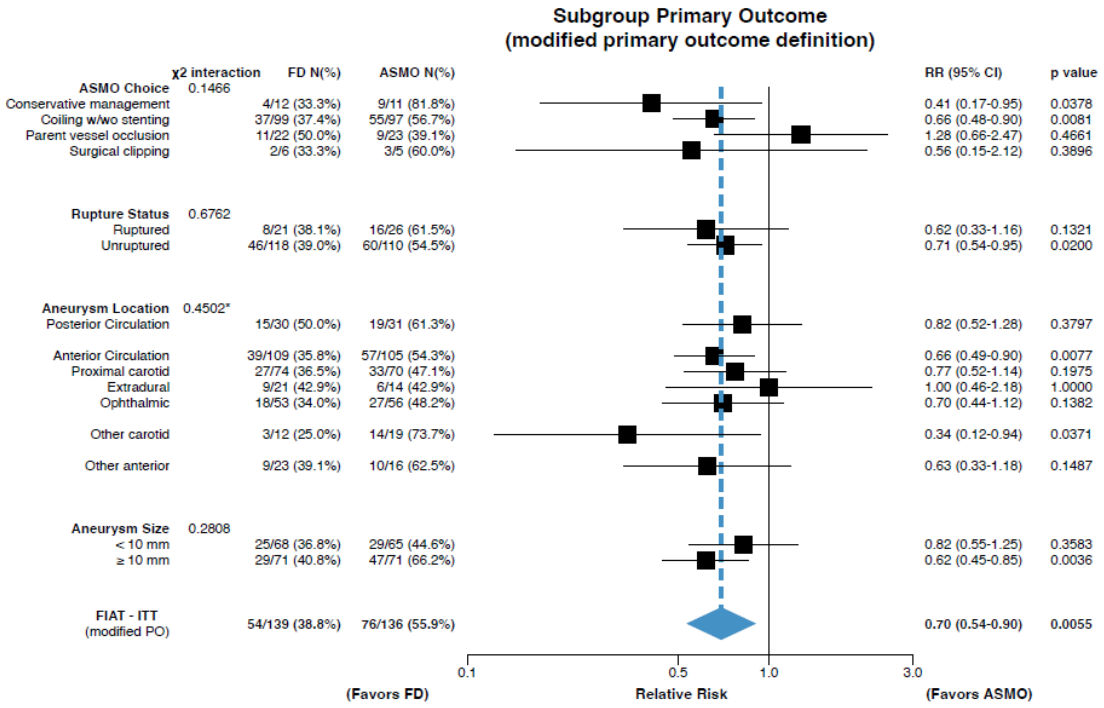
Supplementary online materials

Figure S1. Subgroup analysis with a modified primary outcome definition.



*The interaction term for Aneurysm Location was calculated for the main division into Anterior/Posterior

The angiographic component of the Primary Outcome was modified to comprise only complete occlusions, instead of complete and near-complete occlusions.

Table S1. Patient and aneurysm characteristics for all groups.

Characteristics	Randomization		Registry N = 45	Any Flow Diverter* N = 209
	ASMO N = 139	Flow Diversion N = 139		
Age, Mean (SD)	57 (12)	58 (12)	58 (12)	58 (12)
Female, N (%)	108 (77·7%)	110 (79·1%)	33 (73·3%)	162 (77·5%)
Presentation, N (%)				
Asymptomatic	72 (51·8%)	78 (56·1%)	24 (53·3%)	115 (55·0%)
Mass effect	41 (29·5%)	40 (28·8%)	14 (31·1%)	60 (28·7%)
SAH	26 (18·7%)	21 (15·1%)	7 (15·6%)	34 (16·3%)
Aneurysm size (mm)				
Mean (SD)	13 (9)	13 (10)	16 (12)	14 (11)
Median (range)	10 (2 – 51)	10 (1 – 56)	14 (2–60)	11 (1–60)
0 – 9, N (%)	66 (47·5%)	68 (48·9%)	16 (35·6%)	94 (45·0%)
10 – 25, N (%)	59 (42·4%)	54 (38·8%)	24 (53·3%)	89 (42·6%)
> 25, N (%)	14 (10·1%)	17 (12·2%)	5 (11·1%)	26 (12·4%)
Aneurysm neck (mm)				
Mean (SD)	5 (3)	5 (3)	6 (3)	5 (3)
Median (Min – Max)	5 (2 – 15)	5 (1 – 16)	5 (2 – 16)	5 (1 – 16)
Undefined, N (%)	22 (15·8%)	21 (15·1%)	22 (48·9%)	49 (23·4%)
Location, N (%)				
Anterior circulation	108 (77·7%)	109 (78·4%)	36 (80·0%)	165 (78·9%)
Proximal Carotid	71 (51·1%)	74 (53·2%)	27 (60·0%)	114 (54·5%)
Extradural	14 (10·1%)	21 (15·1%)	10 (22·2%)	34 (16·3%)
Ophthalmic	57 (41·0%)	53 (38·1%)	17 (37·8%)	80 (38·3%)
Other carotid	20 (14·4%)	12 (8·6%)	4 (8·9%)	20 (9·6%)
Other anterior	17 (12·2%)	23 (16·5%)	5 (11·1%)	31 (14·8%)
Posterior circulation	31 (22·3%)	30 (21·6%)	9 (20·0%)	44 (21·1%)

* Any flow diverter includes: All patients randomly allocated FD (n=139), patients who received FD in the registry (45), and patients of the ASMO group who received FD at any time (14 cross-overs included in primary analyses and 11 retreatments after aneurysm recurrence (once the primary outcome of the RCT was completed).

Table S2. Interventions carried out in the randomized groups.

	Randomization	
	ASMO N = 139	**Flow Diversion N = 139**
FD only	11 (7·9%)	106 (76·3%)
FD with coils	2 (1·4%)	20 (14·4%)
FD with stent	1 (0·7%)	3 (2·2%)
Simple coiling	51 (36·7%)	4 (2·9%)
Coiling with stent	36 (25·9%)	1 (0·7%)
PVO	21 (15·1%)	1 (0·7%)
Surgical clipping	6 (4·3%)	1 (0·7%)
Observation	11 (7·9%)	3 (2·2%)

Table S3. Primary safety outcome and safety of flow diversion.[1]

	Randomization			
	ASMO N = 139	**Flow Diversion N = 139**	**Registry N = 45**	**Any Flow Diverter* N = 209**
Death	3 (2·2%)	2 (1·4%)	2 (4·4%)	5 (2·4%)
mRS 3-5	9 (6·5%)	14 (10·1%)	5 (11·1%)	20 (9·6%)
Not available	2 (1·4%)	1 (0·7%)	0	1 (0·5%)
Total	14 (10·1%)	17 (12·2%)	7 (15·6%)	26 (12·4%)
Thromboembolic	7 (5·0%)	7 (5·0%)	3 (6·7%)	11 (5·3%)
Hemorrhagic	3 (2·2%)	4 (2·9%)	1 (2·2%)	6 (2·9%)
Mass Effect	2 (1·4%)	5 (3·6%)	1 (2·2%)	6 (2·9%)
Unrelated	0	0	2 (4·4%)	2 (1·0%)
Not available	2 (1·4%)	1 (0·7%)	0	1 (0·5%)
Total	14 (10·1%)	17 (12·2%)	7 (15·6%)	26 (12·4%)

1: The primary safety outcome was determined at 3 months. After 3 months, serious delayed FD-related complications such as intracranial hematomas and hemorrhages (n=5) and symptomatic arterial thrombosis (n=5) occurred 37 to 586 days after treatment in 10 of 209 patients who received FD at any time (4·8%; 95%CI[2·4%–8·9%]).

* Any flow diverter includes: All patients randomly allocated FD (n=139), patients who received FD in the registry (45), and patients of the ASMO group who received FD at any time (14 cross-overs initially and 11 retreatments after the primary efficacy outcome was reached). Patients allocated to FD, crossed-over to FD, or treated with FD in the registry (n=188) initially received a single FD (n=157) or two or more FDs (n=26). In 5 patients the number and type of device was not recorded. The most common devices used were Pipeline (114 patients), Silk (65) and FRED (4).

Table S4. Primary efficacy outcome in the per protocol analyses.

	Per Protocol (as treated)*	
	ASMO N = 124	**Flow Diversion N = 134**
Poor Outcome**	57 (46·0%)	31 (23·1%)
Clinical	12 (9·7%)	11 (8·2%)
mRS > 2	12 (9·7%)	9 (6·7%)
Aneurysm rupture	0	2 (1·5%)
Angiographic	44 (35·5%)	20 (14·9%)
Retreatment	7 (5·6%)	5 (3·7%)
Residual aneurysm	38 (30·6%)	15 (11·2%)
Good Outcome	67 (54·0%)	103 (76·9%)
Angiographic	67 (54·0%)	103 (76·9%)
Complete occlusion	51 (41·1%)	94 (70·1%)
Residual neck	16 (12·9%)	9 (6·7%)

** "as treated" groups comprise patients having successfully received ASMO or FD on the first attempt*
***RR: 0·50; 95%CI[0·35-·72];P=·0002*

	Per Protocol (as attempted)*	
	ASMO N = 132	**Flow Diversion N = 143**
Poor Outcome**	65 (49·2%)	40 (28·0%)
Clinical	12 (9·1%)	13 (9·1%)
mRS > 2	12 (9·1%)	11 (7·7%)
Aneurysm rupture	0 (0·0%)	2 (1·4%)
Angiographic	53 (40·2%)	27 (18·9%)
Retreatment	7 (5·3%)	5 (3·5%)
Immediate failure	8 (6·1%)	7 (4·9%)
Residual aneurysm	38 (28·8%)	15 (10·5%)
Good Outcome	67 (50·8%)	103 (72·0%)
Angiographic	67 (50·8%)	103 (72·0%)
Complete occlusion	51 (38·6%)	94 (65·7%)
Residual neck	16 (12·1%)	9 (6·3%)

** "as attempted" groups comprise patients having successfully received ASMO or FD on the first attempt, plus those in which ASMO or FD was attempted but could not be successfully carried out*
***RR: 0·57;95%CI[0·42–0·78]; P=·0004*

Table S5. Secondary outcomes.

		Randomization		
		ASMO N = 139	Flow Diversion N = 139	Chi–squared test with exact p–value*
mRS score at discharge				0·848
	mRS = 0 – 2	131 (94·2%)	129 (92·8%)	
	mRS = 3 – 5	7 (5·0%)	8 (5·8%)	
	mRS = 6	1 (0·7%)	2 (1·4%)	
Hospital stay (days)				0·959
	Mean (SD)	7 (26)	5 (12)	
	Median [IQ1–IQ3]	1[1–3]	1 [1–3]	
Discharge disposition				0·779
	Death	1 (0·7%)	2 (1·4%)	
	Hospital	6 (4·3%)	3 (2·2%)	
	Rehabilitation Center	7 (5·0%)	7 (5·0%)	
	Home	125 (89·9%)	127 (91·4%)	
mRS score at 12 months				0·510
	mRS = 0 – 2	123 (88·5%)	127 (91·4%)	
	mRS = 3 – 5	5 (3·6%)	6 (4·3%)	
	mRS = 6	9 (6·5%)	5 (3·6%)	
	Not available	2 (1·4%)	1 (0·7%)	
Successful intervention		131 (94·2%)	130 (93·5%)	1·000
Complications during intervention		17 (12·2%)	17 (12·2%)	0·814
	Thromboembolic	6 (4·3%)	8 (5·8%)	
	Hemorrhagic	3 (2·2%)	1 (0·7%)	
	Other	8 (5·8%)	8 (5·8%)	
Retreatment of index aneurysm		10 (7·2%)	8 (5·8%)	0·808
Angiographic outcome at 12 months				0·071
	Residual aneurysm	49 (35·3%)	36 (25·9%)	
	Residual neck	17 (12·2%)	12 (8·6%)	
	Complete occlusion	71 (51·1%)	91 (65·5%)	
	Not available	2 (1·4%)	0	

* except for Hospital stay (Mann–Whitney U test)

Table S6. Occlusion state of the aneurysm.

	Randomization		Chi-squared test with exact p-value*
	ASMO	**Flow Diversion**	
Complete occlusion	71/137 (51%)	91/139 (65·5%)	0·028
Near-complete occlusion	88/137 (64·2%)	103/139 (74·1%)	0·090

Table S7. Adverse Events.

	Randomization	
	ASMO N = 139	**Flow Diversion N = 139**
Serious AEs	**27 (19·4%)**	**28 (20·1%)**
Early (<1 month)	**18 (12·9%)**	**18 (12·9%)**
Stroke	*11 (7·9%)*	*9 (6·5%)*
Hemorrhage	*2 (1·4%)*	*2 (1·4%)*
Aneurysm rupture	*1 (0·7%)*	*1 (0·7%)*
Mass Effect	*0*	*4 (2·9%)*
Femoral complication	*3 (2·2%)*	*1 (0·7%)*
Systemic	*1 (0·7%)*	*0*
Late	**3 (2·2%)**	**9 (6·5%)**
Stroke	*2 (1·4%)*	*3 (2·2%)*
Aneurysm rupture	*0*	*2 (1·4%)*
Hydrocephalus	*0*	*2 (1·4%)*
Mass Effect	*1 (0·7%)*	*1 (0·7%)*
TIA (hospitalized)	*0*	*1 (0·7%)*
Retreatment-related	**3 (2·2%)**	**1 (0·7%)**
Unrelated	**3 (2·2%)**	**0**
Other AEs	**9 (6·5%)**	**22 (15·8%)**
Early (<1 month)	**6 (4·3%)**	**16 (11·5%)**
New imaging finding	*2 (1·4%)*	*8 (5·8%)*
Cranial nerve palsy	*2 (1·4%)*	*3 (2·1%)*
TIA	*2 (1·4%)*	*5 (3·6%)*
Late	**2 (1·4%)**	**5 (3·6%)**
New imaging finding	*2 (1·4%)*	*4 (2·9%)*
TIA	*0*	*1 (0·7%)*
Retreatment-related	**1 (0·7%)**	**1 (0·7%)**
Unrelated	**0**	**0**
Total	**36 (25·9%)**	**50 (36·0%)**

Table S8. Details of poor clinical outcomes at any time point, for all patients.

Age	Sex	Aneurysm	Procedure carried out	mRS Score	Days since procedure	Details
Allocated toFD						
63	F	20 mm middle cerebral, symptomatic	Coils + Stent	6	511	Arterial rupture during FD retreatment
75	M	3 mm ophthalmic/para-ophtalmic, ruptured	FD	6	8	FD migration and carotid thrombosis
66	M	24 mm vertebro-basilar junction, symptomatic	Coils + PVO	6	1100	Continual degradation from quadriplegia and brainstem oedema, secondary to progressive mass effect
81	F	19 mm carotid cavernous, symptomatic	PVO + Coils	6	424	Delayed death from stroke
57	F	52 mm carotid terminus, ruptured	Coils	6	1	Massive infarction from coiling before FD in delayed setting
56	F	27 mm basilar terminus, symptomatic	FD + Coils	5	95	Progressive mass effect
66	F	27 mm superior cerebellar, symptomatic	FD + Coils	5	30	Progressive mass effect
27	M	30 mm ophthalmic/para-ophthalmic, symptomatic	FD + Coils	5	54	Hydrocephalus treated urgently
52	F	8 mm ophthalmic/para-ophthalmic	FD	5	14	Hemorrhagic infarction
65	M	33 mm carotid cavernous, symptomatic	FD	5	9	Aneurysmal rupture
51	F	19 mm basilar terminus, symptomatic	FD	4	23	Progressive mass effect
72	F	16 mm vertebro-basilar junction	FD	4	0	Stroke
68	F	10 mm basilar terminus	FD + Coils	4	97	Basilar stroke
62	F	30 mm superior cerebellar, symptomatic	FD	4	1	Stroke
42	F	9 mm carotid cavernous, symptomatic	FD	3	525	Failure to reduce mass effect present at registration
74	F	13 mm carotid cavernous, symptomatic	FD	3	56	Progressive mass effect
70	F	13 mm ophthalmic/para-ophthalmic	PVO + Coils	3	0	Stroke from distal perforation during catheter navigation
74	F	13 mm ophthalmic/para-ophthalmic	FD + Coils	3	0	Stroke
Registry for flow diversion						
70	F	14 mm carotid terminus	FD + Coils	6	388	Aneurysmal rupture
50	M	25 mm vertebro-basilar junction, symptomatic	FD	6	586	Basilar artery thrombosis following treatment
82	F	19 mm carotid cavernous, symptomatic	FD + Stent	6	225	Unrelated
73	F	50 mm carotid cavernous, symptomatic	FD	6	8	Aneurysmal rupture
76	M	24 mm vertebro-basilar junction, symptomatic	FD + Stent	6	37	Basilar artery thrombosis
76	F	2mm posterior circulation, ruptured	FD	4	22	Stroke
69	M	2 mm posterior circulation, ruptured	FD	4	6	Initial rupture
38	F	23 mm posterior circulation	FD	4	0	Stroke from FD thrombosis
68	M	2 mm anterior inferior cerebellar, ruptured	FD	3	59	Encephalopathy due to liver disease
Allocated to ASMO						
17	M	30 mm vertebro-basilar junction, symptomatic	FD + Stent	6	427	Vertebro-basilar stroke from FD thrombosis
38	M	8 mm vertebro-basilar junction, ruptured	PVO	6	1	Rebleeding, 2 hours post-procedure
47	F	20 mm ophthalmic/para-ophthalmic, symptomatic	Surgery	6	38	Intraoperative rupture of aneurysm
65	F	15 mm ophthalmic/para-ophthalmic, symptomatic	Coils + Stent	6	242	Hemorrhage following retreatment
68	F	35 mm vertebro-basilar junction	PVO	6	134	Stroke and progressive mass effect
74	F	22 mm vertebro-basilar junction, symptomatic	PVO	6	368	Progressive mass effect
68	F	2mm anterior communicating, ruptured	Surgery	6	442	Lung cancer
75	F	11 mm carotid terminus	FD	6	104	Stroke with hemorrhagic transformation
68	F	16 mm extradural-carotid cavernous	PVO	6	368	Cervical cancer
58	M	50 mm basilar terminus, symptomatic	PVO	5	20	Progressive mass effect
66	F	20 mm carotid cavernous, symptomatic	FD	5	23	Intraparenchymal hemorrhage
38	M	42 mm basilar terminus, symptomatic	PVO	5	298	Failure of interventions to alleviate pre-intervention symptoms
52	M	12 mm posterior cerebral, symptomatic	Coils + Stent	5	270	Stroke from stent thrombosis following retreatment
56	M	25 mm middle cerebral bifurcation, ruptured	PVO	4	0	Stroke
60	M	13 mm anterior choroidal, symptomatic	Coils + Stent	4	33	Stroke after patient failed to take anti-platelets after discharge
59	M	28 mm basilar terminus, symptomatic	Coils + Stent	4	665	Stroke and hydrocephalus
68	F	16-mm carotid cavernous, symptomatic	PVO	3	1	Subdural hemorrhage

Table S9. mRS scores for all RCT patients

	ASMO N = 139	FD N = 139
mRS Primary Safety Outcome (within 3 months)		
6	3 (2.2%)	2 (1.4%)
5	2 (1.4%)	4 (2.9%)
4	5 (3.6%)	7 (5.0%)
3	2 (1.4%)	4 (2.9%)
2	10 (7.2%)	11 (7.9%)
1	47 (33.8%)	34 (24.5%)
0	68 (48.9%)	76 54.7%)
Not available	2 (1.4%)	1 (0.7%)
mRS Primary Efficacy Outcome		
6	9	5 (3.6%)
5	2 (1.4%)	1 (0.7%)
4	2 (1.4%)	3 (2.2%)
3	1 (0.7%)	2 (1.4%)
2	8 (5.8%)	10 (7.2%)
1	51 (36.7%)	39 (28.1%)
0	64 (46.0%)	78 (56.1%)
Not available	2 (1.4%)	1 (0.7%)