The use of the VerifyNow P2Y12 point-of-care device to monitor platelet function across a range of P2Y\textsubscript{12} inhibition levels following prasugrel and clopidogrel administration

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Summary

Variability in response to antiplatelet agents has prompted the development of point-of-care (POC) technology. In this study, we compared the VerifyNow\textsuperscript{\textregistered} P2Y12 (VN-P2Y12) POC device with light transmission aggregometry (LTA) in subjects switched directly from clopidogrel to prasugrel. Healthy subjects on aspirin were administered a clopidogrel 600 mg loading dose (LD) followed by a 75 mg/d maintenance dose (MD) for 10 days. Subjects were then switched to a prasugrel 60 mg LD and then 10 mg/d MD for 10 days (n=16), or to a prasugrel 10 mg/d MD for 11 days (n=19). Platelet function was measured by LTA and VN-P2Y12 at baseline and after dosing. Clopidogrel 600 mg LD/75 mg MD treatment led to a reduction in P2Y\textsubscript{12} reaction units (PRU) from baseline. A switch from clopidogrel MD to prasugrel 60 mg LD/10 mg MD produced an immediate decrease in PRU, while a switch to prasugrel 10 mg MD resulted in a more gradual decline. Consistent with the reduction in PRU, device-reported percent inhibition increased during both clopidogrel and prasugrel regimens. Inhibition of platelet aggregation as measured by LTA showed a very similar pattern to that found with VN-P2Y12 measurement, irrespective of treatment regimens. The dynamic range of VN-P2Y12 appeared to be narrower than that of LTA. With two different thienopyridines, the VN-P2Y12 device, within a somewhat more limited range, reflected the overall magnitude of change in aggregation response determined by LTA. The determination of the clinical utility of such POC devices will require their use in clinical outcome studies.

Keywords

VerifyNow\textsuperscript{\textregistered} P2Y12 light transmission aggregometry, prasugrel, clopidogrel, platelet aggregation

Introduction

A variety of methods have been utilized to assess platelet function and its inhibition during antiplatelet therapy (1, 2). Among the available methods, light transmission aggregometry (LTA) has been the most widely used. However, while LTA is widely utilized to assess platelet function, this method has several limitations, including lack of standard methodology (different agonists, different agonist concentrations, control of platelet count and different endpoints), relatively high sample volume, requirements for sample preparation, length of the assay time, inability to transport specimens and the requirement for skilled technicians. Because of these limitations, it is a challenge to use LTA in daily practice to assess the response to antiplatelet therapy (1, 2). VerifyNow\textsuperscript{\textregistered}, formerly known as the Ultegra Rapid Platelet Function Analyzer, is a point of care (POC) device designed to measure platelet aggregation in whole blood. Three VerifyNow assays are available: the VerifyNow IIb/IIIa assay, the VerifyNow Aspirin assay and the VerifyNow P2Y12 (VN-P2Y12) assay (2). The VN-P2Y12 assay was developed to measure platelet P2Y\textsubscript{12} receptor blockade mediated by clopidogrel (2). The results obtained from the VN-P2Y12 assay are thought to approximate platelet aggregation results obtained with traditional LTA techniques.
Prasugrel is an novel thienopyridine, currently under clinical investigation, with potent inhibition of ADP-induced platelet aggregation, as measured by LTA, after oral dosing (3–7). The phase 3 study of prasugrel (TRITON-TIMI 38) has recently been reported (8). Although VN-P2Y12 has been used to study the effect of clopidogrel on platelet aggregation (9–13), the device has not been assessed at the higher levels of P2Y12 inhibition that can be achieved with a 60 mg loading dose (LD) of prasugrel. We took advantage of a clopidogrel-prasugrel switching study in healthy, aspirin-treated subjects to compare the performance of the VN-P2Y12 POC device with traditional LTA throughout the potential dose-response range.

Methods

Study design and subjects

This study was an open-label, single-center, randomized, fixed-sequence, switching study in healthy male and female subjects designed to assess the safety and pharmacodynamic responses before and after switching directly from clopidogrel to prasugrel (14). The study (unique study identifier H7T-EW-TABF) was conducted at the Lilly Laboratories for Clinical Research, Indianapolis, IN, USA, between February and May 2006. The study protocol was approved by the local investigational review board and was performed in compliance with the principles of good clinical practice and in accordance with the provisions of the Declaration of Helsinki. All subjects provided signed and informed consent.

Forty healthy subjects (male = 26, female = 14) of Caucasian and African descent, aged 18–65 years, were enrolled in the study. Subjects initially received enteric coated aspirin 81 mg daily for a 7-day run-in period, followed by a single 600 mg clopidogrel LD and a 75 mg clopidogrel daily MD for 10 days using commercially available clopidogrel bisulfate ([Plavix®] 75 mg tablets, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, New York, NY, USA). Subjects were then switched directly, without a washout period, to prasugrel administered either as a 60 mg LD followed by prasugrel 10 mg daily MD for 10 days, or as prasugrel 10 mg daily MD for 11 days without a LD, using tablets containing 10 mg prasugrel as the HCl salt, Eli Lilly and Company, Indianapolis, IN, USA. Aspirin was co-administered with the thienopyridines.

VerifyNow P2Y12 (VN-P2Y12)

The VN-P2Y12 assay is a whole-blood, cartridge-based, optical detection system designed to measure platelet aggregation (15). The assay uses ADP, which activates both P2Y1 and P2Y12 ADP receptors, to induce platelet aggregation. It also uses prostaglandin E2 (PGE2) to suppress intracellular calcium levels mediated by ADP, which reduces the P2Y1 contribution, thus reportedly rendering the assay more sensitive and specific for P2Y12. In addition, the assay also includes a separate channel in which iso-TRAP is present as the agonist, providing a “BASE” value for the calculation of percent inhibition (15). The assay reports results as P2Y12 reaction units (PRU), BASE and percent inhibition. The assay was performed according to the manufacturer’s directions (15), Accumetrics, San Diego, CA, USA. In parallel to the instrument-reported percent inhibition, for comparison, we also directly calculated percent inhibition using the following formula:

\[
\text{Inhibition (\%)} = \left( \frac{\text{PRU}_{\text{ADP0}} - \text{PRU}}{\text{PRU}_{\text{ADP0}}} \right) \times 100
\]

where PRU is the baseline PRU value on Day -7 (baseline) before the first aspirin dose, and PRU is the value for each subject at selected time points.

Light transmission aggregometry (LTA)

Venous blood samples (approximately 13.5 ml) were collected into 3.2% sodium citrate tubes for the assessment of platelet aggregation. Platelet-rich and platelet-poor plasma were prepared as previously described (16). Maximum platelet aggregation (MPA) in platelet-rich plasma reflects the maximum LTA value achieved during the eight minutes following addition of 20 μM ADP using a Chrono-Log™ 4-channel, optical aggregometer (Chrono-Log Corporation, Havertown, PA, USA). In addition, residual platelet aggregation (RPA), the percent aggregation value at six minutes after ADP addition, was recorded. Inhibition of platelet aggregation (IPA) was calculated using the following formula:

\[
\text{IPA (\%)} = \left( \frac{\text{MPA0} - \text{MPA}}{\text{MPA0}} \right) \times 100
\]

where MPA0 was the observed baseline MPA at Day -7 prior to the first aspirin dose, and MPA was the observed MPA for each subject at selected time points. Inhibition of RPA was similarly calculated using RPA values.

Safety data collected during the study included the recording of adverse events, clinical laboratory evaluations, measurements of vital signs, electrocardiograms (ECGs) and physical examinations.

Statistical analysis

A linear mixed-effect model was fitted to determine the inhibition effect induced by thienopyridine separately for ADP and BASE from VerifyNow. In each model, treatment (clopidogrel 600 mg LD/ 75 mg MD, prasugrel 60 mg LD/ 10 mg MD, and prasugrel 10 mg MD), time and treatment-by-time interaction were fixed effects; subject, subject-by-treatment and subject-by-time were random effects. The heterogeneous residual error was allowed in this model to reflect the variability change over the time course. Pearson correlation coefficient was employed to evaluate the relationship between the measurements assessed by two assays (VN-P2Y12 and LTA). Lin’s concordance correlation coefficient was applied to assess the agreement between directly reported percent inhibition and calculated percent inhibition from VN-P2Y12.

Results

Subject disposition

Forty healthy subjects were enrolled in the study. One subject was withdrawn during the aspirin lead-in phase due to non-compliance. Thirty-nine subjects received clopidogrel 600 mg LD and daily 75 mg MD. Of these 39 subjects, four were withdrawn...
during clopidogrel MD as a result of non-serious adverse events. The remaining 35 patients switched from clopidogrel MD to prasugrel: 16 subjects switched to a prasugrel 60 mg LD followed by prasugrel 10 mg MD, and 19 subjects switched to a prasugrel 10 mg MD without a LD. All 35 of these subjects completed the study. A more detailed description of safety and adverse events are reported elsewhere (17).

**VN-P2Y12 results**

Figure 1A depicts the PRU values (mean ± SD) from the VN-P2Y12 device obtained following aspirin, clopidogrel and prasugrel-dosing regimens. Daily aspirin reduced the mean PRU from the drug-free baseline (Day -7) PRU of 297 ± 33 to 283 ± 36 on Day 1 pre-clopidogrel LD (p=0.054). Administration of a clopidogrel 600 mg LD further reduced the PRU values with a maximum effect (PRU of 91.1 ± 77.1, p<0.001 vs. Day -7) observed by four hours after dosing and maintained at this level through 24 hours (Fig. 1A). A small increase in PRU from the levels following the LD was observed following 10 days of clopidogrel 75 mg MD.

Subjects were then switched directly to a prasugrel 60 mg LD followed by 10 mg MD for 10 days or to a prasugrel 10 mg MD for 11 days. There was a substantial and statistically significant further reduction in PRU values within 30 minutes of the prasugrel 60 mg LD with PRU decreasing from 136 ± 62 to 23.8 ± 30.3 (p<0.001). The maximal effect (5.6 ± 8.4 PRU) was observed between one and two hours following the prasugrel 60 mg LD and then remained fairly constant through 24 hours. During subsequent daily prasugrel 10 mg MD, PRU values gradually increased and reached a constant level of approximately 33.5 PRU after four to five days of dosing. Switching from clopidogrel MD to prasugrel 10 mg MD also lowered PRU during the first 24 hours relative to clopidogrel MD, but the effect was not as great as that of the prasugrel LD (Fig. 1A). The response to the prasugrel 10 mg MD reached a steady state similar to that of the 60/10 mg regimen after approximately four to five days of MD.

In addition to reporting PRU (Fig. 1A), the VN-P2Y12 device also reports percent inhibition, and these data are shown in Figure 1B. The pattern of results was similar to that observed with results expressed as PRU with increases in percent inhibition reflecting decreases in PRU. A clopidogrel 600 mg LD produced its maximum effect by four hours after dosing (64.6 ± 27.8% inhibition). Percent inhibition increased substantially 30 minutes after administration of the prasugrel 60 mg LD (88.4 ± 16.2 %) and further increased to 97.7 ± 2.9% at two hours and remained at this high level through 24 hours. A new steady-state level of inhibition of about 85% was seen four to five days after initiating a prasugrel 10 mg MD.

**Figure 1**: Comparison of platelet function as measured by VN-P2Y12 and light transmission aggregometry (LTA) in healthy subjects during thienopyridine treatment. A) Mean PRU values reported by VN-P2Y12. B) Mean percent platelet inhibition (% inhibition) reported by VN-P2Y12. C) Mean inhibition of platelet aggregation (%IPA) in response to 20 µM ADP. Clot = clopidogrel; Pras = prasugrel; PRU = P2Y12 reaction units; † post aspirin, pre Clot.
Figure 2: Association between reported percent inhibition by VN-P2Y12 and various measures of LTA induced with 20 µM (left panel) or 5 µM (right panel) ADP. Symbols represent individual measurements under different thienopyridine treatment regimens excluding all baseline values. IPA = inhibition of platelet aggregation; MPA = maximal platelet aggregation; RPA = residual platelet aggregation. Correlation coefficients (r) were calculated by the Pearson method.

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Table 1: Effect of study drugs (aspirin, clopidogrel, prasugrel) on VN-P2Y12 measures at various time points.

<table>
<thead>
<tr>
<th>Time (day/hour)</th>
<th>Study drug (aspirin/thienopyridine)</th>
<th>N (subjects)</th>
<th>PRU (mean ± SD)</th>
<th>P-value vs. –7/0</th>
<th>P-value vs. 1/0</th>
<th>BASE (mean ± SD)</th>
<th>P-value vs. –7/0</th>
<th>P-value vs. 1/0</th>
<th>P-value vs. 10/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>–7/0</td>
<td>–/–</td>
<td>39</td>
<td>297.1 ± 32.7</td>
<td>--</td>
<td>--</td>
<td>291.3 ± 34.5</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>1/0</td>
<td>+/–</td>
<td>39</td>
<td>283.2 ± 35.8</td>
<td>p = 0.054</td>
<td>--</td>
<td>283.9 ± 36.9</td>
<td>p = 0.053</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>1/24</td>
<td>+/Clopidogrel (600 mg/75 mg)</td>
<td>39</td>
<td>88.6 ± 72.2</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>238.4 ± 45.0</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>11/24</td>
<td>+/Prasugrel (60 mg/10 mg)</td>
<td>16</td>
<td>136.1 ± 62.0</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>240.7 ± 44.9</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
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<tr>
<td>11/24</td>
<td>+/Prasugrel (10 mg/10 mg)</td>
<td>19</td>
<td>116.4 ± 71.3</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>253.7 ± 41.7</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>12/24</td>
<td>+/Prasugrel (60 mg/10 mg)</td>
<td>14</td>
<td>6.5 ± 7.5</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>183.1 ± 50.6</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>12/24</td>
<td>+/Prasugrel (10 mg/10 mg)</td>
<td>19</td>
<td>91.3 ± 71.2</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>247.9 ± 47.8</td>
<td>p&lt;0.001</td>
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</tr>
<tr>
<td>22/24</td>
<td>+/Prasugrel (10 mg sequences pooled)</td>
<td>33</td>
<td>46.9 ± 48.1</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>222.9 ± 24.3</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
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</table>

PRU: VN-P2Y12 device reported values; BASE: VN-P2Y12 TRAP channel reported values; *Compare thienopyridines with aspirin-free baseline (–7/0); †Compare thienopyridines with thienopyridine-free, post-aspirin baseline (1/0).

**VN-P2Y12 compared with LTA**

A comparison of percent inhibition reported by VN-P2Y12 (Fig. 1B) to IPA derived from LTA (Fig. 1C) revealed a strikingly similar pattern of platelet inhibition between the two methodologies, a similar agreement was found between PRU and MPA patterns (data not shown). Following administration of thienopyridines, the inhibition reported by the VN-P2Y12 was approximately 10 percentage points higher than that calculated from LTA. In contrast, aspirin treatment resulted in 11.4± 10.2% (p<0.0001) inhibition by LTA while there was minimal change (<5%) with the VN-P2Y12 (p=N.S.) (Fig. 1B, C).

To further explore the relationship between VN-P2Y12 and LTA, we plotted the reported percent inhibition from VN-P2Y12 versus several alternative LTA measures observed with both 20 µM and 5 µM ADP (Fig. 2). To better observe the relative influence of P2Y₁₂ blockade in these plots, all baseline values were excluded. As shown in Figure 2, irrespective of the measure paired with the VN-P2Y12 reported percent inhibition, the relationship appears somewhat sigmoidal reflecting the VN-P2Y12 values reaching 0% and 100% earlier than the LTA measures, which indicates that the dynamic range of the VN-P2Y12 is not as wide as that of LTA. As an example, using the comparison of VN-P2Y12 percent inhibition versus percent IPA (20 µM ADP, Fig. 2 top left), the data indicate that between IPA values of 20% and 70%, VN-P2Y12 percent tended to increase in the same direction; when IPA values fell below 20%, VN-P2Y12 values were largely at 0%; and for IPA values that were above 70%, many VN-P2Y12 values were already at maximum inhibition (100%). Despite this divergence from linearity, the overall values are still in reasonable agreement as reflected in a Pearson correlation coefficient (r) of 0.89 (p<0.001). Figure 2 also provides the Pearson correlation coefficient values for the comparison of VN-P2Y12 to each alternative expression of the LTA data, further demonstrating an association between VN-P2Y12 and LTA results. Correlation coefficient values ranged from a low of 0.74 (IPA with 5 µM ADP) to a high of 0.93 (RPA with 20 µM ADP). As shown by Figure 2, the correlations between LTA and VN-P2Y12 were higher when 20 µM ADP was used as the LTA agonist.

Table 1 reports PRU and BASE values (mean ± SD) for select time points during the study including baseline (Day –7/0), aspirin alone (Day 1/0) and periods of maximal P2Y₁₂ inhibition or steady state resulting from thienopyridine treatment. Aspirin alone resulted in a small but non-significant reduction in both PRU and BASE values (Table 1). Thienopyridine treatment with either clopidogrel or prasugrel, on a background of aspirin, led to reduction in BASE values with the lowest BASE value (183.1 ± 50.6) observed 24 hours after the 60 mg prasugrel LD. At all time points tested, the BASE values were decreased by clopidogrel or prasugrel treatment (p<0.001 compared with Day –7/0), indicating that BASE values are influenced by the inhibition of P2Y₁₂ receptors.

In view of the effect of thienopyridines on the BASE measurement, we compared the device reported percent inhibition with calculated % inhibition from true baseline.

**Figure 3: Relationship between VN-P2Y12 reported % inhibition and calculated % inhibition from true baseline.** A correlation coefficient of 0.98 (p<0.001) was found using Lin’s concordance correlation method.
Discussion

VN-P2Y12 is a rapid, cartridge-based, POC assay system designed to measure platelet function with uniformity by employing a fixed ADP concentration, a fixed observation period and standardized data analysis, all achieved with less resource intensity than required for LTA. The results presented in this report represent a comprehensive study of the performance of this POC assay across the dynamic range of the assay. We chose to incorporate this device into a clopidogrel-prasugrel switching study since it allowed a direct comparison of VN-P2Y12 with traditional LTA measures over a wide range of inhibition levels in the presence of aspirin. These data indicate that the VN-P2Y12 assay effectively detected the effects of both clopidogrel and prasugrel in the presence of aspirin under both LD and MD conditions. While this has been previously reported for clopidogrel in the apparent absence (9) or presence (11, 13, 18) of aspirin, this is the first description of the response of the assay to prasugrel. The results obtained following prasugrel treatment demonstrated a pattern of platelet inhibition similar to that found by LTA. While VN-P2Y12 had a more limited dynamic range than LTA, as manifested as a lack of sensitivity to changes in IPA at IPA values by LTA below 20% and above 70%, it may be useful in providing overall assessment of platelet function in patients receiving currently approved thienopyridine antiplatelet therapy and provide a more convenient and standardized alternative to LTA. However, its use with more potent P2Y12 antagonists under development, such as prasugrel, will require further study at doses that have been shown to be safe and effective.

Within the range of values from 20% to 70% by LTA, there was good agreement within the dynamic range between the various parameters obtained with LTA and the VN-P2Y12 assay, particularly when LTA was performed with 20 µM ADP (Fig. 2). However, some caution should be taken when interpreting the correlations given in Figure 2. Since the relationship was somewhat sigmoidal rather than strictly linear, a concentration of data points at the high and low ends of the scale may have influenced the overall correlation values. Nevertheless, in general there appeared to be a good association between VN-P2Y12 and LTA for both MPA- and RPA-derived parameters. The VN-P2Y12 incorporates PGE1 into the ADP channel to render it more specific to P2Y12-driven platelet reactivity. Likewise, RPA is thought to better reflect P2Y12 function than MPA (19); however, in the present study, the agreement between VN-P2Y12 and RPA-derived data was similar to that of VN-P2Y12 and MPA-derived data. In accordance with our observations, Van Werkum recently concluded that the correlation between PRU and LTA was similar irrespective of the LTA parameter used (11).

The VN-P2Y12 appeared to have limitations compared with LTA when IPA by LTA fell below approximately 20% and above 70%. As shown in Figure 2, VN-P2Y12 appears to be less sensitive to the low levels of inhibition that are detected by LTA (0–20% IPA). This may not be clinically relevant since the goal of thienopyridine therapy is to achieve levels of inhibition substantially higher than 20%. However, discrimination between higher levels of inhibition may be a potentially important limitation of the device with agents in development that provide higher levels of P2Y12 blockade, such as prasugrel and AZD-6140 (ticagrelor), but not for the detection of lower levels of P2Y12 blockade achieved with currently approved doses of clopidogrel. However, the extent of platelet inhibition that would be desirable for optimal clinical benefits awaits the results of clinical trials involving the newer P2Y12 antagonists (19, 20). Of note the phase 3 trial of prasugrel (TRITON-TIMI38) recently indicated significantly reduced ischemic events, including stent thrombosis, but with an increased risk of bleeding compared to clopidogrel in ACS patients undergoing PCI (8).

In addition we noted that VN-P2Y12-reported percent inhibition values were approximately 10 percentage points higher than values obtained by LTA following administration of a thienopyridine. This may, as has been previously discussed, reflect the presence of PGE1 in the VN-P2Y12 ADP channel rendering it more specific for P2Y12 antagonism. In addition, since VN-P2Y12 is performed in whole blood, the higher percent inhibition observed may reflect the presence of erythrocytes and leukocytes which contain CD39 that hydrolyzes ADP, thus possibly limiting the amount of ADP available to activate the P2Y12 or P2Y12 receptor (21–25). Metabolism of ADP by CD39 results in the generation of AMP which may also dampen platelet reactivity (26).

The results presented here and elsewhere (27) demonstrate that aspirin administration results in an approximately 11% inhibition of 20 µM ADP-mediated platelet aggregation measured by LTA. In contrast to higher percent inhibition following the administration of thienopyridines, the VN-P2Y12 showed a minimal change in percent inhibition following aspirin alone. The reasons for the differences in response pattern to thienopyridines and aspirin between LTA and the VN-P2Y12 are not clear.

A potential advantage of utilizing VN-P2Y12 to measure platelet function is its ability to calculate percent inhibition without the need of a baseline (medication-free) measurement, made possible by incorporating the BASE (TRAP) channel in the assay cartridge. The underlying assumption is that the response to TRAP is not affected by aspirin or thienopyridines. Accordingly, we analyzed the BASE data to determine whether aspirin, clopidogrel or prasugrel in various treatment conditions would affect the response to TRAP. Aspirin treatment did not significantly alter the BASE value, confirming that, as used in this device, TRAP-induced platelet aggregation is largely independent of aspirin-mediated platelet inhibition. BASE values for clopidogrel- or prasugrel-treated samples were significantly altered compared with baseline, thus indicating that inhibition of P2Y12 receptor function did influence the aggregation response to TRAP. Since the BASE values were lower in the presence of thienopyridines (Table 1), this could potentially lead to an underestimation of the true percent inhibition of platelet aggregation. However, as indicated by Figure 3, the actual effect on reported percent inhibition appears to be minimal with, as one might expect from the above, a slight divergence of the data above the line...
References


of unity. Nevertheless, the overall data suggest that the effect of thienopyridines on the BASE channel may not have a clinically meaningful effect on instrument-reported percent inhibition.

In summary, the results reported here show that across a broad range of P2Y12 inhibition, produced by two different thienopyridines, the VN-P2Y12 POC device, while demonstrating a somewhat limited dynamic range, generally reflected the overall magnitude of change in aggregation response found by LTA. Its ease of use and standardization renders it a potentially useful alternative to LTA for the measurement of platelet function during thienopyridine treatment, but it requires further validation in clinical studies of newer P2Y12 antagonists.

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