

# A Comparison of Plateletworks™ and Platelet Aggregometry for the Assessment of Aspirin-Related Platelet Dysfunction in Cardiac Surgical Patients

Mark J. Lennon, MBBCh, FCARCSI, FANZCA,\* Neville M. Gibbs, MBBS, MD, FANZCA,\*  
William M. Weightman, MBBCh, FANZCA,\* David McGuire, MBBS,\* and Nick Michalopoulos, BSct

**Objective:** To compare the assessment of aspirin-related platelet dysfunction using Plateletworks™ (Helena Laboratories, Beaumont, TX), a new point-of-care platelet function analyzer, with turbidometric platelet aggregometry, in cardiac surgical patients.

**Design:** Prospective observational study.

**Setting:** University-affiliated teaching hospital.

**Participants:** Fifty consecutive adult patients undergoing elective cardiac surgery for coronary artery bypass grafting or cardiac valve replacement.

**Interventions:** None.

**Measurements and Main Results:** Platelet function was assessed by Plateletworks™ and turbidometric platelet aggregometry before the commencement of anesthesia. Collagen, 10 µg/mL, was used as the agonist for both techniques. The area under the receiver-operator curve for the identification of recent aspirin ingestion ( $\leq 48$  hours  $v \geq 72$

hours) using Plateletworks™ was 0.58 (95% confidence interval [CI] 0.42-0.75) versus 0.77 (95% CI 0.61-0.95) for turbidometric platelet aggregometry. The Spearman correlation coefficient ( $\rho$ ) between preoperative Plateletworks™ and postoperative mediastinal blood loss was 0.07 ( $p = 0.58$ ), and between preoperative turbidometric platelet aggregometry and postoperative mediastinal blood loss was  $-0.31$  ( $p = 0.03$ ). On completion of surgery, the correlation coefficients were 0.14 ( $p = 0.34$ ) and  $-0.29$  ( $p = 0.08$ ), respectively.

**Conclusion:** These findings suggest that Plateletworks™ is of limited use for the detection of aspirin-related platelet defects in cardiac surgical patients.

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**KEY WORDS:** aspirin, platelet function, aggregometry, blood loss, cardiac surgery

MANY PATIENTS PRESENTING for cardiac surgery have recently ingested aspirin. Several studies in cardiac surgical patients have shown that recent aspirin ingestion is associated with increased blood loss.<sup>1-6</sup> However, the effect of aspirin on platelet function has been shown to vary between patients.<sup>7,8</sup> Therefore, the detection of aspirin-related platelet dysfunction in individual patients may be more predictive for perioperative blood loss than a history of recent aspirin ingestion alone.

Unfortunately, there are few options for the detection of aspirin-related platelet dysfunction perioperatively. Turbidometric platelet aggregometry in a hematology laboratory is the current reference standard for the assessment of platelet function but is often impractical in the perioperative period.<sup>9,10</sup> Several devices are available for the assessment of platelet function at the point of care,<sup>11</sup> but all have limitations in their sensitivity or specificity to aspirin. Plateletworks™ (Helena Laboratories, Beaumont, TX) is a new device for the assessment of platelet function using whole blood.<sup>12,13</sup> Plateletworks™ assesses platelet aggregation by comparing the platelet count before and after exposure with a specific platelet agonist.<sup>12,13</sup> The manufacturers of Plateletworks™ claim that it is capable of detecting a wide range of platelet abnormalities, including aspirin-related platelet dysfunction. The device is fully automated and provides a result within 5 minutes, making it suitable for use at the point of care. Such a device may be useful for the rapid assessment of aspirin-related platelet dysfunction in cardiac surgical patients. The aim of the current study was to compare the assessment of aspirin-related platelet dysfunction using Plateletworks™ with standard laboratory

turbidometric platelet aggregometry in patients undergoing elective cardiac surgery.

## METHODS

With institutional approval and informed consent, 50 consecutive adult patients undergoing elective surgery for coronary artery bypass grafting or cardiac valve repair or replacement were studied. Patients who had received intravenous heparin, abciximab, tirofiban, or clopidogrel within the previous week were excluded, as were patients with a known platelet function disorder or a preoperative platelet count  $< 130,000 \times 10^9/L$ . Patients were divided into two groups based on their last ingestion of aspirin. Group 1 patients had received aspirin within the previous 48 hours. Group 2 patients had not received aspirin for at least 72 hours preoperatively. Patients had taken aspirin up to a variable interval before surgery. This interval was based on advice they had received from their surgeon or cardiologist and was not influenced by inclusion in the study. All other nonsteroidal anti-inflammatory medications were withheld for at least 24 hours before surgery.

Perioperative anesthetic management was similar for all patients. Anesthetic premedication consisted of lorazepam, 2 to 3 mg, orally 2 hours preoperatively, followed by morphine, 0.1 mg/kg, intramuscularly and promethazine, 25 mg, intramuscularly 1 hour preoperatively. Patients received their usual cardiac medications on the morning of surgery. These varied among patients but often included  $\beta$ -adrenergic blocking drugs, nitrates, and angiotensin-converting enzyme inhibitors. Anesthesia was induced with fentanyl, 10 to 15 µg/kg, and midazolam, 0.05 mg/kg, supplemented with propofol up to 1 mg/kg. Pancuronium or rocuronium was used to achieve muscle relaxation. Anesthesia was maintained with isoflurane 0.5% to 1.5% (inspired) in oxygen or oxygen-enriched air, and fentanyl up to a total of 30 µg/kg. Flucloxacillin, 2 g, or vancomycin, 25 mg/kg, and gentamicin, 4 mg/kg, were given after induction. Patients received crystalloid solution, 0.5 to 1.0 L/h. Hypotension was treated, if necessary, with phenylephrine, 50 to 100 µg, by intravenous bolus, or an infusion of norepinephrine, 1 to 10 µg/min. Hypertension was treated, if necessary, with nitroglycerin, 0.5 to 3.0 µg/kg/h. Impaired cardiac contractility after cardiopulmonary bypass (CPB) was treated with epinephrine, 1 to 10 µg/min.

Patients had their surgery performed with CPB (on-pump) or without CPB (off-pump) based on surgical considerations. Patients who required CPB received porcine heparin, 300 u/kg, 3 minutes before the onset of CPB. An additional 10,000 U of heparin was added to the CPB priming solution. Further heparin was given as required during CPB to

From the \*Department of Anaesthesia, Sir Charles Gairdner Hospital, Nedlands, Australia; and †PathCentre, Nedlands, Australia.

Address reprint requests to Neville Gibbs, MBBS, MD, FANZCA, Department of Anaesthesia, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia. E-mail: nmg@cylle.uwa.edu.au

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**Table 1. Demographic Data**

	Group 1 Aspirin ≤48 h	Group 2 Aspirin ≥72 h
n	16	34
Age (y, mean, range)	68 (37-79)	63 (37-80)
Gender (M:F)	12:4	26:8
Preoperative platelet count (× 10 <sup>9</sup> /mL, mean, range)	233 (130-373)	238 (144-383)
Postoperative blood loss (mL, mean, range)	640 (120-1250)	532 (150-1310)

maintain an activated coagulation time >480 seconds. Post-CPB, the heparin was reversed with protamine, 1.3 mg per total heparin administered. Hypothermic CPB (28°-30°C) was instituted using a membrane oxygenator, roller pump, and 38- $\mu$ m arterial filter. For patients who did not require CPB, heparin, 100  $\mu$ /kg, was given 3 minutes before commencing the first coronary anastomosis. Additional heparin was given if required to maintain an activated coagulation time >300s. On completion of all coronary anastomoses, the heparin was reversed with 1.3 mg of protamine per total heparin administered. In all patients, postoperative mediastinal blood loss, as defined as the amount of blood collected from mediastinal chest drains in the first 12 hours postoperatively, was recorded.

Blood samples were obtained from a nonheparinized radial arterial catheter before the induction of anesthesia or the administration of other drugs. A 2-syringe technique was used such that the first 5 mL were discarded. For turbidometric platelet aggregometry, 4 mL of blood was collected into a siliconized glass collection tube containing 1 part 3.8% sodium citrate per 9 parts blood. For Plateletworks™, 1 mL of blood was collected into a siliconized glass collection tube containing 1.8 mg of ethylene diamine tetra-acetic acid. A further 1 mL was collected into a similar tube containing 10  $\mu$ g of liquid collagen in 0.035 mL of sodium citrate. The tubes were inverted several times to ensure mixing of the agonist.

For turbidometric platelet aggregation studies, platelet-rich plasma (PRP) was prepared in a hematology laboratory within 60 minutes of blood collection by centrifugation at 300 × g for 5 minutes at 20°C. Platelet-poor plasma (PPP) was prepared by centrifugation at 2000 × g for 5 minutes at 20°C. The platelet count was adjusted to 200 to 250 × 10<sup>9</sup>/L by dilution of PRP by PPP. Turbidometric platelet aggregometry was performed using an optical aggregometer (Monitor-IV, Daiichi Ltd., Kyoto, Japan). The aggregometer was calibrated using normal PRP for 0% light transmission and PPP for 100% light transmission. (The % light transmission is determined by the turbidity of the sample, which is a function of the number of platelets.) The maximum aggregation response within the first 5 minutes was recorded. The technologist performing the laboratory aggregometry was not aware of patient information or Plateletworks™ results.

The platelet count of the Plateletworks™ samples was measured by using an automated impedance technique at the point of care (ICHOR: Helena Laboratories) within 10 minutes of collection. Platelet aggregation (% maximum) was calculated using the following formula:

% maximum aggregation

$$= \frac{(\text{baseline platelet count} - \text{agonist platelet count}) \times 100}{\text{baseline platelet count}}$$

The sensitivity and specificity of Plateletworks™ values (0%-100%) for the identification of recent aspirin ingestion (≤48 hours v ≥72 hours) were calculated. By using this information, a receiver-operator curve (ROC, sensitivity v 1-specificity; ie, true-positive v false-positive rate) was constructed. A similar curve was constructed for turbidometric platelet aggregometry. The Spearman correlation coefficient ( $\rho$ )

between preinduction Plateletworks™ values (% maximum aggregation) and postoperative mediastinal blood loss was determined. Similarly, the relationship ( $\rho$ ) between preinduction turbidometric platelet aggregometry (% maximum aggregation) and postoperative mediastinal blood loss was determined.

## RESULTS

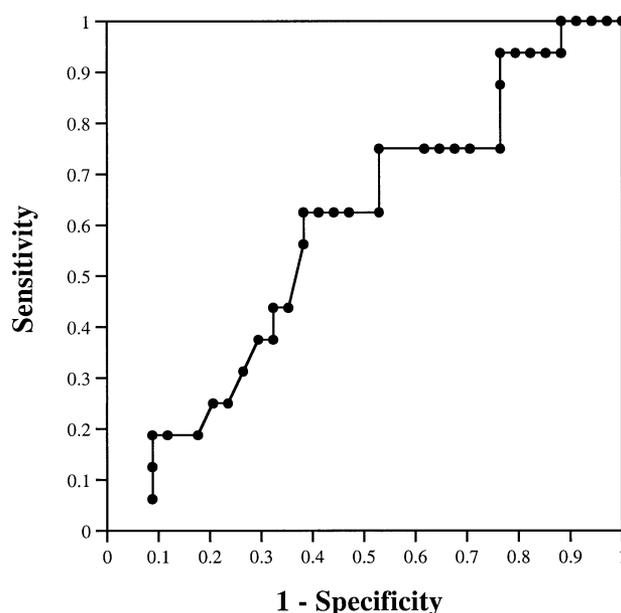
Sixteen patients had ingested aspirin within the previous 48 hours (group 1). The remaining 34 patients had not ingested aspirin for at least 72 hours (group 2). Demographic data for these groups are given in Table 1. The area under the ROC for Plateletworks™ identification of group 1 patients was 0.58 (95% confidence interval [CI] 0.42-0.75) (Fig 1). By comparison the area under the ROC for turbidometric platelet aggregometry identification of group 1 patients was 0.77 (95% CI 0.62-0.95, Fig 2). The difference between the Plateletworks™ area under the ROC and the turbidometric platelet aggregometry area under the ROC was 0.19 (95% CI 0.00-0.37).

Thirty-two patients had their procedure performed with CPB. Of these, 10 patients underwent valve replacement and 22 patients underwent coronary artery bypass grafting. The remaining 18 patients had coronary artery bypass grafting without CPB. In those patients requiring CPB, the mean duration of CPB was 85 minutes (range 45-160 minutes).

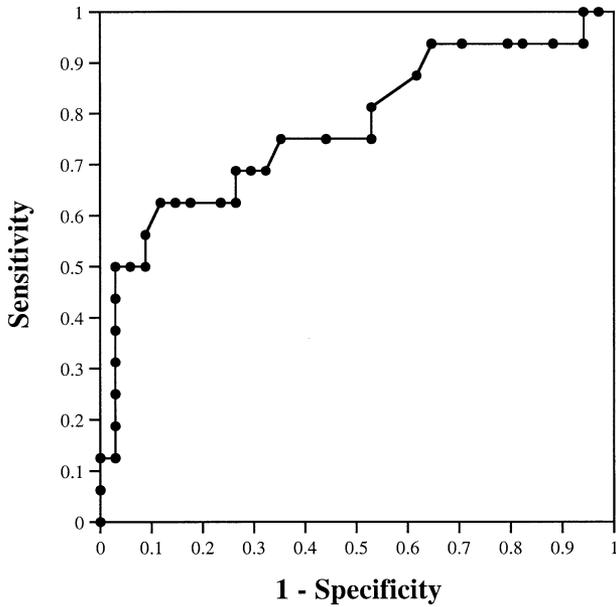
The Spearman correlation coefficient ( $\rho$ ) between preinduction Plateletworks™ and postoperative mediastinal blood loss was 0.07 ( $p = 0.58$ , Fig 3) and between preinduction turbidometric platelet aggregometry and postoperative mediastinal blood loss was  $-0.31$  ( $p = 0.03$ , Fig 4). On completion of surgery, the coefficients were 0.148 ( $p = 0.34$ ), and  $-0.291$  ( $p = 0.08$ ), respectively.

## DISCUSSION

The results indicate that Plateletworks™ is less able than turbidometric platelet aggregometry to identify patients who



**Fig 1. Receiver-operator curve for Plateletworks™ identification of recent aspirin ingestion (n = 50). Area under curve = 0.58.**



**Fig 2. Receiver-operator curve for turbidometric platelet aggregometry identification of recent aspirin ingestion (n = 50). Area under curve = 0.77.**

have recently ingested aspirin. Plateletworks™ is also less able than turbidometric platelet aggregometry to predict postoperative mediastinal blood loss. These findings suggest that Plateletworks™ is of limited use for the assessment of aspirin-related platelet dysfunction in cardiac surgical patients.

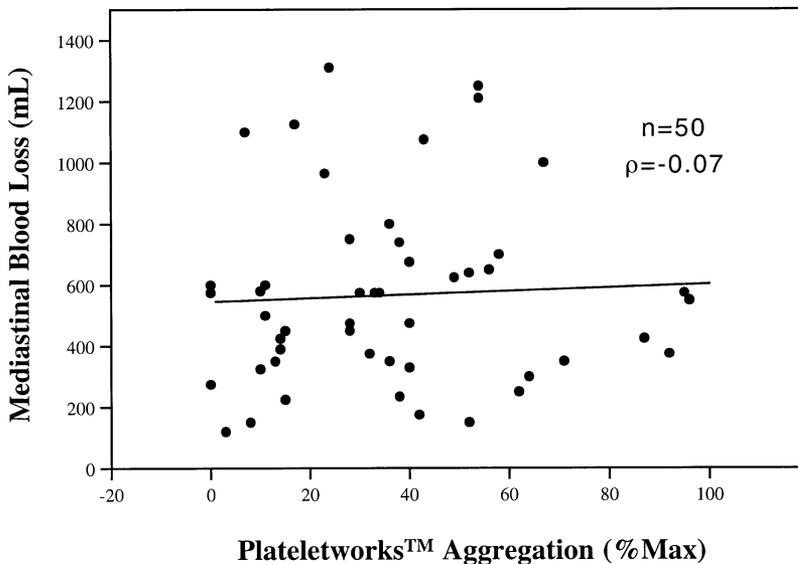
There are many reasons why the detection of aspirin-related platelet dysfunction would be useful in cardiac surgical patients. Aspirin is a commonly used antiplatelet agent, either alone, or in combination with more potent platelet function inhibitors. Aspirin is associated with a significant increase in blood loss in cardiac surgical patients.<sup>1-6</sup> Almost all studies of aspirin and bleeding in first-time elective cardiac surgical pa-

tients, which include several randomized controlled trials, have found that recent aspirin (within 2 days) increases blood loss.<sup>1-6</sup> However, aspirin does not always increase blood transfusion requirements because of the use of red cell scavenging techniques or lower transfusion triggers.<sup>6</sup> Aspirin may also not increase blood loss in redo cardiac surgery.<sup>14</sup> In any event, the American College of Cardiology and the American Heart Association joint guidelines on coronary artery bypass grafting recommend cessation of aspirin 1 week before surgery to reduce blood loss.<sup>15</sup>

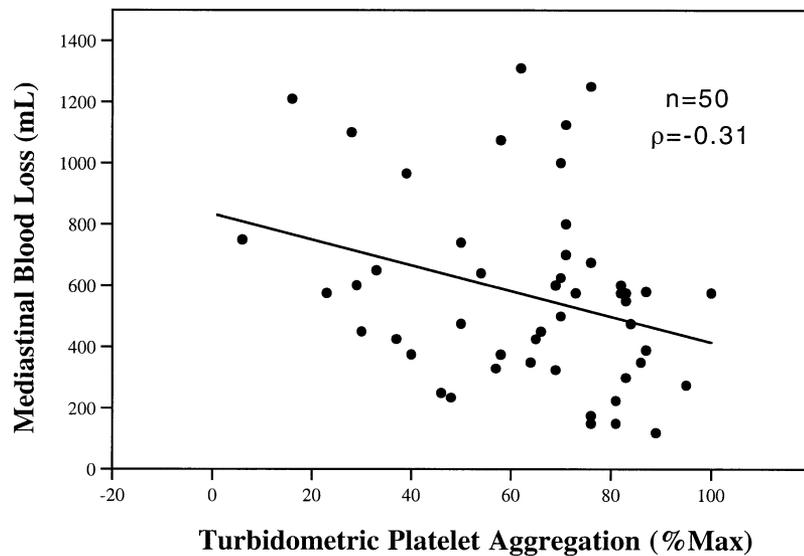
Not all patients respond to aspirin in a similar way. Patients have been classified as aspirin nonresponders, responders, or hyperresponders, although these may represent the same continuum.<sup>7,8</sup> Alternatively, some patients are considered to be aspirin resistant.<sup>16</sup> The variation in response may be because of pharmacokinetic factors as well as biological variation in the response to aspirin.<sup>16</sup> Therefore, identification of an aspirin-related platelet defect may be more specific for the prediction of blood loss than a history of aspirin ingestion alone.

Another variable in the effect of aspirin on platelets is the duration since the last ingestion of aspirin. The effect of aspirin on platelets is irreversible and lasts the life of the platelet (7-10 days). However, there is 10% to 15% turnover of platelets each day, and new platelets generated after cessation of aspirin have new cyclooxygenase.<sup>17</sup> Previous studies have found that aspirin-related platelet dysfunction is most common within 48 hours of ingestion of aspirin.<sup>18-20</sup> After 72 hours, there is a markedly reduced incidence, presumably because of the generation of new platelets. For this reason, in the current study, the definition of “recent” aspirin ingestion was <48 hours.

Other more potent antiplatelet drugs such as thienopyridine derivatives and glycoprotein IIb/IIIa inhibitors have a greater effect on platelet function than aspirin and may contribute to greater blood loss perioperatively. However, these drugs usually supplement aspirin. They are rarely used alone. Therefore, any assessment of the independent effect of these drugs on platelet function must be able to “subtract” the effect of concurrent aspirin. The effect of thienopyridine derivatives and



**Fig 3. The relationship between % platelet aggregation and postoperative blood loss for Plateletworks™. Spearman rank correlation ( $\rho$ ) = 0.07.**



**Fig 4. The relationship between % platelet aggregation and postoperative blood loss for turbidometric platelet aggregometry. Spearman rank correlation ( $\rho$ ) =  $-0.31$ .**

glycoprotein IIb/IIIa inhibitors on Plateletworks™ was outside the scope of this study. Nevertheless, data from the current study may be of use when planning such studies.

The assessment of platelet function is always challenging because of the multiple processes involved in platelet activation and the complex role of platelets in hemostasis.<sup>9,10</sup> There is a wide range of normal values because of wide interpatient variability that makes it difficult to define an abnormal value in any individual patient. The measurement of platelet aggregation in response to specific agonists using a turbidometric technique is currently the most common laboratory method for the assessment of platelet function.<sup>9,10</sup> This technique has its own limitations in relation to sensitivity and specificity and also has a wide range of “normal” values.<sup>9,10</sup> In the future, more sophisticated techniques such as platelet flow cytometry may be more widely available.<sup>21</sup> However, at present, turbidometric platelet aggregometry is the reference standard with which new techniques must be compared.<sup>9,10</sup>

The assessment of aspirin-related platelet dysfunction requires the use of an appropriate platelet agonist, irrespective of the technique used.<sup>22</sup> It is necessary to use a specific agonist such as arachidonic acid or a low concentration of a nonspecific agonist such as collagen. This is to ensure that activation of the platelet occurs via the arachidonic acid pathway and involves cyclooxygenase. More potent agonists such as thrombin, or higher concentrations of agonists such as collagen or adenosine diphosphate, activate platelets through a separate pathway that is independent of cyclooxygenase.<sup>22</sup> In the current study, a low concentration of collagen (10  $\mu\text{g}/\text{mL}$ ) was used as the agonist for both techniques.

Both Plateletworks™ and turbidometric platelet aggregometry provide quantitative data (ie, 0%-100% platelet aggregation). Therefore, the precise cutoff between “normal” and “abnormal” is arbitrary. The determination of sensitivity and specificity require qualitative data (ie, normal *v* abnormal).<sup>23</sup> For this reason, ROC were constructed. These curves plot sensitivity versus 1-specificity (true-positive rate *v* false-positive rate) for a range of test values.<sup>23</sup> The area under the ROC

is a measure of the diagnostic ability of a test.<sup>23</sup> A perfect test would have an area under the ROC of 1.0 (100% true positive and 0% false positive, irrespective of the test value). In contrast, a test with no predictive ability would have an area under the ROC of 0.5 (equal true-positive and false-positive rate for all test values). Unfortunately, very few diagnostic tests approach 100% sensitivity and specificity. In the current study, turbidometric platelet aggregometry had an area under the ROC of 0.77 (95% CI 0.61-0.95, Fig 1), which is consistent with a good predictive test.<sup>23</sup> In contrast, Plateletworks™ had an area under the ROC of 0.58 (95% CI 0.45-0.65, Fig 2), which is close to 0.5 (no diagnostic or predictive ability).

Platelet function is one of many factors that affect postoperative mediastinal blood loss in cardiac surgical patients.<sup>24</sup> Others include patient age and weight, the type and duration of surgery, management of anticoagulation, and management of CPB, if used. The accuracy of measurement of mediastinal blood loss is also a factor. Given these multiple variables, a high correlation between platelet function and postoperative mediastinal blood loss is unlikely. At most, a small correlation would be expected. A small correlation was observed between preinduction turbidometric platelet aggregometry and postoperative mediastinal blood loss of ( $\rho = -0.31$ ,  $p = 0.03$ , Figure 4). In contrast, there was no correlation between Plateletworks™ and postoperative mediastinal blood loss ( $\rho = 0.07$ ,  $p = 0.58$ , Fig 3). A Spearman rank correlation coefficient ( $\rho$ ) for nonparametric data was used rather than a Pearson correlation coefficient ( $r$ ) to compensate for any possible skew in the postoperative mediastinal blood loss data.

On completion of surgery, platelet function might be affected by many variables other than aspirin, such as the use and duration of CPB and the doses of heparin and protamine. Nevertheless, the correlations between platelet function as assessed by the 2 techniques and postoperative mediastinal blood loss were similar to the preinduction values (0.14 for Plateletworks™,  $-0.29$  for turbidometric platelet aggregometry).

The current study was designed to compare the ability of 2 different tests of platelet function to detect aspirin-related plate-

let dysfunction and to predict postoperative mediastinal blood loss. It was not designed to assess the effect of recent aspirin on postoperative blood loss per se. The groups were too small to provide adequate power for statistical comparison, were not randomized, and were heterogeneous in regard to type of surgery. For this reason, no such comparisons were attempted. Intraoperative blood loss was not analyzed, because it is influenced to a greater extent by large-vessel bleeding. In contrast, postoperative blood loss is more a function of capillary bleeding, which is influenced to a greater extent by platelet function. For the same reason, blood transfusion data were not analyzed.

Several previous studies have found a high correlation between Plateletworks™ and turbidometric platelet aggregation, both in healthy volunteers and patients receiving antiplatelet drugs.<sup>25,26</sup> However, correlation is not the most appropriate method of comparing 2 measurement techniques. A high correlation can exist despite a large discrepancy, so long as the size of the discrepancy is relatively constant.<sup>27</sup> A more appropriate method for comparing measurement of graded responses is the calculation of precision and bias using a Bland-Altman ap-

proach.<sup>27</sup> For qualitative responses such as normal or abnormal, the most appropriate approach is to assess sensitivity and specificity and to construct an ROC if necessary.<sup>23</sup> Alternatively, the test variable can be related to an outcome measure. There have been no previous studies examining the sensitivity or specificity of Plateletworks™ for the detection of aspirin-related defects and none relating Plateletworks™ values to an outcome measure such as postoperative blood loss.

The results of this study apply only to the use of Plateletworks™ for the detection of aspirin-related platelet dysfunction in cardiac surgical patients. Cardiac surgical patients may differ from other patient groups in relation to their underlying disease process and the type of surgery involved. Further studies are required to assess the accuracy and utility of Plateletworks™ in other patient groups. Similarly, further studies are required to assess the use of Plateletworks™ for the detection of other platelet defects in patients receiving more potent antiplatelet drugs. Nevertheless, at present, Plateletworks™ cannot be recommended for the detection of aspirin-related platelet defects in cardiac surgical patients.

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