

Morbidity and Mortality in Patients with Posterior Circulation Aneurysms Treated by the Pipeline Embolization Device : A Subgroup Analysis of the IntrePED Registry

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Background

- ❖ The International Retrospective Study of Pipeline™ Embolization Device ([IntrePED](#), [Kallmes et al. 2015 AJNR](#)) was a global, multicenter, single-arm, retrospective registry that investigated the safety outcomes of patients who underwent Pipeline Embolization Device (PED) placement for the treatment of intracranial aneurysms. A subgroup analysis from this registry was conducted to study complications associated with the treatment of posterior circulation aneurysms.



- **Title :** InPrePED
- **Study design :** Retrospective, multicenter, post market registry
- **Target population :** Patients with intracranial aneurysms treated with the PED
- **Inclusion Criteria:**
 - Received PED treatment for an intracranial aneurysm after the date of regulatory approval in that region or country
 - Had a clinical evaluation following treatment during the window of time before institutional review board/ethics committee approval
- **Study period :** From July 2008 to February 2013
- **Primary endpoint :**
 - spontaneous rupture
 - intracranial hemorrhage
 - ischemic stroke
 - asymptomatic/symptomatic parent artery stenosis
 - permanent cranial neuropathy

- Purpose : To study the complications associated with the treatment of posterior circulation aneurysms in the IntrePED registry.
- Among *793 patients with 906 aneurysms* treated with PEDs, *91 patients with 95 posterior circulation aneurysms* were analyzed

Primary Endpoint and Definitions

- **Primary endpoint:** any complication leading to neurologic morbidity or neurologic death
- **Definitions:**
 - **Neurologic morbidity:** the following complications lasting ≥ 7 days:
 - ❖ Spontaneous rupture of the target aneurysm
 - ❖ Intracranial hemorrhage
 - ❖ Ischemic stroke
 - ❖ Asymptomatic/Symptomatic parent artery stenosis
 - ❖ Permanent cranial neuropathy
 - **Major adverse event :** an ongoing clinical deficit at 7 days following the event
 - **Minor adverse event :** event resolved within 7 days with no clinical sequelae

Results: Posterior Circulation Baseline Patient Characteristics

| Characteristics | Patients |
|---------------------------------|--------------------|
| Number of Subjects | 95 |
| Age (years) | |
| <i>Mean ± SD</i> | 57.6 ± 15.8 |
| <i>Median, Range (min, max)</i> | 59.0 (18.0, 86.0) |
| Female, n (%) | 48 (52.7) |
| Follow-up duration (months) | |
| <i>Mean ± SD</i> | 22.4 ± 10.5 |
| <i>Median, Range (min, max)</i> | 21.1 (0.1, 60.5) |
| Procedure time (min.) (N=85) | |
| <i>Mean ± SD</i> | 98.3 ± 51.4 |
| <i>Median, Range (min, max)</i> | 88.0 (34.0, 294.0) |
| Additional coiling, n (%) | 18 (19.8) |

SD: standard deviation

Results: Baseline and Procedural Aneurysm Characteristics

| Characteristics | Aneurysms |
|---|-------------------|
| Number of aneurysms | 95 |
| Aneurysm size (mm) (N=93) | |
| <i>Mean ± SD</i> | 13.8 ± 8.4 |
| <i>Median, Range (min, max)</i> | 11.6, (1.5, 45.0) |
| Aneurysm type according to size (N=93), n (%) | |
| <i>Small</i> | 33 (35.5) |
| <i>Large</i> | 46 (49.5) |
| <i>Giant</i> | 14 (15.1) |
| Aneurysm neck (mm) (N=70) | |
| <i>Mean ± SD</i> | 8.7 ± 7.5 |
| <i>Median, Range (min, max)</i> | 6.6, (1.7, 53.0) |
| Aneurysm shape | |
| <i>Fusiform</i> | 28 (29.5) |
| <i>Saccular</i> | 35 (36.8) |
| <i>Dissecting</i> | 27 (28.4) |
| <i>Other*</i> | 5 (5.3) |
| Aneurysm location | |
| <i>Posterior cerebral artery</i> | 15 (15.8) |
| <i>Basilar artery</i> | 44 (46.3) |
| <i>Vertebral artery</i> | 33 (34.7) |
| <i>Posterior inferior cerebellar artery</i> | 3 (3.2) |
| Presented with ruptured aneurysm | 7 (7.4) |
| Multiple PEDs utilized | |
| ≥3 | 14 (14.7) |
| ≥2 | 36 (37.9) |
| <i>Mean ± SD</i> | 1.7±1.2 |
| <i>Range (minimum, maximum)</i> | 1,9 |

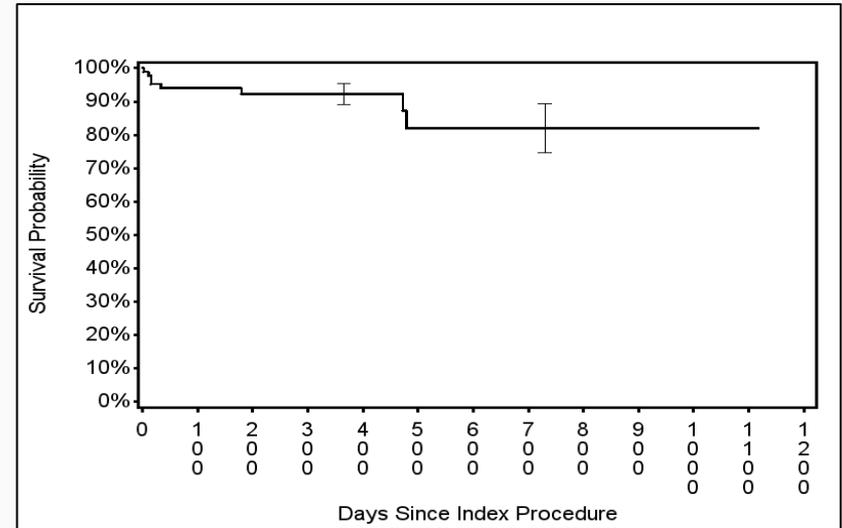
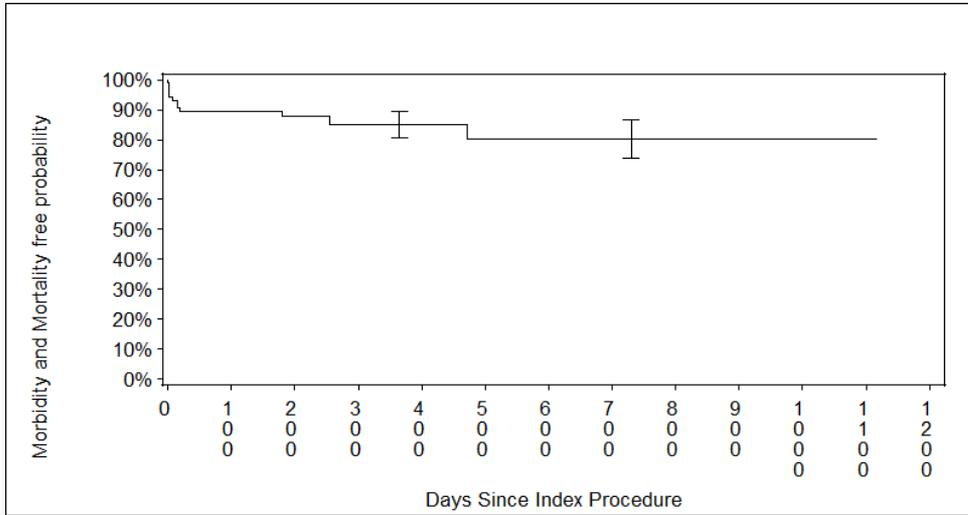
*Three bifurcation aneurysms, 1 mostly thrombosed aneurysm, and 1 blister aneurysm

Results: Clinical Summary of Major Complications

- Median follow-up time: 21.1 months
- Major complications:
 - Spontaneous rupture: 1.1% (1/91)
 - Intracranial hemorrhage: 2.2% (2/91)
 - Ischemic stroke: 6.6% (6/91)
 - Asymptomatic/symptomatic parent artery stenosis: 0% (0/91)
 - Permanent cranial neuropathy: 0% (0/91)
- Death: 7.7% (7/91)

Results: Kaplan-meier Curve for Major Complications

(A) Neurologic Morbidity and Neurologic Mortality (B) Overall Survival



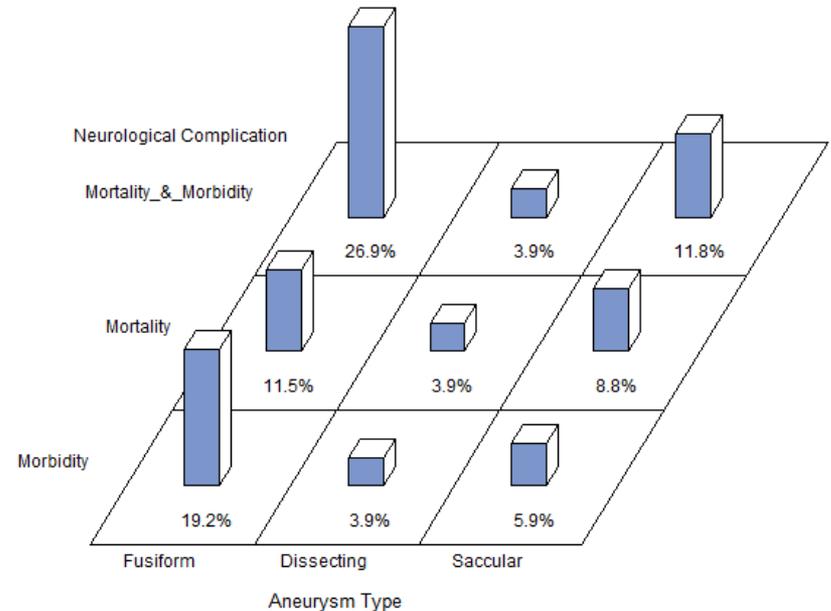
1 year major complications-free survival rate : 85.1% (95% CI, 73.8%-91.8%)
2 year major complications-free survival rate : 80.1% (95% CI, 63.8%-89.7%)
3 years major complications-free survival rate : 80.1% (95% CI, 63.8%-89.7%)

1 year survival rate : 92.3% (95% CI, 83.4%-96.5%)
2 year survival rate : 82.0% (95% CI, 61.8%-92.2%)
3 years survival rate : 82.0% (95% CI, 61.8%-92.2%)

These major complications rate and mortality rate are comparable with **15% of functional dependence** and **9.8% of mortality** after conventional coil embolization in 489 patients with posterior circulation aneurysms in the systematic review by *Lozier AP et al.*

Results: Morbidity and Mortality

- Major complications according to aneurysm shape:
 - **fusiform type versus other types** (dissecting and saccular), $p=0.034$
 - **fusiform type versus dissecting type**, $p=0.0496$

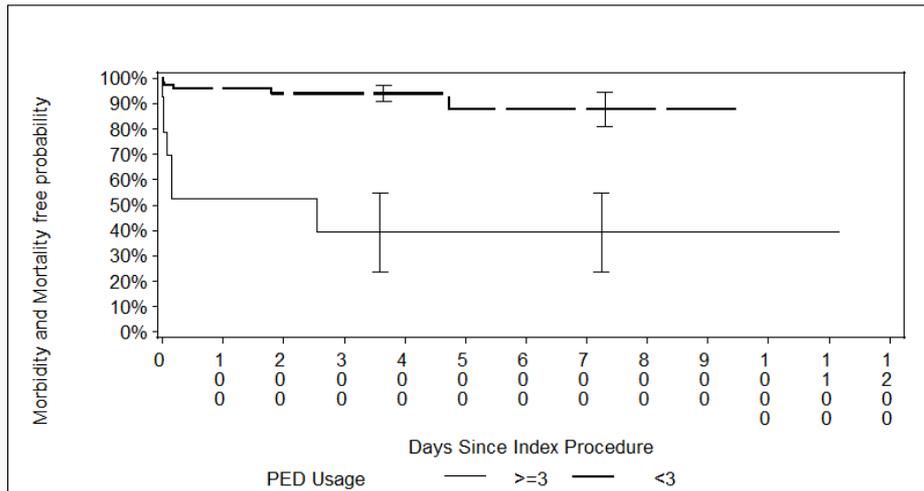


Significantly higher major complication rates with fusiform aneurysms compared to other aneurysm shapes

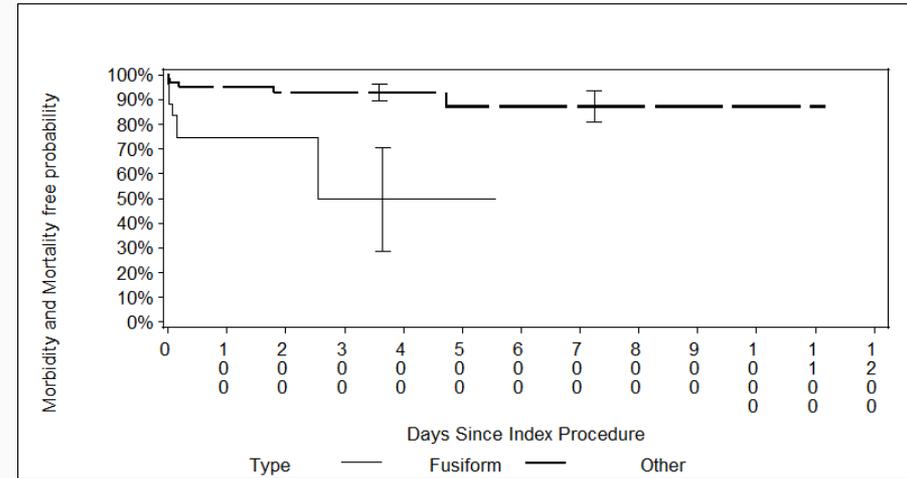
Results: Morbidity and Mortality

- Kaplan-Meier curves for (A) composite of morbidity and mortality according to PED use (log rank test; $P < 0.0001$) and (B) aneurysm shape (log rank test; $P = 0.0021$). "Other" means dissecting or saccular or the other type.

(A)



(B)



Significantly higher combined neurologic morbidity and neurologic mortality rates when 3 or more PEDs were used or fusiform aneurysms were treated

Results: Neurologic Morbidity & Neurologic Mortality Univariate Analysis of Posterior Circulation Aneurysms

| Major Neurological Complications (N = 89) | HR (95% CI) | P value |
|---|--------------------|---------|
| Morbidity | | |
| Age (years) | 0.99 (0.95-1.04) | 0.66 |
| Female | 0.34 (0.06-1.34) | 0.17 |
| Aneurysm size (mm) | 1.11 (1.04-1.18) | 0.0015 |
| Aneurysm neck dimension (N = 70)* | 1.16 (1.07-1.30) | 0.0023 |
| BA vs. PCA + VA + PICA | 2.04 (0.54-8.82) | 0.33 |
| BA + VA vs. PCA + PICA | 4.09 (0.51-529.71) | 0.36 |
| BA + PCA vs. VA + PICA | 1.08 (0.29-4.68) | 0.91 |
| Ruptured vs. unruptured | 0.73 (0.01-5.85) | 0.84 |
| Fusiform vs. saccular or dissecting or others | 4.93 (1.29-21.73) | 0.03 |
| Multiple PEDs ≥ 3 vs. < 3 | 10.0 (2.65-43.38) | 0.0016 |
| PED and coils vs. PED only | 0.95 (0.10-4.40) | 0.95 |
| Mortality | | |
| Age (years) | 1.05 (0.99-1.13) | 0.12 |
| Female | 0.71 (0.16-2.93) | 0.66 |
| Aneurysm size (mm) | 1.10 (1.01-1.18) | 0.0202 |
| Aneurysm neck dimension (N = 70)† | 1.08 (0.96-1.16) | 0.10 |
| BA vs. PCA + VA + PICA | 6.51 (1.35-63.05) | 0.0549 |
| BA + VA vs. PCA + PICA | 4.23 (0.51-550.58) | 0.36 |
| BA + PCA vs. VA + PICA | 2.91 (0.61-27.95) | 0.27 |
| Ruptured vs. unruptured | 4.58 (0.82-19.13) | 0.063 |
| Fusiform vs. saccular or dissecting or others | 3.48 (0.72-16.13) | 0.12 |
| Multiple PEDs ≥ 3 vs. < 3 | 9.91 (2.38-44.89) | 0.0029 |
| PED and coils vs. PED only | 1.48 (0.15-7.36) | 0.69 |
| Morbidity and mortality | | |
| Age (years) | 1.01 (0.98-1.06) | 0.48 |
| Female | 0.63 (0.20-1.89) | 0.43 |
| Aneurysm size (mm) | 1.10 (1.04-1.16) | 0.0008 |
| Aneurysm neck dimension (N = 70)* | 1.14 (1.07-1.25) | 0.0013 |
| BA vs. PCA + VA + PICA | 3.54 (1.12-14.18) | 0.0529 |
| BA + VA vs. PCA + PICA | 6.42 (0.84-823.73) | 0.22 |
| BA + PCA vs. VA + PICA | 1.78 (0.56-7.12) | 0.38 |
| Ruptured vs. unruptured | 2.61 (0.50-9.03) | 0.19 |
| Fusiform vs. saccular or dissecting or others | 5.18 (1.67-17.36) | 0.0066 |
| Multiple PEDs ≥ 3 vs. < 3 | 10.23 (3.38-32.92) | <0.0001 |
| PED and coils vs. PED only | 1.28 (0.24-4.51) | 0.74 |

*Not included in multivariate analysis due to >25% missing data

Results: Combined Neurologic Morbidity and Mortality Multivariate Analysis

| | Variables | Hazard Ratio | 95% CI | P value |
|-------------------------------------|------------------------|--------------|------------|---------|
| Model 1 (N = 91) | Multiple PEDs ≥ 3 | 7.77 | 2.48-25.86 | 0.0007 |
| | Fusiform shape | 3.48 | 1.06-13.39 | 0.0488 |
| Model 2 (N = 89)^a | Multiple PEDs ≥ 3 | 4.67 | 1.07-18.86 | 0.0385 |
| | Fusiform shape | 2.80 | 0.80-10.33 | 0.12 |
| | Aneurysm size (mm) | 1.04 | 0.98-1.11 | 0.23 |

CI, confidence interval; PED, Pipeline™ Embolization Device.

^aTwo patients with missing values of aneurysm size were excluded.

All variables with $P < 0.1$ in univariate Cox regression were included in the final statistical model and all statistical models were performed using backwards selection process with $P < 0.1$ selection criteria with Firth correction.

Multivariate analysis reveals use of 3 or more PEDs and fusiform aneurysm shape were associated with combined neurologic morbidity and neurologic mortality

Results: Neurologic Morbidity and Neurologic Mortality Multivariate Analysis

| Model (N = 89) ^a | Variables | Hazard Ratio | 95% CI | P value |
|-----------------------------|-------------------------|--------------|------------|---------|
| Morbidity | Aneurysm size (mm) | 1.11 | 1.04-1.18 | 0.0015 |
| Mortality | Multiple PEDs ≥ 3 | 14.74 | 3.32-76.27 | 0.0011 |
| | Ruptured vs. unruptured | 8.10 | 1.31-41.26 | 0.0197 |
| | Age (years) | 1.07 | 1.02-1.15 | 0.0262 |

CI, confidence interval; PED, Pipeline™ Embolization Device.

^aTwo patients with missing values of aneurysm size were excluded and all statistical model were performed using backwards selection process with $P < 0.1$ selection criteria. The Firth correction was used to prevent bias in the estimates on the final parameters found using the backwards selection process.

Multivariate analysis shows aneurysm size is associated with neurologic morbidity and use of 3 or more PEDs, aneurysm rupture, and patient age is associated with neurologic mortality

Conclusion

- Major neurologic morbidity and neurologic mortality rates after the implantation of PEDs in posterior circulation aneurysms (14.9%) appear to be comparable to those reported with the use of conventional clipping or coiling.
- The implantation of ≥ 3 PEDs and fusiform shape aneurysms were significant predictors of neurologic morbidity and neurologic mortality in patients with posterior circulation aneurysms.
- Aneurysm size was a predictor of neurologic morbidity and ruptured aneurysm status and patient age were predictors of neurologic mortality.
- This post hoc study suggests that when planning to treat complex posterior circulation aneurysms with the PED, neurointerventionalists should counsel patients on these identified factors associated with neurologic morbidity and mortality.