### Title
P2Y12 hyporesponse (PRU>200) is not associated with increased thromboembolic complications in anterior circulation Pipeline




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ORIGINAL RESEARCH

# P2Y12 hyporesponse (PRU>200) is not associated with increased thromboembolic complications in anterior circulation Pipeline

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## ABSTRACT

**Introduction** Recent reports suggest that thromboembolic complications are associated with Pipeline embolization device (PED) placement cluster in P2Y12 hyporesponders.

**Objective** To evaluate the role of P2Y12 hyporesponse in PED placement by retrospectively reviewing a single-center series of patients.

**Methods** We retrospectively reviewed an institutional review board-approved database of patients with an aneurysm at a single institution and identified all patients with a measured P2Y12 reaction unit (PRU) >200 who had undergone anterior circulation PED placement. Events such as transient ischemic attack, stroke, and hemorrhage were identified as well as demographic and procedural details.

**Results** Fifty-two patients with a PRU >200 had undergone anterior circulation PED placement. Four patients had prior subarachnoid hemorrhage (SAH) (8%) and 11 aneurysms (21%) had been previously treated. The average aneurysm size was 7.6 mm (±6.2). PED thrombosis occurred intraprocedurally in three patients, none of whom developed neurological deficits after abciximab administration. Treatment of all patients was successful and 48 procedures (92%) had no complications. One patient had a major stroke (2%) with permanent hemiparesis. There were three minor complications (6%): one minor stroke with a visual field cut, one 10 cc intracranial hemorrhage with transient left lower extremity weakness, and one transient neurological deficit not verified by imaging. No deaths or cases of SAH occurred.

**Conclusions** P2Y12 hyporesponse (PRU>200) is not associated with increased periprocedural complications in a contemporary series of patients undergoing anterior circulation PED placement. Titration of antiplatelet medications to P2Y12 >200 remains unindicated and may increase the risk of hemorrhagic complications.

## INTRODUCTION

The Pipeline embolization device (PED; Medtronic Neurovascular, Irvine, California, USA) is effective for the treatment of large, wide-necked proximal carotid aneurysms and others that cannot be treated with coiling or clipping.[1–5] Patients are typically maintained on aspirin and clopidogrel (or prasugrel) to mitigate thromboembolic risk; however, responses to these medications vary with the individual and time.[6] Emerging reports suggest that P2Y12 hyporesponders are at increased risk of ischemic complications with PED placement.[7–9] Proponents of this belief have advocated titration of antiplatelet agents;[9] however, prospective studies of PED have obtained low complication rates without using a testing strategy.[5 10] In this study we sought to evaluate the role of P2Y12 hyporesponse in PED placement by retrospectively reviewing a single-center series of patients.

## METHODS

The study was an institutional review board-approved retrospective cohort study from a prospectively collected database of aneurysms treated at the Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center (Baltimore, Maryland, USA). Patients were given dual antiplatelet therapy (DAT) 7 days before the scheduled procedure. Procedures were canceled if significant extremity bruising, gum bleeding, or spontaneous epistaxis was seen. Assessment of P2Y12 response (VERIFYNOW, Accumetrics, San Diego, California, USA) was performed randomly, with increased frequency after January 1, 2014. In selected cases where patients were found to have very low P2Y12 reaction unit (PRU) values and clinical signs of hyper-response, medication changes or dosage adjustments were made and procedures delayed as necessary; no action was taken for patients with elevated PRU values. Patients were identified who underwent PED placement and whose P2Y12 level was >200 within 30 days of the procedure. Pipeline placement was performed as previously described.[1 2 11 12] Patients recovered in the neurocritical care unit and in most instances were discharged home on postoperative day 1. Medical records were reviewed for demographic information, clinical history, and outcomes. Angiograms and operative reports were reviewed for anatomic and technical details. Data were recorded as counts, percentages, and means.

## RESULTS

The database review disclosed 60 patients with P2Y12 >200 who had undergone PED placement and, after excluding posterior circulation and distal anterior cerebral artery aneurysms, 52 patients (87%) remained for analysis. All patients received DAT with aspirin and either clopidogrel (49 patients, 94%) or prasugrel (3 patients, 6%). The duration of preprocedural DAT was at least 4 days in all cases and ≥7 days in 46 cases (88%). P2Y12

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levels were measured within 30 days for all patients and within 1 day of the procedure in 46 cases (88%).

Patients ranged in age from 25 to 85 years with an average age of 57 (±16 years) and 39 (75%) were female. Four patients had prior subarachnoid hemorrhage (SAH) (8%). Ten aneurysms (20%) had previously been treated with either clipping (one aneurysm, 2%), coiling (seven aneurysms, 13%), or flow diversion (three aneurysms, 6%). The average aneurysm size was 7.6 mm (±6.2) and ranged from 2 to 31 mm. There were 40 small (<10 mm) aneurysms (77%), 10 large (10–25 mm) aneurysms (19%), and 2 giant (>25 mm) aneurysms (4%) (figure 1) (table 1).

The most common aneurysm locations were ophthalmic (12 aneurysms, 23%), paraophthalmic (8 aneurysms, 15%), and anterior communicating artery (7 aneurysms, 13%) (table 2).

Intra-procedurally, 46 patients (88%) underwent placement of a single PED, while six (12%) had two PEDs placed. Coils were used adjunctively in five patients (10%). The average fluoroscopy time was 37.7 min (±22) and average radiation exposure was 2050 mGy. Catheter-induced vasospasm requiring treatment with verapamil occurred in two cases (4%) and balloon angioplasty was used for post-PED processing in seven cases (13%). Acute in-stent thrombosis requiring abciximab was seen in three cases after PED deployment. None of these patients had neurological deficits postprocedurally (table 3).

All procedures were successfully completed and 48 (92%) patients had no complications. There were no deaths and no patients with SAH. One major stroke (2%) occurred in a patient who underwent left anterior cerebral artery (ACA) PED placement for a 4 mm recurrent anterior communicating artery aneurysm. The patient developed hemiparesis on post-embolization day 2 and was found to have stent thrombosis, which was managed conservatively owing to concern about hemorrhagic conversion of the left ACA territory stroke (figure 2). There were three minor complications (6%): one patient developed visual field cut and transient expressive aphasia 2 days after the operation with an associated area of restricted diffusion in the left medial occipital lobe on MRI; one patient had a small (<10 cc) right frontal intracranial hemorrhage (ICH) with associated transient left lower extremity weakness; and a third patient developed a transient neurological deficit with left lower extremity weakness, which resolved within 2 days and did not have an associated abnormality on CT or CT perfusion (table 4).

**Table 1** Demographics

| Demographics | Number (range) | Per cent/SD |
|---|---|---|
| Age, years | 57 (25–85) | ±15.6 |
| Female gender | 39 | 75% |
| Prior SAH | 4 | 8% |
| Previously treated | 11 | 21% |
| Clip | 1 | 2% |
| Coil | 7 | 13% |
| Flow diversion | 3 | 6% |
| Size (average), mm | 7.6 (2–31) | ±6.2 |
| Small | 40 | 77% |
| Large | 10 | 19% |
| Giant | 2 | 4% |

SAH, subarachnoid hemorrhage.

## DISCUSSION

Individual response to Plavix is variable and there is controversy about whether a lack of response may increase the risk of stroke with PED. In this retrospective cohort study of 52 Plavix hyporesponders with PRU>200 undergoing PED placement, 48 procedures (92%) were completed successfully without complications and there was a low rate of thromboembolic complications (4%). These results in the largest cohort of Plavix hyporesponders reported suggest that PED can be safely performed in this population and argue against escalating antiplatelet regimens to achieve therapeutic effect before treatment.

The overall rates of cerebral ischemic complications in this study were consistent with rates previously reported for all patients undergoing PED. At this institution, in our initial 35 PED procedures, there was a major and minor stroke rate of 3% each,[1] and in our initial 44 Pipeline Flex cases, the stroke rate was 2.3%.[2] In a meta-analysis including 29 studies of 1451 patients and 1654 aneurysms treated with PED, Brinjikji *et al*[3] found rates of 6% for ischemic stroke and 3% for perforator infarct. Likewise, Kallmes *et al*[4] observed an ischemic stroke rate of 4.7% in a meta-analysis of 793 patients undergoing a PED procedure. The cases included here represent a cross-section of anterior circulation PED procedures from this institution and are not limited to proximal internal carotid artery aneurysms, which are known to have a lower complication rate The cases presented include patients with technically challenging ACA aneurysms, patients with adjunctive coiling, and giant aneurysms, including, for instance, a 70-year-old woman who underwent uncomplicated PED placement with adjunctive coiling of a 26 mm ophthalmic aneurysm with a preprocedural P2Y12 of 252 (figure 1).

The low rates of thromboembolic complications found in this study are in contrast to recently published reports, which

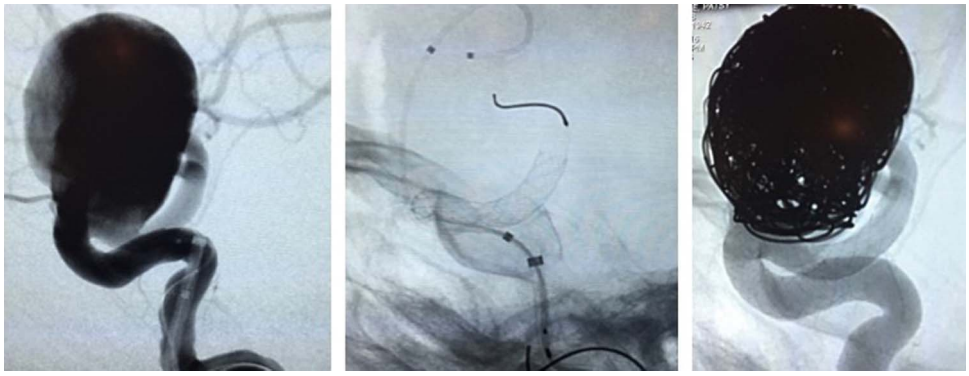

**Figure 1** Pre-embolization, post-Pipeline embolization device, and post-adjunctive coiling DSA in a patient who underwent uncomplicated treatment of a 26 mm ophthalmic aneurysm with a preprocedural P2Y12 of 252.

**Table 2** Aneurysm location

| Aneurysm location | Number | Per cent |
|---|---|---|
| ACA | 10 | 19 |
| A1 | 1 | 2 |
| A1/A2 | 2 | 4 |
| AcomA | 7 | 13 |
| ICA | 42 | 81 |
| Cervical | 1 | 2 |
| Petrous | 1 | 2 |
| Cavernous | 6 | 12 |
| Ophthalmic | 12 | 23 |
| Paraophthalmic | 8 | 15 |
| Clinoidal | 1 | 2 |
| SHA | 1 | 2 |
| Communicating | 5 | 10 |
| Supraclinoid | 6 | 12 |
| Termination | 1 | 2 |

ACA, anterior cerebral artery; AcomA, anterior communicating artery; ICA, internal carotid artery; SHA, superior hypophyseal artery.

**Table 3** Procedural details

| Procedural details | Number (range) | Per cent/SD |
|---|---|---|
| Fluoroscopy time, min | 37.7 (11–108) | ±22 |
| Radiation exposure, mGy | 2050 (398–7266) | ±1149 |
| No of PED | 1.1 (1–2) | ±0.3 |
| Adjunct coil deployment | 5 | 10% |
| Procedural success | 51 | 98% |
| Spasm (verapamil) | 2 | 4% |
| Balloon angioplasty | 7 | 13% |
| Intraoperation rupture | 0 | 0% |
| PED cork/removal | 3 | 6% |
| PED thrombosis | 3 | 6% |

PED, Pipeline embolization device.

suggest that ischemic complications cluster among P2Y12 hyporesponders. In a retrospective cohort study of 248 patients, the ischemic stroke rate among 42 hyporesponders with pre-embolization PRU>200 was 14% (six patients). Multivariate analysis in that study showed that patients with PRU>150 had an OR of 6.1 for cerebral thromboembolic complications.[7] Other studies drawing similar conclusions did not achieve statistical significance or included very small numbers of patients. A retrospective cohort study by Tan *et al*[8] included 39 hyporesponders and showed an OR of 11.32 for symptomatic cerebral thromboemboli among patients with PRU>208, which was not statistically significant. Another retrospective cohort study of 48 patients showed that P2Y12 <60 or >240 was an independent predictor of all thrombotic and hemorrhagic complications but included only two patients who met the threshold for hyporesponse.[9]

As a result of these studies suggesting increased stroke risk, Plavix hyporesponders are treated with escalating antiplatelet regimens at many institutions before PED placement. Some proceed with electively scheduled procedures for hyporesponders but bolus aspirin and Plavix postprocedurally.[8] Others delay the procedure, doubling the daily dose of Plavix or starting alternative agents such as ticlodipine or prasugrel until a threshold response is met.[7 13]

These escalated regimens increase the risk of hyper-response and hemorrhage as the Plavix response builds over time. In one retrospective study of 100 patients treated with clopidogrel 75 mg daily, 21% showed hyper-response (PRU<60) after a 7–10 day loading period. After 30 days of treatment, 59% of patients initially within the therapeutic range became hyper-responders. The mean PRU, which was 137 after eight doses, decreased to 59 after 30 doses.[6] Patients with an appropriate pre-embolization PRU who return with hemorrhagic complications are commonly found to have very low PRU.[14] In the study by Delgado *et al*,[6] there were four cases of ICH and one of SAH among 45 patients with documented hyper-response, whereas there were no major hemorrhagic complications among the 55 patients with PRU that remained >60. In multivariate analysis for a retrospective study of 248 patients that included 63 hyper-responders, Daou *et al*[7] found that PRU<70 had an OR of 4.7 (p=0.02) for cerebral hemorrhagic complications.

On the other side of the debate, studies have shown that a PED procedure can be performed without testing for PRU, with no increase in complication rates.[15 16] The Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial included 107 patients who underwent PED while receiving DAT without PRU assessment, with major complication rates of 2.8% for ischemic stroke and 1.9% for ipsilateral ICH.[5] A second prospective study of 143 patients receiving DAT without PRU assessment showed major and minor stroke rates of 1.4% each and a major ICH rate of 2.1%.[10] Retrospective studies have shown that platelet function testing does not lead to improved outcomes. A subgroup analysis of the IntrePED registry found increased neurological morbidity of 8.2% in 511 patients who underwent a PED procedure after platelet function testing as compared with 2.1% neurological morbidity in 187 who underwent a PED procedure without testing.[17] Although data were not available on the actions taken on the basis of individual results, the inference may be drawn that subsequent manipulation of antiplatelet regimens to achieve therapeutic PRU may increase the risk of complications. In general, outcomes for patients on these escalated regimens are not separately reported, except in one study of 48 patients in which all three major hemorrhagic complications occurred in hyporesponders who were either switched to prasugrel or had the clopidogrel dose increased without rechecking the PRU.[18]

Managing antiplatelet therapy in patients undergoing a PED procedure requires balancing the risk of thromboembolic and hemorrhagic complications, among which, in our experience, hemorrhagic complications are more to be feared. Without knowing the disability associated with each hemorrhagic and thromboembolic complication, it is not apparent which risk should be accepted. For instance, included among the 'major' thromboembolic complications of a PED procedure in a retrospective study by Daou *et al*[7] were retinal emboli causing visual disturbances, a comparatively slight disability. Similarly, to achieve an OR of 11.32 for thromboembolic complications associated with PRU>208, Tan *et al*[8] included three transient deficits and two ischemic insults in which deficits were sustained. Additional retrospective studies suggest that the hemorrhagic complications are more severe.[10 19] In a study of 48 PED procedures in which four thromboembolic and four hemorrhagic complications were seen, the ischemic deficits were transient in three cases, whereas the hemorrhagic deficits were transient in just one patient and resulted in one death and two cases of permanent hemiplegia.[18] In a meta-analysis of 906 patients undergoing PED procedures, 29% of ischemic events were transient with symptoms resolving within 7 days as compared with 21% of hemorrhagic complications.[4]

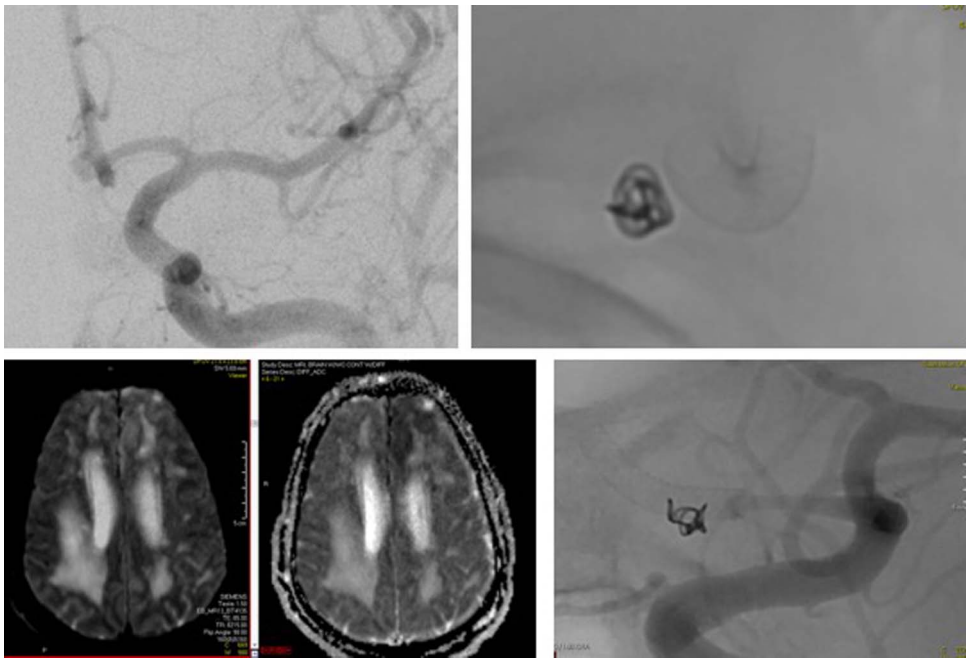

**Figure 2** Clockwise from upper left: Left internal carotid angiogram showing ruptured 4 mm anterior communicating artery aneurysm; after pipeline embolization for recurrence after coiling; post-embolization day 2 MR image demonstrating diffusion restriction in the left anterior cerebral artery territory; angiogram showing a lack of perfusion distal to the stent.

In addition to their reduced associated disability, thromboembolic complications of PED procedures are also more amenable to intervention than hemorrhagic complications. Thromboembolic events are potentially reversible with thrombolysis, angioplasty for parent-vessel stenosis,[13] or blood pressure augmentation during a period of collateral recruitment.[20] Interventions for patients with PED who have an ICH, on the other hand, are limited by the risk of further bleeding associated with surgery while taking antiplatelet agents and the potential for thrombosis associated with efforts to reverse platelet inhibition with exogenous transfusions.[14]

At our institution, there is no PRU threshold that must be met before PED placement. A combination of factors is taken into consideration when deciding whether to proceed with embolization and how to use antiplatelet agents after the procedure. Before each case, patients are examined for clinical signs of hyper-response (extremity bruising, gum bleeding, or spontaneous epistaxis) and the procedure is canceled if these are observed or reported. Thromboembolic risk is assessed based on a combination of preoperative factors, such as increasing aneurysm size and posterior circulation location,[4] and procedural factors, such as longer procedure time or the placement of multiple devices,[8] which are consistently associated with an increased risk of stroke. In our experience, straightforward PED deployment and optimal wall apposition are critical to minimizing thromboembolic risk irrespective of plavix response. PRU gives us a perspective about which risks associated with a case are most prominent but does not itself serve as a contraindication. Indeed, as Daou *et al*[7] recognized, if only those patients within the safest range of PRU 70–150 were to undergo procedures, 67% of procedures would be canceled.

**Table 4** Procedural outcomes

| Procedural outcomes | Number (range) | Per cent/SD |
|---|---|---|
| Length of stay, days | 3.0 (1–14) | ±3.2 |
| Mortality | 0 | 0% |
| SAH | 0 | 0% |
| Major stroke | 1 | 2% |
| Minor stroke | 1 | 2% |
| ICH | 1 | 2% |
| Remote ICH | 0 | 0% |
| Transient deficit | 1 | 2% |
| Cranial nerve palsy | 0 | 0% |
| Iatrogenic dissection | 0 | 0% |
| Groin hematoma | 3 | 6% |
| Groin infection | 0 | 0% |

ICH, intracranial hemorrhage; SAH, subarachnoid hemorrhage.

The limitations of this study include its retrospective, nonrandomized, and unblinded nature. Because of the lack of blinding, we cannot ensure complete procedural parity for PRU hyporesponders. This is a single-arm study without a control group. The scope of the study was deliberately restricted to Plavix hyporesponders to focus on the controversial issue of whether these patients experience increased stroke risk with PED placement. A review of the rest of our experience shows that among comparable patients with anterior circulation aneurysms, excluding those of the distal ACA, patients who responded to Plavix (PRU<200) and patients without a measured PRU had similar rates of major, minor, or any stroke to those of Plavix hyporesponders. A final limitation is that no P2Y12 levels were available for about half of the PED patients at this institution, as their measurement is not routine. However, because no changes in the DAT regimen were made for patients with elevated PRU, we believe this assures the lack of a selection bias of this cohort.

## CONCLUSION

This is the largest cohort of P2Y12 hyporesponders in whom outcomes associated with PED flow diversion have been

reported. Contrary to other reports, P2Y12 hyporesponse (PRU>200) is not associated with higher periprocedural complications in a contemporary series of patients undergoing anterior circulation PED placement. PED can be safely performed in cases of P2Y12 hyporesponse and the increased risk of hemorrhage associated with escalating antiplatelet regimens is not warranted.

**Contributors** All authors contributed significantly to conception, data acquisition, and analysis; all drafted and revised manuscript contents; and all approved the final version of the manuscript.

**Competing interests** ALC is a consultant and proctor for Medtronic, Styker, and Microvention. GPC is a consultant for Medtronic and Microvention.

**Ethics approval** Institutional review board.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** The relevant anonymised patient level data are available on reasonable request from the authors.

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