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ORIGINAL RESEARCH

Prospective study on embolization of intracranial aneurysms with the pipeline device: the PREMIER study 1 year results

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ABSTRACT

Background Preliminary clinical studies on the safety and efficacy of the pipeline embolization device (PED) for the treatment of small/medium aneurysms have demonstrated high occlusion rates with low complications.

Objective To evaluate the safety and effectiveness of the PED for treatment of wide necked small and medium intracranial aneurysms.

Methods PREMIER is a prospective, multicenter, single arm trial. Patients were treated with the PED for unruptured wide necked aneurysms, measuring ≤12 mm along the internal carotid artery or vertebral artery, between July 2014 and November 2015. At 1 year post-procedure, the primary effectiveness endpoint was complete occlusion (Raymond grade 1) without major parent vessel stenosis (≤50%) or retreatment, and the primary safety endpoint was major stroke in the territory supplied by the treated artery or neurologic death.

Results A total of 141 patients were treated with PEDs (mean age 54.6±11.3 years, 87.9% (124/141) women). Mean aneurysm size was 5.0±1.92 mm, and 84.4% (119/141) measured <7 mm. PED placement was successful in 99.3% (140/141) of patients. Mean number of PEDs implanted per patient was 1.1±0.26; a single PED was used in 92.9% (131/141) of patients. At 1 year, 97.9% (138/141) of patients underwent follow-up angiography with 76.8% (106/138) of patients having met the study's primary effectiveness endpoint. The combined major morbidity and mortality rate was 2.1% (3/140).

Conclusions Treatment of wide necked small/medium aneurysms with the PED results in high rates of complete occlusion without significant parent vessel stenosis and low rates of permanent neurologic complications.

Trial registration NCT02186561.

INTRODUCTION

Although surgical clipping, coiling, and stent assisted coiling are well established treatment options for small and medium wide necked aneurysms, these modalities are limited by associated morbidity and/or aneurysm recurrence rates.[1 2] The advent of flow diverters (FD), such as the pipeline embolization device (PED) (Medtronic, Irvine, California, USA) has changed the landscape for intracranial aneurysm treatment by introducing a minimally invasive therapy that could be used to treat wide necked and large/giant aneurysms effectively. However, large and giant aneurysms only encompass a small fraction of all intracranial aneurysms (IAs), as approximately 80% of all unruptured IAs are small or medium in size (≤12 mm).[3] Furthermore, the majority of ruptured IAs are smaller than 10 mm.[3 4]

Several studies have examined the efficacy of the PED for small/medium IAs and shown preliminary promise of high occlusion rates with low morbidity and mortality.[1 2 5–14] The IntrePED study reported outcomes for 793 patients (53% of whom had small/medium aneurysms) and demonstrated an excellent safety profile.[14] However, no prospective trial has yet tested the efficacy of PEDs specifically for small/medium wide necked aneurysms. The purpose of the Prospective Study on Embolization of Intracranial Aneurysms with the Pipeline Device (PREMIER) was to evaluate the safety and effectiveness of the PED in the treatment of wide necked intracranial aneurysms, measuring ≤12 mm, located along the internal carotid artery (ICA) (up to the terminus) or the vertebral artery (VA) segment up to and including the posterior inferior cerebellar artery.

METHODS

Study design, enrollment and patient selection

PREMIER (Clinical Trial Registry No NCT02186561) was a prospective, multicenter, single arm, interventional study. Between July 2014 and November 2015, 197 patients from 22 US participating sites and 1 Canadian center consented to achieve a total of 141 patients treated with PEDs. The study sample size was driven by the primary

safety endpoint, defined as neurological death or major stroke in the territory supplied by the treated artery through 1 year; based on a performance goal of 15% and a postulated primary safety event rate of no more than 9%, a sample size of 141 was required.

The major criterion for inclusion in the study was the presence of wide necked, unruptured IA arising from the ICA (all segments up to the carotid terminus) or VA (up to and including the posterior inferior cerebellar artery), measuring ≤12 mm in diameter, with neck ≥4 mm or a dome to neck ratio ≤1.5. The major cause of patient exclusion was failure to meet pre-procedure P2Y12 reaction units (PRU) (35/56). Patient inclusion and exclusion criteria are detailed in the online supplementary table I .

Aneurysm dimensions were measured using catheter based angiography and three-dimensional rotational angiogram images acquired at the time of patient screening. All images were submitted to an imaging screening committee and patients had to be considered appropriate for inclusion by at least two screening committee members prior to enrollment.

Baseline assessments

Prior to placement of the PED, patients underwent a baseline neurologic assessment using the modified Rankin Scale (mRS) and National InstitutesHealth Stroke Scale (NIHSS). Medical history, pre-existing conditions, and reason for treatment were documented. Baseline imaging consisted of CT angiography, MR angiography, or DSA, taken within 180 days prior to the procedure.

Dual antiplatelet therapy

Patients were tested for antiplatelet drug response using VerifyNow (Accumetrics, San Diego, California, USA) before PED implantation. PRU were required to be between 60 and 200. Patients with a PRU value outside this range were excluded. Patients were placed on aspirin (minimum 81 mg/day for 7 days) and clopidogrel (minimum 75 mg/day for 7 days) prior to PED placement. Clopidogrel loading dose or clopidogrel substitution for prasugrel or ticagrelor was not allowed for study participants. After the procedure, patients were placed on aspirin (81–325 mg/day) for at least 6 months and 75 mg/day of clopidogrel for at least 3 months.

Study device and procedure

The features of PED Classic and PED Flex have been previously described.[15 16] PED Flex was introduced during the second half of the study, with no change in implant procedures. Procedures were performed under either general anesthesia or local anesthesia with sedation by using standard transfemoral or radial approaches. Intravenous heparin was administered at 50–100 U/kg to achieve an activated clotting time >200 s. A 0.027 inch microcatheter (Marksman Catheter; Medtronic, Irvine, California) was used, with additional PEDs allowed, as needed, to completely cover the neck of the aneurysm. Additional coils were used at the operators' discretion. For utilization of PED Flex, the operators were required to have used the device in at least three previous cases.

Follow-up assessments

Patients underwent neurological assessment at 30 days, 6 months, and 1 year post-procedure. Follow-up DSA was mandatory at 1 year. All images were submitted for assessment by an independent core laboratory. Images were evaluated for degree of aneurysm occlusion according to the Roy–Raymond scale,[17] the presence and degree of parent vessel stenosis according to the methods of Samuels *et al*,[18] and the occurrence of implant migration.

Safety reporting

Investigators were requested to report all negative changes in health, and to judge the relationship of the adverse event to both the PED and the placement procedure. All serious adverse events were reviewed and adjudicated by an independent clinical events committee.

Study endpoints

The primary effectiveness endpoint was complete occlusion (Raymond Scale I) of the target IA without significant (≤50%) stenosis of the parent artery or retreatment through 1 year follow-up. The primary safety endpoint was incidence of major stroke (ischemic or hemorrhagic) in the territory supplied by the treated artery, defined as an increase in NIHSS score by 4 points or neurologic death within 1 year after treatment. Secondary endpoints included hemorrhagic complications at 30 days and device deployment success rate. Additional data collected at 1 year included device related neurologic adverse events, mRS score, recurrence and retreatment rates, procedural time, and number of PEDs utilized.

Statistical analysis

Demographic, baseline, and procedural characteristics were summarized and reported as mean±SD, median, and minimum and maximum values for continuous variables. Categorical data were summarized using numbers and percentages. In addition to reporting outcomes based on available data for missing data at the 1 year follow-up, a multiple imputation analysis was performed, which included the primary effectiveness endpoint, primary safety endpoint, and the two secondary safety endpoints. The variables selected for the multiple imputation analysis were age, gender, aneurysm maximal diameter, and parent artery location. Statistical analysis was performed using R (V.3.0 and above, R Foundation for Statistical Computing, Vienna, Austria) and SAS (V.9.0 and above, SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient and aneurysm characteristics

A total of 141 patients were treated; 124 (87.9%) were women. Mean age was 54.6±11.3 years. Median target aneurysm size was 4.6 mm (mean 5.0±1.92 mm) with median neck size of 3.7 mm (mean 4.0±1.42 mm). Among the 141 aneurysms, 119 (84.4%) measured <7 mm in size and 22 (15.6%) measured 7–12 mm on the largest diameter.

There were 136 (96.5%) aneurysms with saccular morphology, of which 47 (34.6%) had side branch involvement. The remaining 5 (3.5%) aneurysms were fusiform. A total of 134 (95.0%) aneurysms were located along the ICA, with the remaining 7 (5.0%) at the V4 segment of the VA. Most aneurysms in the ICA were located at the C6 ophthalmic segment (74.6%, 100/134) and C7 communicating segment (14.2%, 19/134). Patient baseline characteristics, medical history, and aneurysm characteristics are summarized in table 1.

Reasons for treatment of aneurysms are summarized in the online supplementary table II. The most common reason for treatment was patient preference (63.1%, 89/141). A summary of aneurysm risk factors is reported in the online supplementary

Table 1 Baseline patient and aneurysm characteristics

Characteristic	
Demographics (n=141)	
Age (years) (mean±SD)	54.6±11.3
Women (n (%))	124 (87.9)
Baseline mRS (mean±SD (range))	0.2±0.5 (0–2)
Baseline NIHSS (mean±SD (range))	0.1±0.6 (0–4)
Medical history (n=141) (n (%))	
Hypertension	72 (51.1)
Hyperlipidemia	54 (38.3)
Diabetes mellitus	16 (11.3)
Obesity	24 (17.0)
Cerebral atherosclerosis	1 (0.7)
Atrial fibrillation	7 (5.0)
Myocardial infarction	2 (1.4)
Coronary artery disease	9 (6.4)
Sleep apnea	16 (11.3)
Alcohol use	3 (2.1)
Smoking history (n (%))	
Never smoked, or has not smoked within 10 years	79 (56.0)
Not a current smoker, but has smoked within 10 years	21 (14.9)
Current smoker, <1 pack/day	27 (19.1)
Current smoker, ≥1 pack/day	14 (9.9)
Aneurysms characteristics (median (mean±SD))	
Aneurysm size (mm)	4.6 (5.0±1.9)
Neck width (mm)	3.7 (4.0±1.4)
Dome to neck ratio	1.1 (1.1±0.3)
Aneurysm location (n/N (%))	
ICA	134/141 (95.0)
ICA–petrous segment (C2)	1/134 (0.7)
ICA–clinoid segment (C4)	11/134 (8.2)
ICA–cavernous segment (C5)	3/134 (2.2)
ICA–ophthalmic segment (C6)	100/134 (74.6)
ICA–PCom segment (C7)	19/134 (14.2)
Vertebral artery	7/141 (5)

ICA, internal carotid artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PCom, posterior communicating artery.

table III. Aneurysm multiplicity was the most prevalent aneurysm risk factor (37.6%, 53/141).

Procedure

Successful device deployment was reported in 140/141 cases (99.3%). In one patient, a PED was not successfully implanted during the first procedure attempt and was successfully placed during a second procedure. A single PED was used in 131 (92.9%) patients, and multiple PEDs were used for complete neck coverage in 9 (6.4%) patients. The mean number of devices used per patient was 1.1±0.3 (range 0–2). Mean total procedural time was 78.4±40.3 min (range 20–217), and mean time from first PED introduction to last PED delivery system removal was 14.3±15.1 min. PED Classic was used in 64 (45.7%) patients while PED Flex was used in 77 (55.0%) cases. In 5 (3.5%) cases, the operators chose adjuvant use of coils. Core laboratory adjudication demonstrated complete aneurysm neck coverage by PED in 139 (98.6%) cases with complete wall apposition in 119 (84.4%). Procedural details are described in table 2.

Table 2 Procedural details

Characteristic	n=141
Successful device deployment to target site (n (%))	140 (99.3)
Procedure time (min) (mean±SD (range))	78.4±40.3 (20–217)
First pipeline introduction to last device removal time (min) (mean±SD (range))	14.3±15.1 (1–92)
No of pipeline devices per patient (mean±SD (range))	1.1±0.3 (1–2)
Patients with multiple pipeline devices (n (%))	9 (6.4)
Pipeline devices used* (n (%))	
Pipeline embolization device Classic	64/140 (45.7)
Pipeline embolization device Flex	77/140 (55.0)
Balloon used (n (%))	31 (22.0)
Adjunctive devices used (per imaging core lab) (n (%))	
Coils	5 (3.5)
None	136 (96.5)
Complete wall apposition (n (%))	119 (84.4)
Entire neck covered (n (%))	139 (98.6)

*One patient had both type of devices implanted.

Primary effectiveness endpoint

Of the total 141 patients, 138 (97.9%) underwent 1 year follow-up angiography with 81.9% (113/138) of the aneurysms demonstrating complete occlusion (Raymond–Roy grade 1). In the intent to treat population, the primary effectiveness endpoint was met in 76.8% (106/138) of patients. Thirty-two patients (23.2%, 32/138) failed to reach the primary effectiveness endpoint. Reasons for primary effectiveness endpoint failure are described in table 3. There were three patients with missing follow-up images: one died, one refused follow-up, and one agreed to have clinical follow-up but not imaging follow-up.

Primary safety endpoint

Of 140 patients with available data, 3 (2.1%) experienced a primary safety endpoint event (major stroke), with 1 leading to neurological death. These results are summarized in table 4. In one patient, symptoms of a left hemispheric event occurred 15 days after treatment. Head CT revealed an intraparenchymal hemorrhage (unrelated to aneurysm rupture). A second patient presented with seizure and left-sided weakness 165 days after the procedure. Head CT revealed an infarct involving the right middle cerebral artery territory. The patient had discontinued dual antiplatelets a few weeks before this event. A third patient developed a right hemispheric syndrome a few hours after treatment. Head CT demonstrated a large intraparenchymal

Table 3 Summary of failure reasons for primary effectiveness endpoint

Reasons for primary effectiveness endpoint failure	n=138
Residual aneurysm (n (%))	22 (15.9)
Residual neck (n (%))	3 (2.2)
Stenosis >50% (n (%))	4 (2.9)
Target aneurysm retreatment (n (%))	4 (2.9)
Total (n (%))	32 (23.2)*

*One subject had both incomplete occlusion and retreatment.

Table 4 Primary outcomes and secondary safety outcomes at 1 year post-procedure

Event	Observed data (n/N (%))	Multiple imputation (n=141)* (%)
Primary effectiveness outcome		
Complete aneurysm occlusion without significant parent artery stenosis (≤50%) or retreatment	106/138 (76.8)	76.7
Primary safety outcome		
Major stroke in the territory supplied by the treated artery or neurological death at 1 year post-procedure	3/140 (2.1)	2.2
Secondary outcomes		
Major stroke in the territory supplied by the treated artery or neurological death due to procedural complications at 30 days post-procedure	0/140 (0.0)	0.0
Delayed intracerebral hemorrhage >30 days post-procedure	1/140 (0.7)	0.7

*Multiple imputation for patients missing endpoint evaluation.

hemorrhage with significant mass effect, and midline shift with subfalcine and uncal herniation, leading to the patient's death post-procedure.

Other outcomes

There were no cases of intraoperative aneurysm rupture, delayed aneurysm rupture, or documented recurrence after complete aneurysm occlusion. At the 1 year follow-up, 137/139 (98.6%) patients had an mRS score of 0–2, and 4/141 (2.8%) underwent retreatment. The secondary safety endpoint of delayed intracerebral hemorrhage 31 days to 1 year post-procedure occurred in 1 patient (0.7%). The clinical events committee adjudicated this event as non-serious, and device related.

DISCUSSION

PREMIER is the first prospective multicenter study to evaluate the use of FDs in small/medium, unruptured IAs located in the ICA and VA. Treatment of these aneurysms with PEDs results in high rates of complete occlusion with low morbidity, mortality, recurrence, and retreatment, suggesting that the PED is a safe and effective alternative to microsurgery and conventional endovascular techniques in such cases.

While small/medium aneurysms are most often treated with coils, wide necked aneurysms are difficult to coil due to the increased risk of coil migration or protrusion into the parent vessel.[19 20] The PED shape optimizes its ability to cover the aneurysm neck and results in high occlusion rates without the risks associated with microsurgery, and with higher rates of complete occlusion than other endovascular techniques, such as coil embolization with or without stent or balloon assistance, in wide necked aneurysms.[21] Moreover, the PED is often used as a standalone therapy, which simplifies the procedure by not requiring aneurysmal catherization,[9] and reduces procedure time.[22] As the PED is deployed without the need to access the aneurysmal sac, the risk of intraoperative rupture may be substantially reduced.[7–9] The PREMIER study supports this finding, as no intraoperative ruptures were reported. This procedural advantage may be especially important for the treatment of small/medium aneurysms, as the risk of intraoperative rupture during coiling has been reported to be higher compared with large aneurysms.[23 24]

The Pipeline for Uncoilable or Failed Aneurysms (PUFS) study previously demonstrated the safety and efficacy of the PED for aneurysms >10 mm located in the ICA, proximal to the posterior communicating segment, with an occlusion rate of 95% at 5 years and no episodes of recurrence after complete occlusion.[25 26] However, approximately 80% of all aneurysms were small or medium in size (≤12 mm),[3] and the majority of ruptured aneurysms were <10 mm.[3 4] A handful of studies have begun exploring the use of the PED for the treatment of small and medium wide necked aneurysms and have shown a promising safety and effectiveness profile,[1 2 5 6 8 9 11–13 27 28] although these studies are limited by their retrospective design, single center series, and lack of external adjudication of adverse events or angiography. The incidence of thromboembolic events was reported as 7.3–8.7% of patients.[2 28] Mortality rates ranged from 0% to 2.3%,[1 2 8 27 28] and occlusion rates ranged from 70.0% to 91.7%.[1 2 5 6 8 27 28] One major international retrospective study, IntrePED, analyzed the results of 793 patients with 906 aneurysms treated with PEDs in 17 centers.[15] There were 473 (52.2%) small aneurysms (<10 mm), 349 (38.5%) of which were located in the ICA. The combined neurologic morbidity and mortality rate for unruptured aneurysms <10 mm in IntrePED was 4.1% compared with the higher rate of 9.2% seen with larger aneurysms.

In terms of the metal coverage required for effective aneurysm treatment, the PREMIER study had a mean device utilization of 1.1, in contrast with three devices used in PUFS.[25] Multiple devices were used in only 6.4% of cases in PREMIER. Occlusion rates at 1 year for PUFS (87%) were slightly higher than PREMIER, but are difficult to compare statistically due to differences in inclusion criteria and aneurysm characteristics. In a recent meta-analysis of the FD literature,[29] the rate of complete occlusion in 1645 aneurysms was lower than the PREMIER study at 76% (95% CI 70% to 81%).

PREMIER is the first FD study to exclude patients from enrollment based on pretreatment PRU levels outside a prespecified range at all treating sites. Our study reported lower ischemic complication rates, but similar hemorrhagic complications compared with IntrePED. This could be partially explained by collective and individual learning curves with PEDs and introduction of the PED Flex system. However, limiting the use of FDs to patients responsive to antiplatelet therapy seems to yield better results. It remains unknown whether actively monitoring platelet function and adjusting antiplatelet therapy similarly leads to improved outcomes. Although this requires further studies, device surface modification has been proposed as a possible strategy to reduce thromboembolic complications, such as PED Shield, which includes a surface phosphorylcholine biocompatible polymer that has the potential to reduce thromboembolic complications.[30 31]

A major limitation of this study is the single am nature and lack of a comparison group with which to compare outcomes. Furthermore, almost 75% of the aneurysms treated were located in the ophthalmic segment of the ICA; further location focused studies may be needed to demonstrate the effectiveness of PED

throughout the cerebral vasculature. Lastly, PREMIER examines a specific subset of difficult to coil aneurysms, but the lack of large, giant, or unruptured aneurysms means that its results should only be generalized to small/medium wide necked aneurysms.

CONCLUSION

PREMIER is the first prospective, independently adjudicated imaging and clinical outcomes, multicenter study assessing the safety and efficacy of PEDs for the treatment of unruptured IAs measuring ≤12 mm located along the ICA and VA. The present findings provide evidence of high procedural success and high complete occlusion, with low morbidity, mortality, recurrence, and retreatment. Our findings suggest that, when a decision is made to treat these lesions, the PED is a safe and effective alternative to microsurgery and conventional endovascular techniques.

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