Platelet Function Testing in Neurovascular Procedures: Tool or Gimmick?

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Abstract

Background: Platelet inhibitors are used to prevent thromboembolic complications related to neurovascular stenting (NVS) procedures. Despite substantial inter-individual variability of functional platelet inhibition, the value of platelet function tests (PFT) to assess inhibition remains controversial. Objective: This study was conducted to compare differences in thromboembolic complication rates associated with NVS in platelet-inhibited patients with and without PFT. Clinical neurological outcomes were assessed by differences in the modified Rankin Scale (mRS). Materials and Methods: One hundred seventeen consecutive patients underwent elective NVS procedures within a 7-year period. All patients received aspirin and clopidogrel 8 days before the procedure. Fifty-two patients were treated without assessment of platelet inhibition, and 65 patients were tested for clopidogrel resistance. When clopidogrel resistance was revealed, corresponding patients were converted to ticagrelor. Changes in mRS and thromboembolic event rates were compared between the 2 cohorts. Results: Thirty-five percent of patients from the cohort subjected to PFT tests showed inadequate platelet inhibition under clopidogrel and were converted to ticagrelor. Compared to the non-PFT test cohort, neurological deficits were significantly reduced (12 vs. 0\%; \textit{p} = 0.009) and a lower number of thromboembolic events was found (12 vs. 3\%; \textit{p} > 0.05) within the test cohort. Conclusion: PFT appears to identify patients with clopidogrel resistance prior to NVS proce-
dures. When non-responders are converted to alternative platelet inhibitors, neurological outcomes and thromboembolic complication rates may improve. Consequently, this study provides preliminary evidence that PFT may be a useful clinical tool to enhance procedural safety and improve clinical outcomes in NVS procedures.

Introduction

Neurovascular stenting (NVS) is an invaluable tool for the treatment of wide-neck and complex cerebral aneurysms. NVS is used to improve the hemodynamic stability of coil embolization, to enhance aneurysm packing rates, and/or to remodel aneurysm necks with flow-diverting stents (FDS). Unfortunately, NVS is associated with an increased risk of thromboembolic complications due to potential platelet aggregation within deployed stents. Thromboembolism may result in neurological deterioration or death. For NVS-related platelet inhibition and anticoagulation management, only class C evidence is available from the World Federation of Interventional and Therapeutic Neuroradiology (WFITN) and from limited case series [1]. A general consensus exists that dual antiplatelet therapy (DAT) should be applied in NVS procedures. However, there are no current clinical guidelines for the choice of particular platelet inhibitors, for the use of platelet function tests (PFT), or for the duration of DAT [2]. Resistance to clopidogrel-induced platelet inhibition has been described in up to 40% of patients [1, 3–5]. Such non-responders seem to be responsible for the majority of thromboembolic complications following neuroendovascular procedures [6–9]. In consequence, the use of PFT has been promoted to identify individuals with insufficient P2Y12 inhibition. Different studies have found ambiguous results regardless of whether PFT was used or not [1, 10–13]. Consequently, it remains controversial whether PFT adds benefits to procedural safety in NVS procedures.

To assess the clinical value of P2Y12 inhibition assays, we compared neurologic outcomes and thromboembolic event rates for NVS procedures among patients with and without PFT. Corresponding clinical data and medical imaging studies were reviewed.

Methods

Patient Cohorts

Between July 2010 and July 2017, one hundred seventeen unruptured intracranial aneurysms underwent NVS including FDS procedures in a single tertiary neurovascular referral center. The cohort consisted of a predominantly Caucasian population. A retrospective cohort study analysis was performed on prospectively collected data. All of the patients provided informed consent, and this study was approved by the Human Research Ethics Committee (H-0016674). Patients with ruptured intracranial aneurysms were excluded from the analysis, since DAT premedication was non-standardized and variable in clinical emergency settings.

Patients were divided into 2 cohorts for comparative analysis. Cohort A included cases where DAT was administered without PFT. Cohort B comprised cases where PFT was performed to assess DAT-associated platelet inhibition. Patients in cohort A were treated between July 2010 and December 2013, while cohort B patients were treated between January 2014 and July 2017, reflecting the time when PFT became available at our institution. Patients in cohort B were converted to ticagrelor when PFT revealed insufficient platelet inhibition under clopidogrel.

Platelet Inhibition and Functional Testing

Within both cohorts, and in all of the patients, pharmacological platelet inhibition was initiated 8 days prior to the procedure. Acetylsalicylic acid (ASA; 100 mg) and clopidogrel (75 mg) were given as
daily doses. For cohort B, the INNOVANCE PFA-100® P2Y platelet function assay (Siemens Medical Solutions, Malvern, PA, USA) was used 7 days after commencement of clopidogrel and ASA and before NVS was performed. The baseline platelet reactivity before administration of clopidogrel and ASA was not assessed. The application and principles of the INNOVANCE PFA-100 P2Y test have been described before [14–18]. The test is sensitive to P2Y12 inhibitors and comparable to other currently available PFT [15, 17]. Due to the very low rate of non-responders [19], ASA-related platelet inhibition was not investigated in this study.

For the INNOVANCE PFA-100 P2Y test, the manufacturer references a normal P2Y closure time (CT) ≤106 s. To define adequate clopidogrel-related platelet inhibition, a CT offset of >150 s (~50% above the maximum normal CT), was chosen in our series. All patients with inadequate platelet inhibition (CT ≤150 s) were converted from clopidogrel to ticagrelor. An initial loading dose of 180 mg ticagrelor was applied, followed by 90 mg b.i.d. Due to the high efficacy of platelet inhibition under ticagrelor compared to clopidogrel, ASA was reduced to 75 mg daily. With application of ticagrelor, clopidogrel was discontinued. In both cohorts, clopidogrel, or respectively ticagrelor, was continued for 6 months, and ASA was given for a 12-month period. The INNOVANCE PFA-100 P2Y test was not repeated in patients converted from clopidogrel to ticagrelor given the lack of ticagrelor non-responders. Intra-procedurally, during NVS, an intravenous heparin bolus was given to adjust the activated clotting time between 250 and 350 s (i.e., 2–2.5 times the baseline value). Sheaths and micro- and guide catheters were connected to a heparinized normal saline solution (5,000 IU heparin/1,000 mL NaCl 0.9%) on continuous pressurized drip infusion. Generally, no post-procedural reversal or continuation of heparin was applied.

NVS Procedures

All NVS procedures were performed under general anesthesia on a biplanar flat panel angiographic system (Artis Zee Biplane; Siemens, Munich, Germany). The selection of stents was made according to the senior author’s preferences, subject to patient-related factors, comorbidities, aneurysm location, and geometry. The majority of aneurysms were located at vascular bifurcations (Table 1). For NVS, laser cut stents (Solitaire™, Neuroform-Atlas™, and Barrel™), woven stents (Leo™ and LVIS™), and flow-diverting devices (Silk™, Pipeline™, Surpass™, and FRED™) were used.

Data Collection and Follow-Up

Preoperatively, demographic patient-related data, aneurysm location, morphology, and aneurysm size were recorded in a de-identified registry. The type and number of stents used during each procedure were recorded, and peri- and post-procedural thromboembolic complications were noted.

Patients were neurologically assessed before and after the procedure, after 2 and 4 h, and on day 1 after the procedure. Additionally, patients returned for an operator-independent 90-day clinical review. The functional neurologic status was quantified prior to the procedure and at the 3-month follow-up according to the modified Rankin Scale (mRS). Differences between baseline- and follow-up mRS were determined (i.e., ΔmRS). Follow-up cerebral digital subtraction angiography (DSA) was routinely performed after 7 months, 1 month after discontinuation of clopidogrel or, respectively, ticagrelor, to evaluate parent vessel integrity and aneurysm occlusion. Alternatively, magnetic resonance angiography (MRA) was performed when DSA follow-up was not feasible. MRA was conducted at a field strength of 3 T using the time-of-flight technique. Thromboembolic events were assessed from intra-procedural images, follow-up imaging, and clinical data. Acute thromboembolic events were deemed to occur immediately during the procedure or before patients were discharged on day 1 after the procedure. A delayed thromboembolic event was defined when it occurred after discharge from hospital.

Statistical Analysis

Differences in baseline categorical variables, including presence of aneurysm daughter sacs, aneurysm location, and stents used, were assessed for significance using Pearson’s χ² test. Age and differences in aneurysm size between cohorts were analyzed with an unpaired Student t test. Gender variance was assessed using confidence intervals for the difference between population means. For each outcome variable, values were tallied, and median and IQR were calculated where appropriate. Differences between the two cohorts for ΔmRS and thromboembolic events were analyzed using a Mann-Whitney U test for continuous variables not normally distributed. The total number of clinically significant neurological deteriorations was further evaluated with the 2 population Z test.
Results

Cohort Characteristics and Follow-Up

Cohorts A and B consisted of 52 and 65 patients, respectively. In cohort B, PFT identified 23 cases (35%) with clopidogrel resistance (INNOVANCE PFA-100 P2Y CT ≤150 s). Three-month clinical and 7-month imaging follow-up results were available for all patients in both cohorts. DSA follow-up was conducted in 103 cases (88%), while MRA was performed in 14 cases (12%).

| Table 1. Patient cohort characteristics |
|----------------------------------------|
|                                      |
|                                      |
| Gender                                 |
| Male                                   |
| 11 (21)                               |
| 18 (28)                               |
| Female                                 |
| 41 (79)                               |
| 47 (72)                               |
| p value                                |
| 0.53d                                  |
| Age, years                             |
| Median                                 |
| 58                                     |
| 58                                     |
| IQR                                    |
| 51–68                                  |
| 50–68                                  |
| p value                                |
| 0.44d                                  |
| Race                                   |
| Caucasian                              |
| 48 (92)                                |
| 59 (91)                                |
| Other                                  |
| 4 (8)                                  |
| 6 (9)                                  |
| p value                                |
| 0.77d                                  |
| Aneurysm type                          |
| Saccular                               |
| 44 (85)                                |
| 61 (94)                                |
| Fusiform                               |
| 8 (15)                                 |
| 4 (6)                                  |
| Dissecting                             |
| 0 (0)                                  |
| p value                                |
| 0.10c                                  |
| Stent typea                            |
| Laser cut                              |
| 18 (35)                                |
| 15 (23)                                |
| Woven                                  |
| 14 (27)                                |
| 13 (20)                                |
| Flow diversion                         |
| 20 (38)                                |
| 17 (26)                                |
| p value                                |
| 0.76c                                  |
| Maximum aneurysm diameter, mm          |
| Median                                 |
| 5                                      |
| 4                                      |
| IQR                                    |
| 3–10                                   |
| 3–8                                    |
| p value                                |
| 0.33c                                  |
| Dome-to-neck ratio, mm                 |
| Median                                 |
| 1.7                                    |
| 1.6                                    |
| IQR                                    |
| 1–2                                    |
| 1–2                                    |
| p value                                |
| 0.46b                                  |
| Aneurysm location                      |
| VBA                                    |
| 17 (35)                                |
| 19 (30)                                |
| ICA                                    |
| 13 (25)                                |
| 18 (28)                                |
| ACOM                                   |
| 5 (10)                                 |
| 12 (18)                                |
| MCA                                    |
| 9 (17)                                 |
| 5 (8)                                  |
| PCOM                                   |
| 6 (12)                                 |
| 7 (11)                                 |
| PICA                                   |
| 1 (2)                                  |
| 2 (4)                                  |
| PCAL                                   |
| 1 (2)                                  |
| 2 (3)                                  |
| Raymond-Roy class                      |
| 1                                      |
| 43 (83)                                |
| 51 (78)                                |
| 2                                      |
| 4 (8)                                  |
| 8 (12)                                 |
| 3                                      |
| 5 (10)                                 |
| 6 (10)                                 |
| p value                                |
| 0.72c                                  |

Values are presented as numbers (%) unless otherwise stated. VBA, vertebrobasilar arteries; ICA, internal carotid artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; PICA, posterior inferior cerebellar artery (including the superior cerebellar artery); PCAL, pericallosal artery (including A2 segments of the anterior cerebral artery). a In 5 patients (2 in cohort A and 3 in cohort B), more than 1 stent was used; laser cut stents included Solitaire™, Neuroform-Atlas™, and Barrel™. Woven stents included Leo™ and LVIS™, Silk™, Pipeline™, Surpass™, and FRED™ devices were used as flow-diverting stents. b Unpaired Student’s t test. c χ² test. d CI difference between the 2 means (3).
One hundred thirteen aneurysms (97%) were treated de novo. Four cases (3%) were Raymond-Roy class 2 residuals or recurrences after previous microsurgical or endovascular aneurysm treatment. Table 1 demonstrates the patients’ demographic characteristics, aneurysm and stent type, maximum aneurysm diameter, dome-to-neck ratio, aneurysm location, and post-procedural Raymond Roy occlusion class. These baseline categorical variables were similar between groups ($p > 0.05$).

**Clinical Outcome Rate and ΔmRS: Cohort A**

Thromboembolic incidents were seen in 6 out of 52 cases (12%) within cohort A. Four of these events were intra-procedural (8%) and 2 were delayed (4%). All 4 intra-procedural thromboembolic events were detected immediately and treated with intra-arterial application of glycoprotein IIb/IIIa inhibitor and/or mechanical thrombectomy. Complete restoration of blood flow was achieved in all of the affected patients. One event had a minimal impact on neurological function (ΔmRS 1), 2 were associated with a moderate impact (ΔmRS 2), and 1 thromboembolic complication resulted in a severe permanent neurological deficit (ΔmRS 4). All four patients had postoperative MRI studies demonstrating ischemic diffusion restrictions correlating to clinical mRS changes. Figure 1 demonstrates the typical angiographic appearance and management of an intra-procedural partial stent occlusion related to insufficient platelet inhibition in a patient from cohort A.

Both delayed thromboembolic events in cohort A were associated with FDS procedures. One patient developed headaches 4 weeks after the procedure. A subsequent MRA demonstrated occlusion of the FDS within the internal carotid artery. The functional neurologic status was affected severely (ΔmRS 3). A second patient with delayed thromboembolism in cohort A developed a left-sided facial droop and contralateral weakness 2 days after the NVS procedure. Stent occlusion and multiple lacunar embolic strokes were found on MRI. Despite
technically successful emergency mechanical vacuum-assisted thrombectomy, long-term neurological recovery remained compromised (ΔmRS 3).

One patient in cohort A developed a hemorrhage within a preexistent posttraumatic cerebellar defect 8 days after an FDS procedure within the left vertebral artery. After readmission, conservative management, and clinical monitoring, no neurologic compromise resulted (ΔmRS 0). Assuming hypersensitivity, clopidogrel was reduced to alternate application every second day and ASA was reduced to 75 mg daily. No further adverse events were recorded. Details of thromboembolic event rates and ΔmRS for cohorts A and B are provided in Table 2. At the 3-month clinical and 7-month imaging follow-ups, no further thromboembolic events or delayed complications were encountered within cohort A.

Clinical Outcome Rate and ΔmRS: Cohort B
Two intra-procedural thromboembolic complications were encountered in cohort B (3%). One event occurred in a patient receiving NVS treatment of a basilar apex aneurysm. Despite conversion to ticagrelor, the patient developed intra-procedural in-stent thrombosis and required application of intra-arterial glycoprotein IIb/IIIa inhibitor. The occlusion was resolved and no neurological sequelae occurred (ΔmRS 0). A second event also occurred after conversion to ticagrelor. The stent occlusion was successfully treated with selective intra-arterial application of tirofiban, followed by subsequent intravenous administration of heparin and tirofiban over 24 h. Postoperative MRI demonstrated no ischemic lesions, and no long-term neurologic compromise resulted (ΔmRS 0). Delayed thromboembolic events or hemorrhages were not encountered in cohort B, including at the 3-month clinical or 7-month imaging follow-up.

Statistical Comparison
Compared to cohort A, neurological outcomes (ΔmRS) were statistically significantly better in cohort B (p = 0.009, Mann-Whitney U test). Of the 52 patients in cohort A, at the 3-month follow-up, 6 patients (12%) had a clinically significant deterioration in their neurological function (mRS), whereas 0 of the 65 patients in cohort B (0%) had a noticeable neurological difference. This total proportion of patients with neurological change (ΔmRS) following NVS between the 2 cohorts was statistically significant (6/52 vs. 0/65; p = 0.005; 2 population proportions Zscore). Baseline and 3-month follow-up mRS values and ΔmRS are provided in Table 2 for both cohorts, including p values. Baseline and follow-up mRS were similar between the 2 cohorts and at the 3-month follow-up, reflecting cohort demographic similarities and the positive post-procedural results reached by the vast majority of patients (p > 0.05), not taking into account the subtle but clinically significant differences in neurological function of a minority of patients between the two cohorts. Despite the higher incidence in cohort A, the thromboembolic event rate did not reach statistical significance compared to cohort B (12 vs. 3%; p = 0.15, t test).

Among 65 patients in cohort B, PFT identified 23 patients (35%) with insufficient P2Y inhibition. Mean INNOVANCE PFA-100 P2Y-CT values for clopidogrel responders and non-responders are summarized in Table 3. Compared to responders, CT were significantly shorter in non-responders (272.8 ± 58.4 vs. 87.7 ± 37.6 s; p = 0.0001, t test).

No significant difference was found regarding the stent type used stent among the two cohorts. Two stents each were used in 2 patients in cohort A (4%) and cohort B (3%) to treat complex bifurcation aneurysms. One additional patient in cohort B received 3 stents (1.5%). All other patients in both cohorts received 1 stent only. No statistical difference was found between the 2 cohorts regarding the number of stent implants (p = 0.84, χ² test).


**Discussion**

Current rationales for platelet inhibition management in NVS procedures predominantly rely on literature related to percutaneous coronary interventions (PCI) [2, 13]. Based on PCI experience, platelet inhibitors are routinely applied in neurovascular procedures when stents are used. However, in terms of demographics and risk factors, NVS patients differ significantly from PCI ones [13]. Stents in PCI are used to treat atherosclerotic disease or dissec-

### Table 2. Thromboembolic event rates

|                        | Cohort A (n = 52) | Cohort B (n = 65) | \( p \) value** |
|------------------------|-------------------|-------------------|----------------|
| **Thromboembolic events, n (%)** |                   |                   |                |
| Present                | 6 (12)            | 2 (3)             | 0.71\textsuperscript{a} |
| Absent                 | 46 (88)           | 63 (97)           |                |
| Acute                  | 4 (8)             | 1 (1.5)           | 0.15\textsuperscript{a} |
| Delayed                | 2 (4)             | 1 (1.5)           |                |
| **Baseline mRS**       |                   |                   |                |
| 0                      | 47                | 61                |                |
| 1                      | 4                 | 3                 |                |
| 2                      | 1                 | 1                 |                |
| 3                      | 0                 | 0                 | 0.90\textsuperscript{b} |
| 4                      | 0                 | 0                 |                |
| 5                      | 0                 | 0                 |                |
| 6                      | 0                 | 0                 |                |
| **3-month follow-up mRS** |                   |                   |                |
| 0                      | 41                | 61                |                |
| 1                      | 5                 | 3                 |                |
| 2                      | 3                 | 1                 |                |
| 3                      | 2                 | 0                 | 0.15\textsuperscript{b} |
| 4                      | 1                 | 0                 |                |
| 5                      | 0                 | 0                 |                |
| 6                      | 0                 | 0                 |                |
| **ΔmRS**               |                   |                   |                |
| 0                      | 46 (88)           | 65 (100)          | <0.01\textsuperscript{b} |
| 1                      | 1 (2)             | 0 (0)             |                |
| 2                      | 2 (4)             | 0 (0)             |                |
| 3                      | 2 (4)             | 0 (0)             |                |
| 4                      | 1 (2)             | 0 (0)             |                |

Values are presented as numbers (%) or numbers. A deterioration of baseline mRS of 1 scale point during follow-up was graded as ΔmRS 1, a decline of 2 points as ΔmRS 2, etc. \textsuperscript{a} Pearson’s \( \chi^2 \) test. \textsuperscript{b} Mann-Whitney U test.

### Table 3. Innovance PFA-100 P2Y test results for cohort B

|                        | P2Y CT\( \textsuperscript{a}, s \) | \( p \) value\textsuperscript{b} |
|------------------------|-------------------------------------|----------------------------------|
| Responders             | 272.8±58.4                          | <0.0001                          |
| Non-responders         | 87.7±37.6                           |                                  |

Values are presented as means ± SD. CT were significantly prolonged in responders. In our study, the cut-off threshold for clopidogrel resistance was defined as a CT <150 s. \textsuperscript{a} Normal values are ≤106 s. \textsuperscript{b} t test.
tions, while NVS procedures are commonly applied in non-atherosclerotic vessels to treat wide-neck intracranial aneurysms.

The current literature is conflicted whether PFT is clinically beneficial for preoperative assessment of patients on DAT for NVS – or not. The very low number of ASA non-responders makes general monitoring unnecessary [19]. In contrast, a variable rate of response to clopidogrel is described, with up to 40% of the population being resistant [1, 3–5]. Common terminologies used to describe the response to clopidogrel-related platelet inhibition are “low-responder,” “hypo-responder,” “semi-responder,” and “suboptimal responder” [20]. In general, patients showing <70 but >30% aggregation are defined as hypo-responders and those with <30% aggregation as resistant, based on previously established systematic cardiology definitions for clopidogrel antiplatelet therapy [21]. This terminology seems to highlight that a relevant cut-off to distinguish poor responders from good responders has not been properly defined for currently available PFT [14, 19].

PFT Proponents

Proponents for PFT rely on small NVS case series advocating PFT testing. Similar to findings from our cohort B, Fifi et al. [9] identified 36.5% clopidogrel-resistant patients in their study of 96 patients undergoing NVS procedures. A total of 16.7% of their patients developed thromboembolic events, compared to 1.6% in nonresistant patients \( (p < 0.01) \), which again is similar to our findings. Neurologic outcomes were not analyzed in the series of Fifi et al. [9]. Kim et al. [7] associated clopidogrel resistance with increased diffusion-positive lesions on cerebral MRI imaging in asymptomatic patients 48 h after coil embolization, promoting adjustment of platelet inhibitors. Ryu et al. [8] advocated PFT in NVS and FDS procedures and found increased thromboembolic complication rates in patients with clopidogrel resistance when compared to clopidogrel responders. No statistical analysis was provided in their series, and DAT remained unadjusted for non-responders [8]. Two studies from Gurbel et al. [22, 23] found improved clinical outcomes when patients with clopidogrel resistance were converted to ticagrelor. Similarly, Hanel et al. [5] reported successful P2Y inhibition after ticagrelor administration in 18 NVS patients when clopidogrel resistance was identified. In their series, no patients developed immediate thromboembolic events. Unfortunately, a control group was not available and no clinical or imaging follow-up data were provided [5].

PFT Opponents

Conversely, several other studies have argued against the use of PFT in NVS procedures. Kass-Hout et al. [10] found no significant change in clinical outcomes or stent thrombosis rates with PFT in NVS procedures. Their study cohort was rather heterogeneous and included both cervical and intracranial atherosclerotic lesions, and intracranial aneurysms, all treated with a variety of different stent types. Similarly, Song and Shin [11] found no significant difference in thromboembolic events between clopidogrel responders and non-responders in their study of 99 NVS patients. Neither of these studies \( (n = 136) \) adjusted the antiplatelet regime in the setting of proven clopidogrel resistance. Sedat et al. [24] found similar rates of thromboembolic events when either clopidogrel or prasugrel was used. A study from Brinjikji et al. [12] assessed neurologic morbidity and mortality in patients with and without PFT for clopidogrel resistance in NVS procedures. This retrospective multicenter study comprised 698 patients treated exclusively with the Pipeline Embolization Device™ and found increased neurologic morbidity and mortality rates for the PFT testing group compared to the non-testing group \( (8.8 \text{ vs. } 3.2\%; \ p = 0.01) \). A reasonable explanation for these findings was not provided. The study of Brinjikji et al. [12] was subsequently criticized for several shortfalls, including a lack of standardization between participating centers and no modification of
platelet inhibitors in clopidogrel non-responders following PFT testing. Within their PFT testing group, significantly more patients received multiple stents compared to the non-testing cohort (38 vs. 27.9%; \( p = 0.01 \)).

**INNOVANCE PFA-100 P2Y Test**

To assess clopidogrel-related platelet inhibition, the INNOVANCE PFA-100 P2Y test was used in our cohort B as it is widely available, reliable for monitoring of the effects of P2Y\(_{12}\) receptor antagonists, and comparable to other currently available PFT [15, 17]. Unfortunately, the first clinical data available with the PFA-100 test to predict clinical outcomes in patients undergoing PCI was erroneous [25]. The INNOVANCE PFA-100 P2Y test cartridge was included in this series, but it only became available halfway through this study. Consequently, the sample size of the INNOVANCE PFA-100 P2Y test was associated with insufficient statistical power to detect a relationship between high on-treatment platelet reactivity and clinical outcome. Additionally, the authors misinterpreted their test data, i.e., short CT were classified as being abnormal and prolonged CT as being normal, which is directly opposite to the correct interpretation. This resulted in false cut-off values and OR for all clinical endpoints [18].

**PFT Thresholds**

One of the main issues with the use of any PFT is establishing an adequate reference number to determine whether an individual is responsive or nonresponsive to DAT. With the INNOVANCE PFA-100 P2Y test, CT \( \leq 106 \) s are considered normal. The maximum CT is 300 s and CT \( > 300 \) s are considered as non-closure. Consequently, some authors have considered CT \( > 106 \) s as abnormal in reference to the manufacturer’s reagent instruction booklet. The related studies viewed any CT \( \leq 106 \) s as clopidogrel non-responders [14]. To better reflect variable response rates to clopidogrel, other authors have suggested a reactivity threshold of more than 50% platelet inhibition to prevent recurrence of ischemic events during clopidogrel treatment [26, 27]. This threshold was based on clinical observations that, among patients receiving clopidogrel in PCI, none of the subjects with a residual platelet reactivity of <50% presented with ischemic events, while 100% of subjects with recurrence of thrombosis had >50% residual platelet reactivity [19]. Our study has endorsed the latter approach. We considered adequate clopidogrel-related platelet inhibition when the INNOVANCE PFA-100 P2Y CT offset was \( > 150 \) s (~50% above the maximum normal CT). Consequently, all patients with inadequate platelet inhibition (CT \( \leq 150 \) s) in cohort B were converted from clopidogrel to ticagrelor.

**P2Y Inhibitors**

In our study, ticagrelor was chosen over prasugrel as an alternative platelet inhibitor for patients with clopidogrel resistance. Ticagrelor is a nucleoside analog and it interacts reversibly with ADP receptors of the subtype P2Y\(_{12}\). Unlike clopidogrel, ticagrelor does not require metabolic activation but it is primarily active via the CYP3A4 enzyme. According to PCI-related studies, ticagrelor and prasugrel both seem to provide similarly effective P2Y\(_{12}\) inhibition. However, ticagrelor seems to be associated with a faster onset of platelet inhibition and a shorter half-life when compared to clopidogrel or prasugrel [22, 23]. Since non-responders to ticagrelor are extremely rare, we did not consider repeat PFT after conversion, and the dose of ticagrelor remained unadjusted in our series.

**Study Results**

This study contributes one of the largest series to date evaluating the clinical significance of incorporating PFT using the INNOVANCE PFA-100 P2Y test in NVS procedures. It is one of
the few studies in the current literature evaluating neurological outcomes following PFT and subsequent conversion of DAT from clopidogrel to ticagrelol in the setting of insufficient platelet inhibition. Although there is no demonstrable statistical significance in reduction of overall thromboembolic events, presumably secondary to small cohort sample numbers, following conversion to ticagrelol in patients with CT > 150 s, a clinically significant reduction of the number and severity of neurological outcome deterioration in patients where clopidogrel resistance was identified using the INNOVANCE PFA-100 P2Y test (6 out of 52 patients with neurological deterioration without PFT vs. 0 out of 65 patients with PFT; *p* = 0.005). The objective neurological scores measured (ΔmRS) were also statistically significant between the two cohorts (*p* = 0.009). The mechanism of the deterioration of neurological outcomes in the cohort not tested with PFT is not precisely understood, and it is likely multifactorial. In the cardiology literature, non-responsiveness to clopidogrel is blamed for the increased risk of clinically significant ischemic cardiovascular events [28–30]. Additionally, in the neurovascular literature, clopidogrel resistance has been linked to an increased incidence of radiologically detected cerebral small vessel disease [31]. It is likely that clopidogrel resistance is linked to complex, but poorly understood, pathological alterations in the interactions between platelets and the cerebral vascular walls, which may contribute poor neurological outcomes if not identified.

**Limitations**

Our study is associated with certain limitations. Device technology evolved during the 7-year evaluation period. Early days of FDT were associated with higher complication rates. Consequently, the retrospective nature of this study may have been affected by a progressive learning curve with potentially better outcomes in cohort B. Variables in our study were limited by a standardized DAT and PFT protocol. The procedural techniques used by the senior author remained constant during the study period. The result of the INNOVANCE PFA-100 P2Y test may be affected by platelet counts, von Willebrand factor levels and activity, hematocrit, blood group, and patient age. In addition, inflammation markers like monocyte count and C-reactive protein might also influence related CT [18]. Such parameters were not analyzed in our study population. Despite the limited statistical power, our study represents one of the largest systematic series to date in investigation of PFT. Future prospective and standardized multicenter trials would be valuable to solidify our findings and further identify reliable PFT offsets for definition of adequate platelet inhibition.

**Conclusion**

Considering the current controversies in PFT and platelet inhibition management, results from our cohort study may appear provocative. The wide variety of available PFT, often using different methodologies, the apparent lack of standardization, and finally the emerging evidence on the clinical value of platelet function inhibition have resulted in considerable clinical uncertainty regarding how to deal with the issue of PFT. In our NVS series, there appeared to be improved neurologic outcomes when PFT were used and when pharmacological platelet inhibition was adjusted, relative to the cohort that was not tested with PFT. Similarly, we observed a decreased incidence of thromboembolic events in our PFT cohort. Consequently, our results seem to indicate that PFT may not be a gimmick, but rather a useful clinical tool to enhance procedural safety and clinical outcomes in NVS procedures.
Statement of Ethics

This study was approved by the Tasmanian Human Research Ethics Committee (approval reference H-016674).

Disclosure Statement

None declared.

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Author Contributions

All authors made substantial contributions to the design of this study and analysis and interpretation of data for this work. All of the authors drafted and/or revised this paper critically and provided final approval of the version to be published. They also agree to be accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved.

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