Long-Term Aspirin and Clopidogrel Response Evaluated by Light Transmission Aggregometry, VerifyNow, and Thrombelastography in Patients Undergoing Percutaneous Coronary Intervention

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BACKGROUND: A reduced response to aspirin and clopidogrel predicts ischemic events, but reliable tests are needed to identify low responders. We compared 3 platelet-function tests during long-term dual treatment with aspirin and clopidogrel.

METHODS: Patients who underwent a percutaneous coronary intervention and were receiving a combination of 325 mg/day aspirin and 75 mg/day clopidogrel were followed for 1 year. Blood was sampled 5 times during this period for 3 tests: light transmission aggregometry (LTA) assay, with 5.0 mmol/L ADP or 0.1 mmol/L arachidonic acid (AA) as an agonist; VerifyNow™ assay, with the P2Y12 or aspirin cartridge (Accumetrics); and thrombelastography (TEG), stimulated by 2.0 mmol/L ADP or 1.0 mmol/L AA.

RESULTS: Twenty-six of 33 patients completed all scheduled visits. A low response to clopidogrel was found in a few patients at variable frequencies and at different visits, depending on the method and criteria used. We found a moderate correlation between the LTA (ADP) and VerifyNow (P2Y12 cartridge) results, but the TEG (ADP) results correlated poorly with the LTA and VerifyNow results. A low response to aspirin was found with the VerifyNow (aspirin cartridge) and TEG (AA) methods on 6 and 2 occasions, respectively, but not with the LTA (AA) method, except for 1 occasion caused by probable noncompliance.

CONCLUSIONS: Detecting a low response to clopidogrel depends largely on the method used. Which method best predicts ischemic events remains uncertain. A low response to aspirin is rare with AA-dependent methods used at the chosen cutoffs. In some patients, the response to clopidogrel or aspirin may be classified differently at different times, even with the same method.
sured by light transmission aggregometry (LTA), has been linked to a poorer prognosis in patients with coronary artery disease (CAD) who are treated with a combination of aspirin and clopidogrel (5–12). Quickier and more user-friendly analyses that do not require the expertise and labor required for the gold standard LTA assay are needed, and the VerifyNow (Accumetrics) and thrombelastography (TEG) systems have been proposed as alternatives to LTA for assessing ALR and CLR (6, 15, 16).

Previously published studies did not evaluate platelet function during aspirin and clopidogrel therapy beyond 1 month, and most reports are based on single measurements, either alone or in comparison with a baseline value (5–13). Therefore, it is unknown whether patients’ responses to aspirin and clopidogrel change during long-term therapy. Consequently, we conducted a prospective study to investigate the long-term effects of aspirin and clopidogrel in CAD patients undergoing percutaneous coronary intervention (PCI). We found no general tendency toward development of CLR or ALR during long-term therapy, as assessed by LTA and VerifyNow methods (17). We compare 3 platelet-function tests (LTA, VerifyNow, and TEG assays) to evaluate their agreement in assessing and classifying ALR and CLR during long-term follow-up.

Materials and Methods

Patients undergoing elective PCI at Vancouver General Hospital, Vancouver, Canada, were eligible for this study. The inclusion criteria were male or female patients at least 18 years of age who had taken aspirin (80–325 mg) for at least 5 days. The exclusion criteria were known allergy or intolerance to clopidogrel, a combination of 75 mg/day clopidogrel and 325 mg/day aspirin was not permitted because of its long half-life. A combination of 75 mg/day clopidogrel and 325 mg/day aspirin was prescribed for 1 year after the PCI.

**BLOOD SAMPLING**

After informed consent was obtained and before the interventional procedure, baseline blood samples were collected from the arterial sheath into Vacutainer tubes (BD Medical Systems) containing EDTA, sodium citrate (3.2%), and heparin (in separate tubes). Postprocedural blood samples were drawn on day 1 (at 16–24 h), 1 month, 6 months, and 12 months by peripheral venipuncture into Vacutainer tubes containing the anticoagulants listed above. The first 3 mL of blood were always discarded. The study patients fasted for at least 4 h before each visit.

Platelet-rich plasma (PRP) was prepared by centrifuging sodium citrate–anticoagulated whole blood at 150g for 12 min at 24 °C. The recovered supernatant (PRP) was kept in a capped plastic tube at 37 °C. The PRP was used for LTA without any adjustment of the platelet count, as previously recommended (19). The mean PRP platelet count was 315 × 10^9 cells/L (SD, 80 × 10^9 cells/L), as measured with the ADVIA 120 hematology analyzer (Siemens Healthcare Diagnostics). Platelet-poor plasma was isolated by centrifuging the blood remaining after PRP removal at 800g for 15 min.

**LTA ANALYSIS**

LTA was performed within 2 h after blood sampling with Chrono-Log Lumi-Aggregometer model 810 and the Aggrolink software (Chrono-Log Corporation) according to the principles described by Born (20). Platelet-poor plasma was used as a reference for maximal light transmission, and 500 μL of PRP was stimulated with 1.0 mmol/L arachidonic acid (AA) and 5.0 μmol/L ADP (final concentrations; Chrono-Log). During analysis, the PRP was stirred at a fixed speed of 1000 rpm. Relative light transmission was measured at the maximum (LTA-AA, LTA-ADP_max) and after 6 min when ADP was used (LTA-ADP_6_min). The aggregation assays were run in duplicate with the mean recorded as percent aggregation. The mean was used in analyses (Figs. 1 and 2). An LTA-AA value >20% was considered to indicate ALR (21). We used 2 published definitions for CLR based on LTA: (a) a <10% absolute decrease in LTA-ADP_max from the baseline (22), or (b) an LTA-ADP_max value >50% during treatment (10).

**VerifyNow ASSAY**

The VerifyNow system is a whole-blood assay based on light transmission measurements. We used the aspirin- and P2Y_{12}-specific cartridges to assess platelet dysfunction caused by aspirin and clopidogrel, respectively. In the aspirin-specific assay, AA in the aspirin-specific cartridge activates platelets, and the activated platelets bind to fibrinogen-coated beads to form an aggregate.
The degree of aggregation is quantified by a corresponding increase in light transmission and is reported in aspirin reaction units (ARU). A value \( \geq 550 \) ARU indicates ALR. The P2Y\(_{12}\)-specific cartridge has 2 chambers. In the first chamber, ADP activates the platelets. This chamber also contains prostaglandin E\(_1\) to suppress activation via the P2Y\(_1\) receptor. The measured change in light transmission is converted into
P2Y₁₂ reaction units (PRU). In the second chamber, thrombin receptor–activating peptide stimulates platelets, producing a value (“BASE”) used for calculating percent platelet inhibition: $\frac{100}{\text{BASE}} \times (\text{BASE} - \text{PRU})/\text{BASE}$, which is equal to percent inhibition of the contribution from ADP-stimulated platelets to maximal clot strength (as measured with the VerifyNow method) (VerifyNow-ADP-Inhib). In accordance with a previous recommendation (23), a value >264 PRU was defined as CLR.

**TEG PLATELET-MAPPING ASSAY**

The TEG<sup>®</sup> Hemostasis Analyzer with Platelet Mapping Assay (Haemonetics Corporation) measures clot formation, clot strength, and clot degradation in whole blood. In brief, 360 μL of citrate- or heparin-anticoagulated blood is pipetted into an oscillating cup with or without a heparinase coating. A pin connected to a torsion wire is immersed into the blood. The addition of appropriate stimulators initiates the coagulation process. The oscillating motion of the cup is transferred to the torsion wire as the blood clot sticks to the cup and the pin, with increasing strength during clot formation and with decreasing strength during clot lysis. The amplitude of the motion transferred through the tension wire is recorded. The maximal amplitude (MA) corresponds to the maximal clot strength. The fibrin contribution to the maximal clot strength

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**Fig. 2. Individual curves.**

Various test results shown individually. Mean values are in red. Shown are ADP-dependent analyses (A, C, and E) and AA-dependent analyses (B, D, and F). Cutoff values for ALR and CLR are indicated with dashed lines. One patient (*) responded typically after 2 weeks of compliance with aspirin therapy. The discontinuity of some lines is due to patient dropout. COX-1, cyclooxygenase 1.
(MA_fibrin) is quantified by the addition of an activator (reptilase and activated factor XIII), which facilitates the formation of the cross-linked fibrin clot. The contributions of the cyclooxygenase 1 pathway (MAAA) and the P2Y12 pathway (MAADP) to maximal clot formation is measured by adding activator and either AA (final concentration, 1 mmol/L) or ADP (final concentration, 2 μmol/L) to 360 L of heparinized whole blood. The maximum-possible clot strength (MAthrombin) is measured in 360 L of sodium citrate–anticoagulated whole blood by adding kaolin and calcium chloride (final concentration, 10.5 mmol/L). Percent platelet inhibition [the contribution from AA-stimulated platelets to maximal clot strength (TEG) (TEG-AA-Inhib) or the contribution from ADP-stimulated platelets to maximal clot strength (TEG) (TEG-ADP-Inhib)] by either aspirin or clopidogrel is computed as:

\[
\frac{(MA_{thrombin} - MA_{fibrin})}{MA_{fibrin}} \times 100 - 100
\]

We considered <50% and <30% inhibition of AA- and ADP-induced clot formation (i.e., TEG-AA-Inhib, TEG-ADP-Inhib) to be ALR and CLR, respectively, as previously suggested (10, 21).

STATISTICAL ANALYSIS

Data were analyzed with Stata™ software (version 9.2; StataCorp). To accommodate nonnormality, we used the Spearman correlation coefficient (r) for methods comparisons.

Results

We enrolled 33 patients, 26 of whom completed all of the study visits. Detailed baseline demographic characteristics of these 26 patients have previously been reported (17). Of the 7 patients who stopped prematurely (4 before the 1-month visit, and 3 before the 6-month visit), 2 had contraindications to long-term dual antiplatelet therapy (nosebleed and surgery for colon cancer). The other 5 patients withdrew for personal reasons.

MONITORING CLOPIDOGREL THERAPY

Table 1 presents intra- and interindividual SDs for each measurement. Duplicate measurements were performed with LTA only, and the SDs within duplicates were 4.7% and 9.7% for LTA-ADP_{max} and LTA-ADP_{6 min}, respectively, at baseline and 3.0% and 3.3%, respectively, between day 1 and 12 months.

Table 2 presents the numbers of patients with CLR at each visit according to the various definitions. One CLR definition is based on the decrease in aggregation from the baseline LTA-ADP_{max} measurement to later LTA-ADP_{max} measurements (\Delta LTA-ADP_{max}). With CLR defined as a \Delta LTA-ADP_{max} value of <10% (18), 4 patients showed CLR at 3 or 4 of 4 visits. The baseline LTA-ADP_{max} values were <30% in these patients. When CLR was defined as an LTA-ADP_{max} value >50% (10), 1 patient appeared to have CLR at the last

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**Table 1. Variation of the measurements.**

<table>
<thead>
<tr>
<th>Method</th>
<th>Interindividual SD</th>
<th>Intraindividual SD</th>
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<tbody>
<tr>
<td>LTA-ADP_{max}, %</td>
<td>10.50</td>
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<tr>
<td>LTA-ADP_{6 min}, %</td>
<td>9.87</td>
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<td>VerifyNow, PRU</td>
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<td>VerifyNow-ADP-Inhib, %</td>
<td>17.08</td>
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<tr>
<td>TEG-ADP-Inhib, %</td>
<td>15.66</td>
<td>19.62</td>
</tr>
<tr>
<td>LTA-AA, %</td>
<td>0.26</td>
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<tr>
<td>VerifyNow, ARU</td>
<td>23.16</td>
<td>46.85</td>
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<tr>
<td>TEG-AA-Inhib, %</td>
<td>2.55</td>
<td>9.17</td>
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</table>

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**Table 2. Patients with CLR.**

<table>
<thead>
<tr>
<th>Definition</th>
<th>1 Day</th>
<th>1 Month</th>
<th>6 Months</th>
<th>1 Year</th>
<th>&gt;1 Visit</th>
<th>All visits</th>
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<tr>
<td>(\Delta LTA-ADP_{max} &lt;10%)</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>2</td>
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<td>(LTA-ADP_{max} &gt;50%)</td>
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<td>3</td>
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<td>2</td>
<td>1</td>
<td>0</td>
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<tr>
<td>VerifyNow &gt;264 PRU</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TEG-ADP-Inhib &lt;30%</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>0</td>
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<tr>
<td>All definitions</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

* Numbers of patients with CLR are listed by visit and method.

* Numbers of patients appearing to have CLR at >1 visit and at all visits.
3 consecutive visits, whereas 6 patients fulfilled this criterion only once. When CLR was defined as a VerifyNow value >264 PRU (23), we identified 4 patients with CLR at 1 or 2 visits. The most frequent occurrence of CLR was defined as a TEG-ADP-Inhib value of <30% (21). Ten patients seemed to have CLR at 1–3 visits.

The 2 LTA definitions of CLR were concordant on 1 occasion but were discordant on 20 other occasions (Fig. 1A). Fig. 1, B and D, illustrates the agreement between the VerifyNow- and LTA-based definitions. Concordance regarding CLR was found on 1 and 3 occasions, respectively, and discordance was found on 12 and 6 occasions, respectively. As shown in Fig. 1, C, E, and F, the TEG result was concordant with LTA-ADPmax and VerifyNow results on 1 to 2 occasions and was discordant on 15–22 occasions.

Table 3 summarizes the correlation analyses. The best observed correlation was between the results for the VerifyNow PRU and LTA-ADPmax assays ($r = 0.66; P < 0.001$).

**MONITORING ASPIRIN THERAPY**

Table 1 shows intra- and interindividual SDs for each measurement. The SDs within duplicates were 0.6% and 1.2% for LTA-AA at baseline and between day 1 and 12 months, respectively.

Table 4 summarizes the ALR results as defined by each method. ALR was a rare finding, and none of the patients showed ALR more than once with any of the methods.

At 12 months, 1 patient showed ALR by all 3 criteria; however, a repeat measurement by LTA carried out 2 weeks later after compliance was ensured showed this patient to be responsive to aspirin (VerifyNow and TEG analyses were not repeated), suggesting that the patient had not been compliant to prescribed aspirin intake.

**Table 3. Correlations between methods.**

<table>
<thead>
<tr>
<th>Method a</th>
<th>Method b</th>
<th>Baseline</th>
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<th></th>
<th></th>
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<tbody>
<tr>
<td>TEG-ADP-Inhib</td>
<td>TEG-MA ADP</td>
<td>$r^*$</td>
<td>0.87</td>
<td>19</td>
<td>$&lt;0.001$</td>
<td>0.92</td>
<td>78</td>
<td>$&lt;0.001$</td>
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<tr>
<td>LTA-ADP&lt;sub&gt;max&lt;/sub&gt;</td>
<td>LTA-ADP&lt;sub&gt;6 min&lt;/sub&gt;</td>
<td>0.93</td>
<td>30</td>
<td></td>
<td>$&lt;0.001$</td>
<td>0.88</td>
<td>112</td>
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<tr>
<td>VerifyNow PRU</td>
<td>VerifyNow-ADP-Inhib</td>
<td>-0.20</td>
<td>21</td>
<td>0.39</td>
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<td>-0.83</td>
<td>87</td>
<td>$&lt;0.001$</td>
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<tr>
<td>LTA-ADP&lt;sub&gt;max&lt;/sub&gt;</td>
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<td>0.82</td>
<td></td>
<td>0.66</td>
<td>87</td>
<td>$&lt;0.001$</td>
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<tr>
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<td>LTA-ADP&lt;sub&gt;6 min&lt;/sub&gt;</td>
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<tr>
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$^a$ Spearman correlation coefficient.

**Table 4. Patients with ALR.$^a$**

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<tr>
<th>Definition</th>
<th>Baseline</th>
<th>1 Day</th>
<th>1 Month</th>
<th>6 Month</th>
<th>1 Year</th>
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<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>VerifyNow &gt;550 ARU</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEG-AA-Inhib &lt;50%</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All definitions</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1*</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

$^a$ Numbers of patients exhibiting ALR are listed by visit and method.

$^b$ Numbers of patients appearing to have CLR at $>1$ visit and at all visits.
Comparison of Long-Term Aspirin and Clopidogrel Response

Table 3 presents the correlation coefficients for comparisons of ADP-dependent methods at baseline (i.e., affected by aspirin only).

Discussion

Our study compared the point-of-care devices, VerifyNow and thrombelastography, with the gold standard LTA assay for assessing the long-term effects of concomitant aspirin and clopidogrel therapy on platelet inhibition in patients treated with elective PCI. The most important comparison is the classification of typical (“normal”) and low responders. Most of the results for typical responders were concordant in the tests, whereas those for the low responders were often discordant. Although the small number of low responders makes this comparison more uncertain, it does illustrate that the knowledge about the use of tests for this purpose must be improved before they will be clinically useful. Second, we must assume some correlation between the methods; that is, different methods should measure high and low activity more or less equally. The correlations between methods, however, were generally rather poor, especially at baseline, once again illustrating the need to improve methods or define the best method for clinical purposes.

In this study, we used previously defined criteria for CLR and ALR. These criteria, however, are not well established and are not necessarily correct. Dichotomizing patients in groups of responders and low responders is a somewhat crude simplification, but it may be the first step to an improved risk stratification of the individual patient, which should be evaluated by clinical end points.

MONITORING THE CLOPIDOGREL RESPONSE
The 2 LTA criteria for CLR correlated poorly, and we found very little agreement in identifying patients with CLR (Fig. 1A). Other cutoff values have been proposed (24), but as one can infer from Fig. 1A, there was no cutoff with a good match between the relative criterion (ΔLTA-ADPmax = 10%) and the absolute criterion (LTA-ADPmax >50%) for CLR in our population. Aiming for a specified (low) platelet reactivity during treatment seems preferable. If only the change from baseline is used, a “normal” responsiveness to clopidogrel is possible with considerable residual platelet reactivity (e.g., 70% aggregation, corresponding to a baseline value of at least 81%), or, as observed in this study, the patients who presented with CLR (ΔLTA-ADPmax = 10%) more than once exhibited very low LTA-ADPmax values at baseline (<30%). In contrast, 39 LTA-ADPmax results >30% (range, 31%–63%) above the baseline value were found among the rest of the patients. Thus, a large proportion of the apparently typical responsive patients exhibited a higher degree of platelet reactivity than those who evinced CLR on aspirin alone. Similarly, Samara et al. (25) reported marked variation in baseline LTA-ADPmax values among 62 CAD patients who were treated with aspirin and were starting clopidogrel treatment. CLR was associated with low pretreatment platelet reactivity. In addition, high residual platelet reactivity was seen despite an apparently typical responsiveness. We agree with these authors’ suggested use of posttreatment measures of platelet reactivity to avoid overestimating the risk in patients with a low baseline reactivity and underestimating the risk in patients with high posttreatment reactivity, despite a substantial absolute decrease from the baseline value. The correlation between LTA-ADPmax and LTA-ADPmin was high (Table 3) and in agreement with previous reports (26, 27), suggesting that these values are equally informative.

The VerifyNow results correlated reasonably well with LTA-ADPmax and LTA-ADPmin results during clopidogrel therapy (Fig. 1D, Table 3), a finding that is supported (despite the use of different ADP concentrations) by a study of 211 clopidogrel-treated CAD patients who underwent PCI (27). In the largest comparison of the LTA-ADPmax (2 μmol/L and 10 μmol/L ADP) and VerifyNow assays to date, Paniccia et al. (23) reported correlation coefficients of 0.62 (2 μmol/L) and 0.64 (10 μmol/L). The concordance in defining CLR in this study was moderate: With 10 μmol/L ADP, 65% were concordant typical (“normal”), 14% had concordant CLR, and 21% were discordant (κ = 0.43).

The correlation between ADP-dependent LTA and TEG results was poor, a finding that contrasts with previous findings by Bliden et al. (10). We used citrated whole blood reactivated with calcium chloride and stimulated with kaolin for the measurement of MAthrombin as recommended by Haemoscope, whereas Bliden et al. used heparinized blood reactivated with heparinase and stimulated with kaolin. The MAADP, however, was measured identically in the 2 studies. In our study, the MAADP also correlated weakly (r = 0.35; P = 0.001) with LTA-ADPmax, indicating that the discrepancy cannot be explained solely by differences in MAthrombin. Concordant classification was also better in that study (10), with the finding of CLR in 16 patients, whereas 21 patients were classified differently with the TEG and LTA methods, which appear to show a moderate match.

The TEG and VerifyNow results were not correlated, nor were they in agreement in defining CLR (Fig. 1F; Table 3). These 2 methods for measuring the clopidogrel response have not previously been compared.
MONITORING THE ASPIRIN RESPONSE

Correlation and agreement analyses of the 3 methods used are not meaningful, given the small LTA-AA values and the generally rare finding of ALR. LTA stimulated with AA can be regarded as a method for ensuring aspirin inhibition of platelet cyclooxygenase 1. Studies that use this method for evaluating the aspirin response generally find a very low prevalence of ALR, and such results may likely be due to noncompliance (21, 28–31). Our results were in agreement with these observations.

The VerifyNow analysis is less operator dependent than the LTA method and therefore could be an attractive alternative. Some individual variation was observed between the time points (Fig. 2D). In fact, 19% of the patients would be regarded as having ALR if only tested at the 12-month visit, whereas no patient expressed ALR at both day 1 and 6 months. This finding suggests that this test detects too many patients with ALR, because LTA-AA values did not increase in these patients, confirming a low cyclooxygenase 1 activity. Of note is that we obtained our results during dual antiplatelet therapy, which should stabilize platelet function more than aspirin alone, because clopidogrel also inhibits AA-stimulated aggregation to some extent (32).

In agreement with other reports (10, 21), the TEG analysis detected very few patients with ALR, and this finding was consistent over time.

STRENGTHS AND LIMITATIONS OF THE PRESENT STUDY

For the first time, multiple measurements of platelet function were carried out throughout a 12-month period, permitting observation of the individual fluctuation of platelet reactivity with time. The small number of low responders makes the comparison more uncertain, but despite the small number of patients, the study revealed substantial disagreement between the tests. Results on day 1 might have been affected by the use of epifibatide, although its use was discontinued at least 10 h before blood sampling (33). We planned the timing of blood sampling according to the schedule of Schröer et al. (18). The effect on platelets on day 1, however, does not change our conclusions regarding agreement and correlation between methods. Unfortunately, we were unable to include flow cytometric analysis of vasodilator-stimulated phosphoprotein (VASP) phosphorylation. Both LTA and VASP-phosphorylation results have been linked to clinical ischemic events, but LTA may be the better predictor (9). That thromboxane B2 was not measured to ensure aspirin compliance may be considered a shortcoming of this study; however, other studies have reported a very good agreement between LTA-AA and serum thromboxane B2 results (29, 34), indicating that LTA-AA may also be a reliable test for compliance. Finally, the study was not powered to detect any possible relationship between the test results and clinical events.

Which platelet-function test predicts the worst prognosis is still unknown. The impact of CLR on ischemic events (6–12), however, indicates that a potential exists for improving antiplatelet treatment in patients with CLR after PCI, if it is guided by a reliable and easily accessible test. Our data suggest that in the absence of a strong consensus among methodologies, it remains difficult for clinicians to decide which assay result reflects the patient’s true platelet activity.

References

5. Reny JL, de Moerloose P, Dauzat M, Fontana P.
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