platinum coils in the endosaccular treatment of intracranial aneurysms. The study received appropriate ethics committee approval from 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. The study is entirely funded by MicroVention Inc. Funding bodies of the study have no role in study design, data analysis, data interpretation, or writing of the report. The study is registered in the German Clinical Trials Register (DRKS-ID: DRKS00003132). A 1:1 randomization with blocks of sizes 2, 4, and 6, stratified by rupture status, was employed to ensure balance concerning the rupture status (recently ruptured [within 30 days] versus unruptured aneurysms) between the two arms of the study. Randomization was performed via a web-based randomization application (Randoulette, Institute for Medical Informatics, Biometry, and Epidemiology, Ludwig-Maximilians-University, Munich, Germany).

Inclusion and exclusion criteria

Patients presenting with a previously untreated cerebral aneurysm measuring 4–12 mm in maximal diameter (the maximum size for hydrogel coils at the outset of the trial) deemed to require endovascular coil embolization were eligible for inclusion if they were 18–75 years of age, were World Federation of Neurosurgeon (WFNS) grade 0–3, had anatomy such that endovascular occlusion was considered possible, had not previously been randomized into the trial, and the neurointerventionalist was content to use either bare platinum or hydrogel coils. Patients were excluded if they had >1 aneurysm requiring treatment, unless the treatment was to be staged with only 1 aneurysm being treated at one sitting. Written informed consent had to be obtained from patients with WFNS grades 0 and 1 prior to randomization. In patients presenting with subarachnoid hemorrhage, the consent process differed between the participating centers in France and Germany. In France, appropriate written consent was sought from the patient or from their next of kin before randomization. In Germany, the ethics committees approved randomization without prior informed consent in patients with WFNS grades 2 + 3, because both procedures (bare platinum coils vs. hydrogel coils) were performed with coils that had European Conformity (CE) mark approval. In the recovery phase, patients were asked to give written consent allowing the use of their clinical data. The accumulating data were analyzed by the trial statistician and reviewed in strict confidence by the Data Safety Monitoring Board (DSMB) after randomization of 100 and 300 patients (two times during the course of the trial). All members of the DSMB were totally independent.

Embolization procedure

Standard local procedures for the coiling of aneurysms were followed. With both hydrogel and bare platinum coils, complete angiographic aneurysm occlusion was the goal. In the hydrogel arm of the study, at least 50 % of the total coil length deployed should constitute of hydrogel coils. These recommendations were for guidance only and not a rigid requirement. Any bare platinum coils were permitted, as were assist devices such as remodeling balloons or endovascular stents. The antiplatelet and anticoagulation regimens were left to individual operator's discretion as part of the clinical practice at each center.

Data collection and analysis

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 the following: number of aneurysms, aneurysm sizes (in mm), aneurysmal 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 [14]. In addition, adverse events as well as serious adverse events were collected. Study data was entered locally into the trial data base via web-based electronic case record forms by the treating physicians or a dedicated study nurse. Study monitors visited participating centers to ensure data base completion and verify consistency with source data. Also, they supervised the resolution of queries generated from computerized plausibility checks of the data base.

A core lab composed of two independent investigators (H.D., J.F.), blinded for treatment, reviewed baseline angiograms and angiographic controls which had been performed at the end of the endovascular procedure. They were asked to perform a plausibility check on the aneurysm sizes given by the centers. In addition, they looked for signs of coil herniation, thrombus formation, and vessel occlusions on the angiographic controls performed at the end of the coiling procedure. Finally, they were asked to assess the degree of aneurysm occlusion according to the three-point Raymond scale (complete, residual neck, residual aneurysm) [14].

Formulas

$$\text{Total aneurysm volume}\left(\text{mm}^3\right) : 4/3 \times \pi \times \text{height(mm)} \times \text{width(mm)} \times \text{length(mm)}$$

$$\text{Volume of one coil}\left(\text{mm}^3\right) : \pi \times \left(\text{Coil diameter(mm)}\middle/2\right)^2 \times \text{Coil length(mm)}$$

$$\text{Total coil volume}\left(\text{mm}^3\right) : \text{Sum of volume of all coils placed inside the aneurysm}$$

$$\text{Packing density}(\%) : \text{Total coil volume}\middle/\text{Total aneurysm volume} \times 100$$

For calculation of the HydroSoft/HydroFrame coil volume, the coil diameter used in the above formula represents the coil

diameter after full expansion of the hydrogel component. The HydroSoft/HydroFrame coil volume increases by 15 % with full hydrogel expansion.

Statistical analysis

Patients were evaluated in the arm to which they were randomized irrespective of treatment received. However, randomized patients that received flow diverting stents and intrasaccular flow diverters, as well as patients where the intervention was stopped after the initial digital subtraction angiography (DSA), and patients with missing outcomes were excluded (modified intention-to-treat analysis). The lead investigator [C.A.T.] determined these treatment-based patient exclusions after final data cleaning of the data base with respect to procedural data. For binary outcomes, the absolute difference of the proportions of outcome events between the two arms, expressed as percentages, was calculated along with a two-sided Newcombe 95 % confidence interval (CI) with Cochran-Mantel-Haenszel weights, stratified by rupture status [15]. Ordinal and continuous data were compared by van Elteren's Wilcoxon rank sum test stratified for rupture status [16]. p values were two-sided and considered statistically significant if below 0.05. All analyses were performed using the Statistical Analysis System (SAS version 9.2). Additional information concerning the design of the GREAT study and the calculation of the sample size has been reported previously [13].

Results

Recruitment started in October 2009 and ended in January 2014. The data base lock for the part containing baseline information took place in December 2014. An update for early safety and mortality data was performed in September 2015. Angiographic as well as clinical 6- and 18-month follow-up data are still being collected. Five hundred thirteen patients were randomized in 15 centers in France and 7 centers in Germany. Two hundred fifty-six patients were randomized to aneurysmal treatment with hydrogel coils, and 257 were randomized to coil embolization with bare platinum coils. Twenty patients were excluded from the study because of missing informed consent, of these nine patients had been randomized into the hydrogel arm and 11 patients into the bare platinum arm of the study. Additional nine patients were excluded based on treatment-related criteria: In four patients randomized to hydrogel coils, embolization was not feasible for various reasons (no working projection possible, MCA branch deriving directly from the base of the aneurysm, access not possible due to marked tortuosity of the CCA); among the patients assigned to the bare platinum arm, three were treated with additional flow diverters ($n=2$) or flow diverters alone ($n=1$), one patient was treated with an intra-aneurysmal flow disruptor (Web Device), and in one patient, the aneurysm that was supposed to be treated could not be found. The remaining study sample consists of 243 patients randomized to aneurysm treatment with hydrogel coils, and 241 patients who were randomized to aneurysm coiling with bare platinum coils. Among those allocated to hydrogel coils, five patients were treated with bare platinum coils alone. Of those randomized to bare platinum coils, six patients received additional hydrogel coils. These were analyzed as randomized (modified intention-to-treat approach). Figure 1 summarizes randomization allocation and the treatment received.

Table 1 shows a well-balanced distribution of sex, age, baseline rupture status, aneurysm location, target aneurysm size, target aneurysm neck size, dome-to-neck ratio, aneurysm shape, and the use of assist devices between the two arms of the study. The majority of patients treated were female (hydrogel 71 %, bare platinum 67 %). The mean age was comparable (hydrogel 52.9 years, bare platinum 54.1 years). The majority of patients were treated for unruptured aneurysms (hydrogel 58 %, bare platinum 56 %). The distribution of WFNS grades in patients with ruptured aneurysms is outlined in Table 1. Most aneurysms treated were located in the anterior circulation (hydrogel 74 %, bare platinum 76 %). Mean aneurysm sizes were comparable (hydrogel 6.8 mm, bare platinum 7.1 mm). An unfavorable dome-to-neck of ≥1.5 was present in the majority of aneurysms treated (hydrogel 62 %, bare platinum 63 %). The use of assist devices was slightly more common in aneurysm treated with hydrogel coils (balloon remodeling 53 %, stent 24 %) when compared to aneurysms treated with bare platinum coils (balloon remodeling 46 %, stent 21 %). These differences did not reach statistical significance (balloon remodeling: $p=0.12$; stent: $p=0.41$). Violations of eligibility criteria were observed in a number of patients (hydrogel 22/243 [9.1 %], bare platinum 28/241 [12 %]). These patients were included in the analysis, and the protocol violations are specified in greater detail in Table 1.

Table 2 summarizes procedure and disease-related adverse events as well as the mortality rate within 14 days from treatment. Parent vessel dissections and parent vessel perforations happened one each in either arm of the study. Parent vessel occlusions occurred in two patients (0.8 %) assigned to hydrogel coils and in four patients (1.7 %) randomized to bare platinum coils. Reported procedural aneurysm ruptures were evenly distributed between the two arms of the study (hydrogel five patients [2.1 %], bare platinum seven patients [2.9 %]). The same holds true for thromboembolic events and strokes (hydrogel: thromboembolic events 4.5 %, strokes 2.5 %; bare platinum: thromboembolic events 5.4 %, strokes 2.5 %). Coil migration was observed in 3.7 % of patients assigned to hydrogel versus 2.5 % in subjects allocated to bare platinum (rate difference 1.2 %, 95 % CI [−2.1 to 4.7 %], $p=0.47$). The overall procedural complication rate was

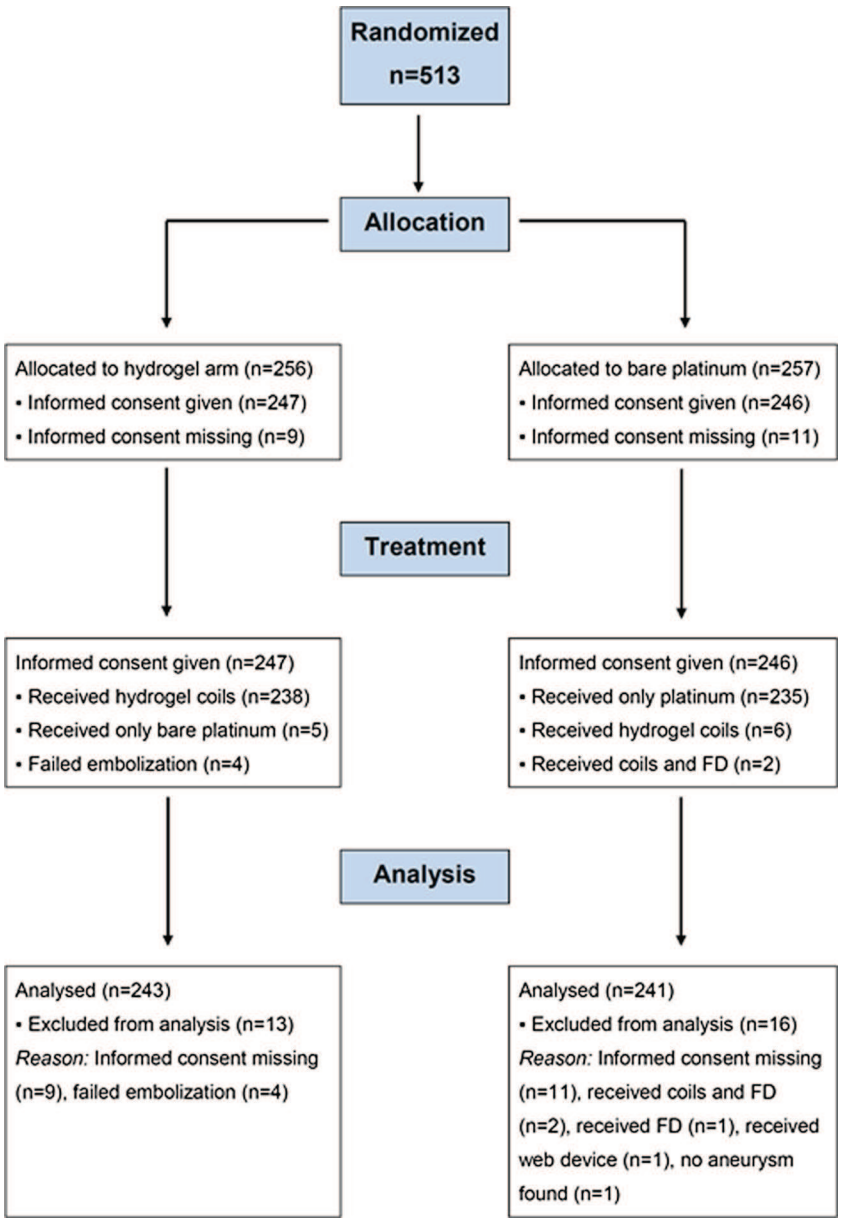

Fig. 1 Trial profile

11.5 % in patients assigned to hydrogel coils and 12.4 % in patients allocated to aneurysm treatment with bare platinum coils (rate difference −0.9 %, 95 % CI [−6.7 to 5.0 %], $p = 0.77$). Procedure-related stroke or death occurred in 3.3 % of patients, both for those assigned to hydrogel coils and to bare platinum coils. The 14-day mortality rates were also identical in both arms of the study (2.1 %; rate difference 0.0 %, 95 % CI [−3.2 to 3.0 %], $p = 0.99$). Except for one patient that died in relation to procedural aneurysm rupture, the remaining fatalities occurred in patients that had presented with recently ruptured aneurysms.

The members of the core lab were asked to review the DSA data for the presence of predefined adverse events (Table 2). Parent vessel occlusion occurred more often in patients assigned to bare platinum coils (hydrogel 2.5 %, bare platinum coils 5.0 %; rate difference −2.5 %, 95 % CI [−6.3 to 1.1 %], $p = 0.17$). Coil herniation seemed to be a common finding in both arms of the study (hydrogel 37 %, bare platinum 34 %, rate difference 3.2 %, 95 % CI [−5.4 to 11.7 %], $p = 0.47$). Both the occurrence of thrombus adhering to the coils at the level of the aneurysmal neck and distal emboli were observed slightly more frequently in patients assigned to bare platinum coils (hydrogel versus bare platinum: thrombus on coil 5.9 versus 6.3 %, rate difference −0.4 %, 95 % CI [−4.9 to 4.1 %], $p = 0.86$; distal emboli 4.2 versus 5.5 %, rate difference −1.2 %, 95 % CI [−5.3 to 2.8 %], $p = 0.55$).

Technical details on the coil embolization are displayed in Table 3. The median number of coils administered per

Table 1 Baseline data by randomized treatment (modified intention-to-treat)

	Randomized treatment				
	Hydrogel		Bare platinum		
	No.	%	No.	%	
Total no. of patients	243		241		*p* value
Gender					0.35
Female	172	71 %	161	67 %	
Male	71	29 %	80	33 %	
Age (years)					0.25
Mean ± SD (range)	52.9 ± 12.6 (24–79)		54.1 ± 11.8 (21–82)		
Baseline rupture status					0.79
Yes, in previous 30 days	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	3.9 %	3	2.9 %	
WFNS 5	1	1.0 %	1	1.0 %	
Missing					
Aneurysm location					0.54
Anterior	177	74 %	182	76 %	
Posterior/other	62	26 %	56	24 %	
Missing	*n* = 4		*n* = 3		
Target aneurysm size (mm)					0.18
Mean ± SD (range)	6.8 ± 2.1 (2–15)		7.1 ± 2.5 (2–18)		
Size aneurysm neck (mm)					0.17
Mean ± SD (range)	3.5 ± 1.3 (1–8)		3.6 ± 1.3 (2–9)		
Missing	*n* = 5		*n* = 4		
Dome-to-neck ratio					0.93
<1.5	90	38 %	90	38 %	
≥1.5	147	62 %	150	63 %	
Missing	*n* = 6				
Aneurysm shape					0.98
Regular	136	56 %	133	55 %	
Irregular/lobulated	107	44 %	107	45 %	
Missing	*n* = 0		*n* = 1		
Assist device used					
Balloon	129	53 %	110	46 %	0.12
Stent	59	24 %	50	21 %	0.41
Violations of eligibility criteria in patients included in the modified intention-to-treat analysis					
WFNS >3	5	2.1 %	4	1.7 %	
WFNS missing	*n* = 5		*n* = 3		
Age >75 years	7	2.9 %	5	2.1 %	
Aneurysm <4 mm	5	2.1 %	7	2.9 %	
Aneurysm >12 mm	2	0.8 %	8	3.3 %	
Aneurysm diameter missing	*n* = 1		*n* = 0		
>1 aneurysm/session planned	1	0.4 %	4	1.7 %	
Planned no./session missing	*n* = 0	*n* = 2			

Table 1 (continued)

	Randomized treatment			
	Hydrogel		Bare platinum	
	No.	%	No.	%
Aneurysm pretreated	1	0.5 %	1	0.4 %
Missing	$n=23$		$n=17$	
Patient was randomized on a second occasion (second randomization was ignored)	2	0.8 %	1	0.4 %
Any of these violations	22	9.1 %	28	12 %

aneurysm was 6 in both arms of the study. Although the median coil length administered was less important in aneurysms of the hydrogel arm (38 cm), both the calculated coil volume (0.032 mm^3) and the median packing density (39 %) were higher when compared to aneurysms assigned to bare platinum coils (median coil length 41 cm, $p=0.065$; calculated coil volume 0.024 mm^3, $p=0.023$; median packing density 31 %, $p<0.001$). The mean hydrogel coil length on the total coil length administered within the hydrogel arm of the study was 83 %. Due to crossover between the two study arms, six patients in the bare platinum arm received hydrogel coils, resulting in an average of 0.8 % hydrogel coil length in the bare platinum arm of the study. Median percentages of hydrogel coils administered were 93 and 0 % in the hydrogel and bare platinum arms, respectively.

The angiographic outcome has been established by the operators and was reviewed by an independent blinded core lab according to the Raymond scale (Table 4). According to the self-assessed angiographic outcome, complete occlusion rate was identical between the two

Table 2 Procedure-related adverse events (modified intention-to-treat)

	Randomized treatment				Rate difference hydrogel	*p* value
	Hydrogel		Bare platinum			
	No.	%	No.	%	–	
Total no. of patients	243		241		Bare platinum [95 % CI]	
Self-reported						
Parent vessel perforation	1	0.4 %	1	0.4 %	0.0 % [−1.9 to 1.9 %]	1.00
Parent vessel dissection	1	0.4 %	1	0.4 %	0.0 % [−1.9 to 1.9 %]	1.00
Parent vessel occlusion	2	0.8 %	4	1.7 %	−0.8 % [−3.4 to 2.0 %]	0.56
Procedural aneurysm rupture	5	2.1 %	7	2.9 %	−0.8 % [−4.0 to 2.2 %]	0.60
Thromboembolic event	11	4.5 %	13	5.4 %	−0.9 % [−5.0 to 3.2 %]	0.68
Stroke (treatment through discharge)	6	2.5 %	6	2.5 %	0.0 % [−3.2 to 3.4 %]	1.00
Coil migration	9	3.7 %	6	2.5 %	1.2 % [−2.1 to 4.7 %]	0.47
Procedure-related AEs with outcome death (treatment through discharge)	2	0.8 %	3	1.2 %	−0.4 % [−3.2 to 1.9 %]	0.73
Any of the previous complications and AEs	28	12 %	30	12 %	−0.9 % [−6.7 to 5.0 %]	0.77
Other procedure-related AE (treatment through discharge)	21	8.6 %	19	7.9 %		
14-day mortality	5	2.1 %	5	2.1 %	0.0 % [−3.2 to 3.0 %]	0.99
Core-lab assessed						
Parent vessel occlusion	6	2.5 %	12	5.0 %	−2.5 % [−6.3 to 1.1 %]	0.17
Coil herniation	89	37 %	81	34 %	3.2 % [−5.4 to 11.7 %]	0.47
Thrombus on coil ball	14	5.9 %	15	6.3 %	−0.4 % [−4.9 to 4.1 %]	0.86
Distal embolization	10	4.2 %	13	5.5 %	−1.2 % [−5.3 to 2.8 %]	0.55
Missing/incomplete DSA images	$n=4$		$n=3$			

AE adverse event, *CI* confidence interval

Table 3 Coil embolization (modified intention-to-treat)

	Randomized treatment		
	Hydrogel	Bare platinum	
Total no. of patients	243	241	*p* value
Number of implanted coils	6.5 ± 3.7, 6 (1–25)	7.0 ± 4.5, 6 (1–27)	0.46
Coil length administered (cm)	51.2 ± 43.3, 38 (2–259)	61.6 ± 59.4, 41 (3–352)	0.065
Coil length missing	*n* = 1	*n* = 0	
Calculated coil volume (mm^3)	0.0414 ± 0.0354, 0.032 (0.002–0.235)	0.0381 ± 0.0416, 0.024 (0.002–0.300)	*0.023*
Packing density (%)	41.1 ± 16.0, 39 (8–152)	32.9 ± 16.0, 31 (6–95)	*<0.001*
Packing density missing	*n* = 8	*n* = 9	
Length hydrogel coil administered (%)	83.2 ± 21.4, 93 (0–100)	0.8 ± 7.4, 0 (0–100)	

Mean ± SD, median (range), *p* values considered statistically significant are italicized

arms of the study (hydrogel 70.4 %, bare platinum 70.5 %). Residual necks were observed more frequently in patients treated with bare platinum coils (hydrogel 21 %, bare platinum 26 %), whereas the presence of residual aneurysms was reported more frequently in patients randomized to hydrogel coils (hydrogel 8.2 %, bare platinum 3.4 %). A comparable pattern was observed by the independent core lab, yet occlusion rates were far less prominent (hydrogel 54 %, bare platinum 52 %), and the number of residual aneurysms turned out to be considerably higher (hydrogel 26 %, bare platinum 25 %). The tests for differences between treatment groups on the three-level scale from complete occlusion through residual necks to residual aneurysms did not reach statistical significance using either the core-lab values ($p = 0.80$) or the self-assessed values ($p = 0.62$).

Discussion

The aim of this randomized controlled study was to compare the efficacy and safety of hydrogel coils with bare platinum coils. The article summarizes the adverse procedural events, core-lab-assessed angiographic outcome, and the 14-day mortality rate. This study provides evidence that aneurysm treatment with hydrogel coils has a similar safety and efficacy profile when compared with bare platinum coils.

Our overall treatment results are matching with published study data on endovascular aneurysm treatment in 3176 patients from three randomized controlled trials [4–6] and three registries [11, 17, 18]. The reported procedural complication rates in these studies ranged from 4.7 to 22 % (GREAT 12 %). The early mortality rates varied between 0 and 2.2 % (GREAT 2.1 %). Residual aneurysms at the end of procedure were observed

Table 4 Initial angiographic outcome, self-reported (modified intention-to-treat)

	Randomized treatment				
	Hydrogel		Bare platinum		
	No.	%	No.	%	
Total no. of patients	243		241		*p* value
Self-reported					
Complete obliteration	171	70 %	169	71 %	0.62
Residual neck	52	21 %	61	26 %	
Residual aneurysm	20	8.2 %	8	3.4 %	
Missing	*n* = 0	*n* = 3			
Core-lab assessed					
Complete obliteration	130	54 %	124	52 %	0.80
Residual neck	47	20 %	55	23 %	
Residual aneurysm	62	26 %	58	24 %	
Missing/incomplete DSA images	*n* = 4		*n* = 4		

between 5.4 and 19.3 % of cases in studies that used operator assessed data (GREAT 5.8 %). The rate of residual aneurysms in studies that relied on independent core-lab assessment of post procedural angiograms ranged from 12 to 37.3 % (GREAT 25.2 %). Table 5 exemplifies the safety and efficacy profiles of the corresponding studies in comparison to the GREAT trial.

In the GREAT study, the use of hydrogel coils was not associated with an increased incidence of parent vessel perforation, parent vessel occlusion, procedural aneurysm rupture, and thromboembolic events. A similar proportion of patients in both arms of the study had residual aneurysm necks and residual aneurysms on angiographic controls at the end of the procedure both in the self-reported angiographic outcome and in the core-lab data. The early mortality rate at 14 days was strictly the same in both study arms.

The analysis of administered coil lengths showed a nonsignificant trend that less total coil length was administered in the hydrogel arm of the study. As was observed in the HELPS trial, a RCT that compared aneurysm treatment with HydroCoils and bare platinum coils, the final calculated coil volumes as well as the packing density were higher in aneurysms treated with the new class of hydrogel coils. Whether these factors lead to an improved stability of aneurysm occlusion remains to be determined.

The study sample seems sufficiently high to reliably compare aneurysm treatment with hydrogel and bare platinum coils. Specific features known to have a major impact on complication rate and clinical and angiographic outcome such as patient age, rupture status, aneurysm size, location, dome-to-neck ratio, and the use of adjunct devices were very well balanced between the two arms of the study. The use of balloon remodeling or stents for aneurysm treatment seemed representative for current practice in most European centers.

We have a balanced crossover rate between the two arms of the study. In addition, we kept a number of patients with violations of eligibility criteria in the analysis (hydrogel 22 patients, bare platinum 28 patients). These protocol violations are specified in greater detail in Table 1. There was no difference in results when the data were analyzed by received treatment (in patients who crossed over) compared to the analyses by randomized treatment (data not shown). The important difference between the self-reported angiographic outcomes and the core-lab-assessed data has commonly been observed in the medical literature (Table 5) and once more exemplifies the necessity to implement independent core labs for the analysis of clinical study endpoints.

There are some limitations to our study. Due to the inclusion procedure, we may have underreported bad outcomes in our study. According to the study protocol, we were entitled to randomize and treat patients with ruptured aneurysms and WFNS scores of 2 and 3 without informed consent, because both hydrogel and the various bare platinum coils used in this study carry a CE mark. We needed informed consent from the patient or the relatives in order to be allowed to use these patients' data. In patients with a bad clinical outcome, we were, in some cases, unable to obtain informed consent and subsequently forced to remove the patient data from our data base. With 9 missing informed consents in the hydrogel arm of the study and 11 missing in patients randomized to treatment with bare platinum coils, we do not expect this to influence the comparison of the two types of coils.

It might be considered a limitation of this study that the only clinical outcome parameter is the 14-day mortality rate. The use of short-term clinical endpoints is fairly heterogeneous. Some trials report modified Rankin Scale (mRS) score or NIHSS at 24 h, others the discharge mRS, or the mRS at 1 month. In our study, we are dealing with a high percentage of patients that

Table 5 GREAT results compared to other coil studies

Study	Year	Number of patients	Type	Coil type	Ruptured aneurysms	Procedural complication rate	Mortality	Residual aneurysm at the end of procedure (%)	
								Self-reported	Core-lab assessed
HELPS [6]	2007	499	RCT	Hydrogel first generation + BP	53 %	22 %	1 (0.2 %)	18 %	n.a.
ATENA [17]	2008	649	Registry	Matrix + BP	0 %	15 %	9 (1.4 %)	19 %	n.a.
CLARITY [18]	2010	782	Registry	Matrix + BP	100 %	17 %	7 (0.9 %)	5.4 %	n.a.
KOREAN [11]	2011	120	Registry	Hydrogel second generation	28 %	4.7 %	0	n.a.	12 %
CERECYTE [4]	2012	500	RCT	Cerecyte + BP	47 %	13 %	2 (0.4 %)	9 %	12 %
MAPS [5]	2014	626	RCT	Matrix + BP	36 %	15 %	14 (2.2 %)	n.a.	37 %
GREAT	2015	484	RCT	Hydrogel second generation + BP	43 %	12 %	10 (2.1 %)	5.8 %	25 %

RCT randomized controlled trial, *Hydrogel first generation* HydroCoil, *Hydrogel second generation* HydroSoft and/or HydroFrame, *BP* bare platinum, *n.a.* not available

were treated for ruptured aneurysms. In this group of patients, the clinical outcome should be evaluated after a longer time period. For that reason, we chose to determine the clinical outcomes together with the angiographic outcome at 6 and 18 months.

Conclusion

Second-generation hydrogel coils can be used in a wide spectrum of aneurysms with a risk profile equivalent to that of bare platinum. Packing density was significantly higher in aneurysms treated with hydrogel coils. Whether this leads to an increased mid- and long-term stability of aneurysm occlusion after coil embolization remains to be determined.

Acknowledgments The study was funded by MicroVention Inc., the manufacturers of the HydroSoft/HydroFrame coils. MicroVention Inc. supplied the electronic case report form for data entry. We would also like to thank the following: Core Lab: Hubert Desal and Jens Fiehler. Trial Steering Committee: Christian Taschner (Lead Investigator), Alain Bonafé (Co-ordinator: French Centres), Martin Schumacher, Matthias Reinhard and Vera van Velthoven. Data Monitoring and Safety Committee: Daniel Rüfenacht (Chair), Werner Hacke and Meinhard Kieser (Statistician).

Compliance with ethical standards We declare that all human studies have been approved by the leading ethics committee (Faculty of Medicine, Freiburg University, Freiburg, Germany [077/09]) and the local ethics committees and were authorized by the competent French and German authorities and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest CAT has consulted for MicroVention Inc, Stryker Neurovascular, and Acandis GmbH.

References

1. Molyneux A, Kerr R, Stratton I et al (2002) International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 360:1267–1274
2. Taschner CA, Leclerc X, Gauvrit JY et al (2007) Safety of endovascular treatment of intracranial aneurysms with a new, complex shaped Guglielmi detachable coil. Neuroradiology 49:761–766
3. Slob MJ, Sluzewski M, van Rooij WJ et al (2005) The relation between packing and reopening in coiled intracranial aneurysms: a prospective study. Neuroradiology 47:942–945
4. Molyneux AJ, Clarke A, Sneade M et al (2012) Cerecyte coil trial: angiographic outcomes of a prospective randomized trial comparing endovascular coiling of cerebral aneurysms with either cerecyte or bare platinum coils. Stroke 43:2544–2550
5. McDougall CG, Johnston SC, Gholkar A (2014) Bioactive versus bare platinum coils in the treatment of intracranial aneurysms: the MAPS (Matrix and Platinum Science) trial. AJNR Am J Neuroradiol 35:935–942
6. White PM, Lewis SC, Gholkar A et al (2011) Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. Lancet 377:1655–1662
7. Tsumoto T, Niimi Y, Berenstein A (2009) Evaluation of the new HydroSoft coil in a canine model of bifurcation aneurysm. Lab Investig J Neurosurg 111:11–16
8. Killer M, Kallmes D, Jones R et al (2010) Long-term angiographic and histological results of a new hydrogel-containing filling coil in experimental rabbit aneurysms. Minim Invasive Neurosurg 53:97–105
9. Guo XB, Fan YM, Zhang JN (2011) HydroSoft coil versus HydroCoil for endovascular aneurysm occlusion study: a single center experience. Eur J Radiol 79:e42–e46
10. Waldau B, Turk AS 3rd, Yashar P et al (2012) Perioperative safety of HydroSoft coils. J Neurointerv Surg 4:375–378
11. Park JH, Kang HS, Han MH et al (2011) Embolization of intracranial aneurysms with HydroSoft coils: results of the Korean multicenter study. AJNR Am J Neuroradiol 32:1756–1761
12. Lee JY, Seo JH, Lee SJ et al (2014) Mid-term outcome of intracranial aneurysms treated with HydroSoft coils compared to historical controls treated with bare platinum coils: a single-center experience. Acta Neurochir 156:1687–1694
13. Taschner C, Chapot R, Costalat V et al (2015) GREAT-a randomized aneurysm trial. Design of a randomized controlled multicenter study comparing HydroSoft/HydroFrame and bare platinum coils for endovascular aneurysm treatment. Neuroradiology 57:599–604
14. Roy D, Milot G, Raymond J (2001) Endovascular treatment of unruptured aneurysms. Stroke 32:1998–2004
15. Yan X, Su XG (2010) Stratified Wilson and Newcombe confidence intervals for multiple binomial proportions. Stat Biopharm Res 2(3):329–335
16. van Elteren PH (1960) On the combination of independent two-sample tests of Wilcoxon. Bull Int Stat Inst 37:351–361
17. Pierot L, Spelle L, Vitry F (2008) Immediate clinical outcome of patients harboring unruptured intracranial aneurysms treated by endovascular approach: results of the ATENA study. Stroke 39:2497–2504
18. Pierot L, Cognard C, Ricolfi F et al (2010) Immediate anatomic results after the endovascular treatment of ruptured intracranial aneurysms: analysis in the CLARITY series. AJNR Am J Neuroradiol 31:907–911