Platelet aggregation testing on a routine coagulation analyzer: a method comparison study

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Abstract
Platelet function (PF) plays a pivotal role in both hemostasis and thrombosis, and manual light transmission aggregometry (LTA) is considered the standard of care for platelet function testing but is an error-prone and time-consuming procedure. We aimed to test the agreement regarding maximum aggregation (MA), velocity (VEL), and lag-phase (LagP) of platelet aggregation of the automated Sysmex CS-2100 analyzer (Siemens, Germany) against the APACT 4004 (Elitech, France) in samples derived from healthy participants and patients with hemostaseologic disorders. In total, 123 patient-derived samples were investigated, including 42 patients with acetylsalicylic acid and/or clopidogrel intake and 20 patients with other hemostaseologic disorders. Both MA and VEL showed good or excellent intermethod correlation. Agreement between the testing methods was only partially achieved, and values were indicative for a systematic bias to lower measurements below a threshold of 50% MA with the CS-2100i compared to the APACT 4004. All patients with impaired PF in the APACT 4004 were successfully identified with the CS-2100i, and reference values for automated LTA are provided. Conclusively, automated LTA with the CS-2100i is a highly standardized and reliable PF testing method and represents a decisive step in the simplification of platelet function testing in clinical routine.

Keywords
light transmission aggregometry, thrombocyte function, platelet rich plasma, platelet aggregation, thrombocyte dysfunction

Introduction
Platelets play a pivotal role in both hemostasis and thrombosis. Accordingly, the accurate measurement of platelet function is crucial to identify patients with suspected inherited or acquired dysfunction; moreover, evaluation of platelet function has become increasingly important for the monitoring of modern oral antiplatelet therapy.1

The historical “gold standard” of platelet function testing is optical aggregometry (light transmission aggregometry [LTA]), which is based on the detection of light transmission changes due to platelet aggregation with a photometer after addition of a platelet agonist to platelet-enriched plasma (PRP). However, the LTA is a time-consuming and labor-intensive procedure, and many work steps have to be carried out manually, which increases the susceptibility to errors.2-6 Additionally, although some efforts have been made toward standardization, the analytical processes still vary among laboratories, and data interpretation requires familiarity and expertise limiting the diagnostic implementation to highly specialized centers.5,8

In recent years, several attempts have been made toward the automation of routine LTA in order to partly overcome the limitations of manual LTA assessment, all of which were carried out on different generations of the fully automated Sysmex CS coagulation analyzer.9-12 However, these studies were performed with limited sample numbers,9 focused on technical

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aspects or excluded samples derived from patients with inherited or acquired platelet dysfunction, limiting the informative value for the daily application of automated LTA in hemostaseologic routine.

We therefore aimed to test the agreement between the automated Sysmex CS-2100i coagulation analyzer (Siemens, Munich, Germany) against the standard-of-care routine light transmission aggregometer APACT 4004 (Labitec, Ahrensburg, Germany) for platelet function testing in a large number of samples involving healthy participants as well as samples from patients with inherited or acquired hemostaseologic disorders in daily routine practice.

Materials and Methods

Patient Selection and Material Preparation

Blood samples were collected as part of a routine visit at the Hemophilia Treatment Center of the University Clinic Frankfurt am Main. Patients were eligible to participate in the study if the following key inclusion criteria were fulfilled: Age >18 years and a known inherited or acquired hemostaseologic disorder including patients with ASS and/or clopidogrel intake (cohort B = patients with ASS and/or clopidogrel intake; cohort C = patients with acquired or inherited hemostaseologic disorders other than ASS/clopidogrel-related). A separate reference cohort comprised of healthy participants (cohort A) with no (inherited or acquired) hemostaseologic disorder and no medication intake (e.g., NSAR) for at least 10 days. Platelet counts above 100 $\times 10^9$/L were necessitated for subsequent platelet function testing, and patients with platelet counts below 100 $\times 10^9$/L were excluded from participation. A single blood sampling of 20 to 30 mL was collected in 10 mL sodium citrate buffer solution (S-Monovette; Sarstedt, Nümbrecht, Germany) yielding a final buffer–blood ratio of 1:9 according to the manufacturer’s instructions and processed within 180 minutes in accordance with the local standard operation procedures that follow the LTA guidelines provided by the International Society of Thrombosis and Hemostasis and Clinical and Laboratory Standards Institute (CLSI). Nonadjusted equally aliquoted PRP was run simultaneously on 2 different analyzer platforms (see below) for a reading period of 600 seconds according to the CLSI guidelines using different platelet agonists purchased from Hyphen Biomed, Neuville, France: adenosine diphosphate (ADP; final concentration in test cuvette: 5 $\mu$mol/L), arachidonic acid (AA, 1 mmol/L), ristocetin (RIS, 1 mg/mL), collagen (COL, 2 $\mu$g/mL), epinephrine (EPI, 5 $\mu$mol/L). It was ensured that the sample waiting time (particularly on the CS-2100i) was less than 180 minutes to avoid falsifying effects due to platelet sedimentation. Approval from the responsible institutional review board was obtained before data collection (approval number: EK 376/14). All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all individual participants included in this study.

Analyzers

Platelet aggregation was determined on 2 LTA-based analyzers:

APACT 4004: The APACT 4004 (Elitech, Puteaux, France) is a 4-channel light transmission platelet aggregometer that was used as a reference instrument to evaluate platelet function. The APACT 4004 detects platelet aggregation in PRP by changes in light transmission (wavelength: 740 nm, 37°C). It has a graphical user interface with a
touch screen. Parameters are presented automatically. The reaction curves are shown in real time with printing possibilities (screenshot and conventional printer). Results can be exported as an Excel file, a Word document, or as a pdf document. The APACT 4004 offers 4 channels for simultaneous determination of different methods with independently regulated stirrer speeds. The maximum measurement time is up to 60 minutes. Blanking of the optical channel was performed with platelet-poor plasma.

Sysmex CS-2100i System: The Sysmex CS-2100i System is a fully automated high-performance coagulation analyzer provided by Siemens, Munich, Germany. According to the manufacturer, 48 samples can be processed for platelet function analysis within 1 hour for a respective measuring time of 5 minutes per sample; 24 samples can be processed for platelet function analysis within 1 hour for a respective measuring time of 10 minutes per sample. According to the manufacturer, the platelet sedimentation does not affect the sample stability and result validity up to 3 hours of waiting time in the analyzer. The automatic pipettor is coated to avoid platelet activation due to surface contact, and spontaneous clotting is not observed without the addition of agonists, according to the manufacturer. Blanking of the optical channel was automatically performed using platelet-poor plasma.

Parameters determined were Lag-phase (LagP), velocity (VEL), and maximum platelet aggregation (MA). As the Sysmex CS-2100i software does not provide an algorithm for de-aggregation measurements, this parameter was not assessed.

Statistical Analysis and Study Aim

All variables collected were depicted using descriptive statistics. Differences between testing methods were evaluated using the paired t test. Correlation between methods was assessed using the Pearson R coefficient, and agreement was analyzed using the Passing-Bablok regression test and the Bland Altman analysis.
The primary study aim was to compare the performance of the automated Sysmex CS-2100 system to the APACT 4004 reference instrument with regard to acceptance criteria for validation (agreement) predefined as a Pearson correlation coefficient of \( r \geq .85 \), a slope concordance of 0 ± 0.15, and an intercept concordance of 0 ± 10 in the Passing-Bablok analysis for each combination of thrombocyte agonist and the above-stated parameters. Data output was transferred to Microsoft Excel spreadsheets (Microsoft, Redmond, Washington). All variables collected were processed using Prism, Version 6 (GraphPad Software, San Diego, USA) and Analyse-it Method Validation Edition, Version 5.2 (Analyse-it Software, Leeds, UK).

### Results

#### Study Population and Correlation of Methods

In total, between January 2016 and November 2016, 123 patient samples were investigated: 22 patients taking ASS, 20 patients taking clopidogrel (17 patients plus ASS; cohort B, \( n = 42 \)), another 20 patients with inherited or acquired hemostaseologic disorders other than ASS or clopidogrel-related (cohort C, \( n = 20 \)), and 61 healthy controls (cohort A, \( n = 61 \)). Patients with hemostaseologic disorders comprised of inherited (non-2B) von Willebrand disease (VWD; \( n = 8 \)), acquired VWD (\( n = 1 \)), immune thrombocytopenia (\( n = 3 \)), Glanzmann thrombasthenia (\( n = 1 \)), thrombocyte dysfunction of unknown origin (\( n = 2 \)), dysfibrinogenemia (\( n = 1 \)), liver cirrhosis-related thrombocytopenia (\( n = 1 \)), severe hemophilia A (\( n = 1 \)), antithrombin deficiency (\( n = 1 \)), and protein C deficiency (\( n = 1 \)). Concentration of thrombocytes in the nonadjusted PRP probes (range, 110-1277 \( \times 10^9/L \)) was well balanced between the testing methods (\( P = .48 \)), and 90.4% (111/123) of all PRP samples showed platelet concentrations between 150 and 600 \( \times 10^9/L \). Figure 1 illustrates the MA, VEL, and LagP for the overall study cohort; the corresponding comparative descriptive statistics are summarized in Tables 1-3.
Correlation of MA met the predefined acceptance criteria for agreement ($r \geq .85$) across all subgroups of tested agonists (Table 1). An excellent correlation of VEL between methods was also seen for the agonists COL ($r = 0.94$), RIS ($r = 0.87$), and AA ($r = 0.94$), whereas comparison of ADP ($r = .80$) and EPI ($r = .77$) induced VEL failed to meet the predefined acceptance criteria (Table 2) but still yielded statistical significant correlation. There was weak or no correlation between the testing methods in regard to the LagP, irrespective of the used agonist in the overall study population ($r = .20$; Table 3).

Platelet maximum aggregation was consistent between the analyzers in most subgroups; still, we encountered a significantly reduced AA-induced MA in samples derived from patients taking ASS and/or clopidogrel analyzed with the CS-2100i compared to the APACT 4004. Velocity of aggregation was systematically lower across all agonists measured with the CS-2100i; however, this finding was less pronounced in samples derived from patients with hemostaseologic disorders. Visual comparison of aggregation curves overall showed consistent kinetics; a representative example for a 300-second measurement period in material derived from a patient with VWD type I is shown in Figure 2.

### Agreement of Testing Methods

Figure 3 illustrates the agreement between the testing methods according to the Bland Altmann analysis. With regard to MA, there was good agreement between the CS-2100i and APACT 4004 for ADP (95% limits for agreement, $15.9$ to $15.9$) and COL (95% limits for agreement, $15.1$ to $12.0$) with evidence for systematic lower values in patients with an MA below 50% with the CS-2100i. The dispersion of values for MA across the agonists RIS (95% limits for agreement, $-20.3$ to $16.8$), AA (95% limits for agreement, $-23.9$ to $14.4$), and EPI (95% limits for agreement, $-29.8$ to $20.8$) was higher, especially for lower MA values indicative of a systematic bias to lower measurements below a threshold of 50% MA with the CS-2100i compared to the APACT 4004. Figure 4 displays the Passing

| Healthy controls   | N   | Median Max % (5-95 percentile) | Median Max % (5-95 percentile) | P Value | Pearson R |
|--------------------|-----|--------------------------------|--------------------------------|---------|-----------|
| ADP                | 62  | 18.2 (13.8-28.3)               | 17.7 (11.6-21.1)               | .19     | .30b      |
| Collagen           | 61  | 62.9 (48.6-83.6)               | 46.0 (35.4-63.5)               | <.0001  | .56b      |
| Ristocetin         | 62  | 24.5 (15.1-46.9)               | 14.7 (10.2-30.0)               | <.0001  | .45b      |
| Arachidonic acid   | 61  | 58.1 (41.2-93.3)               | 24.4 (19.0-99.0)               | <.0001  | -.05      |
| Epinephrine        | 62  | 49.3 (31.7-130.7)              | 22.8 (10.8-151.0)              | .0018   | .49b      |

| ASS                | N   | Median Max % (5-95 percentile) | Median Max % (5-95 percentile) | P Value | Pearson R |
|--------------------|-----|--------------------------------|--------------------------------|---------|-----------|
| ADP                | 22  | 18.7 (11.9-39.6)               | 17.6 (13.2-42.6)               | .87     | -.06      |
| Collagen           | 22  | 71.0 (8.7-163.9)               | 52.4 (15.0-70.8)               | .0041   | -.43      |
| Ristocetin         | 22  | 23.1 (11.8-87.0)               | 12.5 (10.8-27.0)               | .0002   | .03       |
| Arachidonic acid   | n/a | n/a (n/a)                      | 10.5 (7.8-151.6)               | n/a     | n/a       |
| Epinephrine        | 22  | 49.5 (34.1-228.3)              | 12.1 (10.1-35.4)               | .0002   | .13       |

| Clopidogrel (+ ASS) | N   | Median Max % (5-95 percentile) | Median Max % (5-95 percentile) | P Value | Pearson R |
|---------------------|-----|--------------------------------|--------------------------------|---------|-----------|
| ADP                 | 20  | 21.9 (15.3-35.7)               | 17.4 (12.7-20.7)               | <.0001  | .32       |
| Collagen            | 20  | 86.7 (0.0-112.8)               | 61.5 (40.9-78.4)               | .30     | -.29      |
| Ristocetin          | 20  | 21.6 (17.0-45.4)               | 18.1 (9.2-26.9)                | .0017   | -.042     |
| Arachidonic acid    | 3   | 71.4 (66.8-105.1)              | 15.9 (9.4-131.6)               | .044    | .99b      |
| Epinephrine         | 20  | 49.5 (34.1-228.3)              | 12.1 (10.1-35.4)               | .0006   | .06       |

| HD                  | N   | Median Max % (5-95 percentile) | Median Max % (5-95 percentile) | P Value | Pearson R |
|---------------------|-----|--------------------------------|--------------------------------|---------|-----------|
| ADP                 | 17/20| 20.4 (10.5-55.9)               | 18.2 (0.8-22.4)                | .026    | .80b      |
| Collagen            | 20  | 74.2 (2.5-218.6)               | 57.1 (10.7-81.9)               | .027    | -.45b     |
| Ristocetin          | 13/20| 45.3 (22.8-199.2)              | 12.3 (10.3-28.1)               | .008    | -.28      |
| Arachidonic acid    | 13/19| 73.3 (48.6-142.2)              | 32.6 (12.0-77.6)               | .0017   | -.15      |
| Epinephrine         | 12/20| 90.1 (20.7-271.0)              | 11.9 (9.6-33.6)                | .051    | -.22      |

| Total cohort        | N   | Median Max % (5-95 percentile) | Median Max % (5-95 percentile) | P Value | Pearson R |
|---------------------|-----|--------------------------------|--------------------------------|---------|-----------|
| ADP                 | 123 | 19.1 (13.8-34.0)               | 17.8 (12.2-21.6)               | .0004   | .20b      |
| Collagen            | 122 | 66.7 (7.2-108.6)               | 51.7 (35.4-70.5)               | <.0001  | -.15b     |
| Ristocetin          | 116 | 24.6 (15.1-59.2)               | 12.6 (10.2-28.3)               | .001    | .13       |
| Arachidonic acid    | 77  | 60.4 (42.1-96.0)               | 27.9 (9.8-99.4)                | <.0001  | .08       |
| Epinephrine         | 115 | 50.4 (32.4-202.9)              | 19.6 (10.2-129.9)              | <.0001  | .14       |

Abbreviations: ADP, adenosine diphosphate; LagP, lag-phase; HD, hemostaseologic disorder.

*a* Adenosine diphosphate (final concentration in test cuvette: 5 μmol/L), arachidonic acid (1 mmol/L), ristocetin (1 mg/mL), collagen (2 μg/mL), and epinephrine (5 μmol/L).

**b** Significant correlation.
Bablok indicators and its 95% confidence intervals in relation to the predefined acceptance criteria for agreement. Overall (with the exception of RIS-induced VEL), the agreement between methods missed the predefined level of acceptance.

We therefore questioned the clinical significance of missing statistical agreement between the testing methods focusing on MA: The median of absolute differences and the corresponding 95th percentiles (in parenthesis) for the agonists ADP, COL, RIS, AA, and EPI were 4.7 (16.4), 3.2 (15.6), 5.9 (16.5), 4.8 (19.6), and 6.4 (28.2), respectively, between the CS-2100i and the APACT 4004. Furthermore, we focused on those patients with inherited or acquired hemostaseologic disorders (ASS and/or clopidogrel intake, n = 42; VWD, n = 9; genetically confirmed Glanzmann thrombasthenia, n = 1; thrombocyte dysfunction of unknown origin, n = 2) who were all successfully identified with the CS-2100i system (Figure 5) in reference to the values measured with the APACT 4004.

**Agreement in Dependence of PRP Concentration**

We next sought to determine the agreement of the CS-2100i system in dependence of the platelet concentration in PRP using linear regression. We found a significant influence of the platelet concentration in PRP on the agreement of the CS-2100i system in COL-induced MA ($P < .001$) with lower agreement between the analyzers in lower PRP concentrations; however, the overall deterministic impact was low (Pearson $R^2 = .098$). There was no statistically significant dependence for the other agonists (ADP [$P = .29$], RIS [$P = .62$], AA [$P = .14$], and EPI [$P = .54$]). In addition, we examined the impact of PRP thrombocyte concentration on the MA values in both testing methods: There were significant relationships across the agonists ADP, COL, and EPI for both coagulation analyzers; in particular, there were lower MA values in those samples with lower PRP concentrations. However, the overall impact was low for all agonist subgroups but highest for ADP tested with the CS-2100i (Pearson $R^2 = .18$).
Discussion

The current study aimed to test the agreement between the standard-of-care LT aggregometer APACT 4004 against the fully automated coagulation analyzer Sysmex CS-2100i System and was carried out under real-world conditions at a single comprehensive care hemophilia treatment center.

We saw an excellent overall correlation for MA and a good correlation for VEL between the methods. In terms of inter-method agreement, the overall concordance between the testing methods for MA and VEL was good yet insignificant according to the predefined acceptance criteria. Less agreement was observed for LagP between the CS-2100i and the APACT 4004, underscoring the necessity of defining separate reference values for automated coagulation analyzers. Platt et al provided first reference values for healthy volunteers in dependence of the final agonist concentration in the test cuvette.11

We confirm and refine the published reference values for agonist concentrations analogous to the CLSI guidelines5 by narrowing the published reference range. In addition, we provide first reference values for thrombocyte function impairment due

![Figure 3. Bland-Altmann analysis between the CS-2100i and APACT of the whole study cohort (n = 123): curves in dependence of the different platelet agonists for maximum aggregation, velocity, and LagP. LagP indicates lag-phase.](image)
to ASS and/or clopidogrel intake on a CS-2100i that may be used for local laboratory verification. It is important to mention that our study did not aim to identify or establish a platelet reactivity threshold for patients considered to be nonresponders (high post-treatment platelet reactivity) to ASS/clopidogrel treatment (cohort B) and such values are currently not provided by the manufacturer either.

In general, some attempts\textsuperscript{13,14} were made to establish cutoff values for LTA-assessed platelet function in clopidogrel-treated patients; however, to the best of our knowledge, a broadly adapted consensus for the identification of nonresponders to antiplatelet therapy has not been established yet. Additionally, there are conflicting results regarding the clinical benefit of tailored antiplatelet treatment based on platelet function monitoring, and most randomized prospective trials have failed to show improvement in patient outcomes.\textsuperscript{15-17} More clinical trials involving automated LTA, such as the CS-2100i, are mandatory to define specific cutoff values for antiplatelet nonresponsiveness. The minor role of post-treatment platelet monitoring in clinical routine explains our long recruitment period of 11 months; in particular, the filling of cohort b with a reasonable number of patients, referred for post-treatment monitoring, was time consuming.

Absolute differences for MA between the testing methods were low for most patient-derived samples, and more importantly, all patients with inherited and acquired thrombocyte dysfunction as referenced by the APACT 4004 were successfully identified with the CS-2100i. Conclusively, although our study did not meet its primary aim, and the predefined criteria for agreement between the testing methods were only partially achieved, we consider the statistical disagreement for MA and VEL as clinically insignificant for routine and high-throughput purposes.

Platelet function testing is a multistep, error-prone procedure that requires a high standardization of preanalytical and analytical procedures and still varies in detail between the stated international guidelines and among laboratories. We therefore fully acknowledge that the results presented here may only be valid for comparable settings in terms of preanalytical sample preparation as well as type and final concentrations of the used agonists. According to the CLSI guidelines, PRP adjustment is recommended for platelet function testing and was not performed in our study to avoid delayed sample preparation and sample instability. Indeed, platelet concentration in PRP had statistically significant influence on the accuracy of the CS-2100i System as well as MA values of both testing

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**Figure 4.** Agreement blot for the Passing Bablok method for maximum aggregation, velocity, and LagP; dotted lines indicate predefined significance intervals for agreement. LagP indicates lag-phase.

**Figure 5.** Maximum aggregation values for single sample pairs in patients with inherited or acquired platelet function disorders. *The patient with genetically confirmed Glanzmann thrombasthenia; #§ patient each with platelet dysfunction of unknown origin.
methods. However, the overall influence was only small, and previous studies carried out with automated coagulation analyzers suggest no significant effect on MA.\textsuperscript{10} Additionally, we did not test different agonist concentrations to examine their influence on MA, VEL, and LagP measurements. It has been shown previously that in particular increasing concentrations of ADP significantly influence MA levels in CS-2X00 systems\textsuperscript{11}; therefore, transferring our results of method agreement to different agonist concentrations or different agonists (e.g., PGE1) should be done with caution. Additionally, conclusions cannot be drawn to patients with rare platelet function disorders, particularly storage pool defects as there were no such participants in our study. Finally, we did not test for repeatability of the CS-2100\textsuperscript{i} System; however, others did and found a high intra-method reliability for the CS-2100\textsuperscript{i}.\textsuperscript{10}

In conclusion, performing automated LTA with the CS-2100\textsuperscript{i} is a highly standardized procedure that proved to be capable of identifying patients with normal and acquired platelet impairment as suggested by the standard-of-care LTA analysis (APACT 4004). Additionally, all 3 patients with inherited platelet dysfunction were successfully identified. Although the primary aim of statistical agreement between the standard-of-care LTA and the automated coagulation analyzer was not met, we consider the overall accuracy of the CS-2100\textsuperscript{i} as sufficient for routine platelet function testing. It is important to define distinct reference ranges for automated LTA assessment that may differ among testing methods. The development of automated platelet function instrumentation represents a decisive step in the simplification of platelet function testing in clinical routine, not only for laboratorians who struggle with current cumbersome methodology but also for clinicians who need faster result reporting times.

More studies are needed to evaluate the performance of automated LTA analyzers in a wider range of utility, for example, with alternative platelet agonists or in patients with rare inherited platelet disorders.

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Declaration of Conflicting Interests
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References
1. Le Quellec S, Bordet JC, Negrier C, Dargaud Y. Comparison of current platelet functional tests for the assessment of aspirin and clopidogrel response. A review of the literature. \textit{Thromb Haemost}. 2016;116(4):638-650. doi: 10.1160/TH15-11-0870.
2. Cattaneo M, Cerletti C, Harrison P, et al. Recommendations for the standardization of light transmission aggregometry: a consensus of the working party from the platelet physiology subcommittee of SSC/ISTH. \textit{J Thromb Haemost}. 2013. doi: 10.1111/jth.12231.
3. Harrison P, Mackie I, Mumford A, et al. Guidelines for the laboratory investigation of heritable disorders of platelet function. \textit{Br J Haematol}. 2011;155(1):30-44. doi: 10.1111/j.1365-2141.2011.08793.x.
4. Hayward CPM, Moffat KA, Raby A, et al. Development of north American consensus guidelines for medical laboratories that perform and interpret platelet function testing using light transmission aggregometry. \textit{Am J Clin Pathol}. 2010;134(6):955-963. doi: 10.1309/AJCP9V3RRVNZMKDS.
5. Christie DJ. \textit{Platelet Function Testing by Aggregometry: Approved Guideline}. Clinical and laboratory standards institute. Wayne, PA: CLSI; 2008.
6. Hayward CPM, Eikelboom J. Platelet function testing: quality assurance. \textit{Semin Thromb Hemost}. 2007;33(3):273-282. doi: 10.1055/s-2007-971814.
7. Hayward CPM, Pai M, Liu Y, et al. Diagnostic utility of light transmission platelet aggregometry: Results from a prospective study of individuals referred for bleeding disorder assessments. \textit{J Thromb Haemost}. 2009;7(4):676-684. doi: 10.1111/j.1538-7836.2009.03273.x.
8. Hvas AM, Favaloro EJ. Platelet function analyzed by light transmission aggregometry. \textit{Meth Mol Biol}. 2017;1646:321-331. doi: 10.1007/978-1-4939-7196-1_25.
9. Lawrie AS, Kobayashi K, Lane PJ, Mackie IJ, Machin SJ. The automation of routine light transmission platelet aggregation. \textit{Int J Lab Hematol}. 2014;36(4):431-438. doi: 10.1111/jilh.12161.
10. Ling LQ, Liao J, Niu Q, et al. Evaluation of an automated light transmission aggregometry. \textit{Platelets}. 2017;28(7):712-719. doi: 10.1080/09537104.2016.1265923.
11. Platton S, McCormick Á, Bukht M, Gurney D, Holding I, Moore GW. A multicenter study to evaluate automated platelet aggregometry on Sysmex CS-series coagulation analyzers-preliminary findings. \textit{Res Pract Thromb Haemost}. 2018;2(4):778-789. doi: 10.1002/rth2.12140.
12. Frère C, Kobayashi K, Dunois C, Amiral J, Morange PE, Alessi MC. Assessment of platelet function on the routine coagulation analyzer Sysmex CS-2000i. \textit{Platelets}. 2018;29(1):95-97. doi: 10.1080/09537104.2017.1353683.
13. Gurbel PA, Bliden KP, Guyer K, et al. Platelet reactivity in patients and recurrent events post-stenting: results of the prepare post-stenting study. \textit{J Ame Colle Cardiol}. 2005;46(10):1820-1826. doi: 10.1016/j.jacc.2005.07.041.
14. Gurbel PA, Bliden KP, Samara W, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST study. \textit{J Ame Coll Cardiol}. 2005;46(10):1827-1832. doi: 10.1016/j.jacc.2005.07.056.
15. Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (testing platelet reactivity in patients undergoing elective stent placement on clopidogrel to guide alternative therapy with prasugrel) study. J Ame Colle Cardiol. 2012;59(24):2159-2164. doi: 10.1016/j.jacc.2012.02.026.

16. Collet JP, Cuisset T, Rangé G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med. 2012;367(22):2100-2119. doi: 10.1056/NEJMoa1209979.

17. Cayla G, Cuisset T, Silvain J, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): An open-label, blinded-endpoint, randomised controlled superiority trial. Lancet. 2016;388(10055):2015-2022. doi: 10.1016/S0140-6736(16)31323-X.