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Perioperative assessment of platelet function by Thromboelastograph® Platelet Mapping™ in cardiovascular patients undergoing non-cardiac surgery

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Abstract Five percent of patients on dual antiplatelet therapy after coronary artery stent implantation will need non-cardiac surgery within the first year of therapy, and many more will need surgery later on. A function assay that evaluates platelet reactivity and inhibition by drug therapy is beneficial for such patients. Platelet Mapping assay (PM™) using the TEG® analyzer was tested in surgical patients. After IRB approval, 60 patients on combined aspirin and clopidogrel therapy were consented and enrolled. The TEG® maximal amplitude (MA) and the percentage (%) platelet inhibition were recorded and analyzed. Fifty-seven patients (mean age 65.7 ± 10.9 years) had preoperative data only. Distribution of preoperative ADP (43.6 ± 24.4 %) and AA inhibition (52.8 ± 30.2 %) was determined, as well as for the preoperative MA ADP (43.1 ± 15.9 mm) and MA AA (37.2 ± 19.6 mm), showing an offset of the effect of both medications starting from day 3. Patients with complete pre- and postoperative data were stratified depending on duration off antiplatelet therapy (≤3 days, 3–7 days and >7 days): $n = 27$, ADP % preop inhibition (43.2 ± 21.6 %), ADP % postop inhibition (32.3 ± 18.3 %), $p = 0.048$. Distribution of immediate pre- and post- ADP and AA % inhibitions, showing a possible reduction in Δ of inhibition for clopidogrel at 3 days, were also assessed. Conclusion: According to the findings, the TEG® PM™ assay might be a feasible approach to objectively evaluate the effects of aspirin and clopidogrel during the perioperative period and potentially guide drug management.

Keywords Aspirin · Clopidogrel · Platelet inhibition · Platelet function tests · Aggregation · Thrombelastography

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Introduction

Coronary artery disease is the largest cause of mortality in the USA, accounting for 32.8 % of deaths in the country [1]. Percutaneous coronary intervention (PCI) and coronary artery stenting are mainstays of treating this serious condition, and dual antiplatelet therapy (DAPT) consisting of aspirin (ASA) and clopidogrel in coronary artery disease (CAD) patients needs to be continued for at least 12 months in patients with drug eluting stents presenting for non-cardiac surgery (NCS) [2]. About 5 % of these patients will present during the first year of implantation, but many more may need surgery after that. Most procedures will be of a non-cardiac nature and, besides original evidence that 12 months is safer, a conflicting concern is that, even after 12 months, the risk may not be as low as expected. With single antiplatelet therapy increasing the risk of surgical hemorrhage to 20 % and DAPT increasing it to 50 %, the assessment of platelet function in these patients for guiding appropriate DAPT management pre-, peri- and postoperatively has become essential [3].

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Current American Heart Association and College of Cardiology guidelines recommend that DAPT be continued for 12 months, ASA be continued during NCS surgery, and clopidogrel be stopped 5–7 days before NCS (if requested by surgeon, ASA may also be stopped 7–10 days before NCS) [4, 5]. However, it has been demonstrated that not all patients respond similarly to antiplatelet therapy [6]. The risk of excessive intraoperative bleeding must therefore be carefully balanced against the increased risk that discontinuing antiplatelet therapy before NCS has on myocardial infarction and stroke [7]. Simple and rapid methodologies to evaluate platelet function in treated patients might be useful for clinical practice. The TEG® (Haemonetics, Brain Tree, MA, USA) is an example of one such platelet function analyzer; now that it has the added technology of Platelet Mapping assay (TEG® PM™), it is of even more value in measuring the hemostatic function of patients.

The aims of this pilot observational study were to: (1) assess patients' preoperative platelet function based on days off of antiplatelet therapy, and (2) evaluate changes in platelet function after NCS. Our original hypothesis set forth that (a) preoperative platelet inhibition would be lower than expected (<90 % population) at the time of preoperative assessment and (b) the postoperative inhibition for patients with preoperative values between 50 and 75 % would change to a lower value postoperatively. The hypothesis was based on the effect of drug pharmacogenetics, pharmacokinetics, and surgical stress induced prothrombosis.

Methods

After approval from the Committee for the Protection of Human Subjects (CPHS), 60 adult patients who were receiving or had recently suspended combined aspirin and clopidogrel therapy due to either coronary stent implantation or grafting were enrolled. Exclusionary criteria included any anticoagulatory medication other than aspirin and clopidogrel, end-stage renal failure, liver disease with recognized coagulopathy, or recent utilization of nonsteroidal anti-inflammatory drugs (NSAIDs). All patients gave their written informed consent and were surgical candidates scheduled for an elective operative procedure who presented to either the preoperative anesthesia clinic or the day surgery area. Subjects were questioned on reasons for surgical procedure, duration of antiplatelet therapy, and timing of the last dose of aspirin and clopidogrel. Patient demographics, current medications, and surgical procedures have been reported in Table 1.

Blood sampling

Baseline blood samples were drawn in the preoperative anesthesia clinic on the day of anesthesiological examination or in the day-surgery area on the day of surgery for those patients not presenting to the preoperative anesthesia clinic (Fig. 1). Postoperatively, blood samples were obtained the day of surgery in the peri-anesthesia care unit (PACU) from 27 patients on clopidogrel therapy (clopidogrel group) and from 28 patients on aspirin therapy (aspirin group). Per standard practice to avoid shear activation, blood samples for the TEG® PM™ were drawn from a single clean puncture of a forearm vein in the preoperative anesthesia clinic after routine blood for routine surgical work-up was drawn, or from an already placed intravenous line in the day surgery and PACU units. Blood (3–4 mL) was collected in a 4.0 mL test tube containing lithium heparin 14.5 U mL^{-1} (Vacuette™) and whole fresh blood (2 mL) in a 3 mL regular syringe.

Table 1 General demographics, length of aspirin/clopidogrel suspension, and TEG® PM™ values

Gender			
Male			$n = 30$ (53 %)
Female			$n = 27$ (47 %)
Surgical procedures			
Neuro/ortho			20 (35 %)
General surgery			16 (28 %)
ENT			10 (17 %)
Urology			6 (11 %)
Others			5 (9 %)
	Mean ± SD	Median	25–75 Interquartile
Age	65.7 ± 10.9	67.0	60.0–71.0
Days off of clopidogrel	5.3 ± 8.8	4.0	1.0–7.0
Days off of aspirin	3.1 ± 4.9	1.0	0.0–4.0
Baseline SP (min)	5.7 ± 2.5	5.7	4.4–6.9
Baseline R (min)	7.0 ± 2.7	6.8	5.5–8.2
Baseline K (min)	2.3 ± 0.9	2.2	1.8–2.6
Baseline Angle (degrees)	60.0 ± 9.0	60.3	54.9–65.0
Baseline MA (mm)	68.8 ± 5.1	68.7	65.1–72.4
Preop-ADP ($n = 57$)			
MA (mm)	43.1 ± 15.9	45.2	32.9–56.0
% Inhibition (%)	43.6 ± 24.4	42.8	24.8–59.6
Preop-AA ($n = 57$)			
MA (mm)	37.2 ± 19.6	40.3	18.5–52.9
% Inhibition (%)	52.8 ± 30.2	52.1	26.1–74.7
Postop-ADP ($n = 27$)			
MA (mm)	49.3 ± 13.1	50.0	43.0–55.5
% Inhibition (%)	30.7 ± 18.6	27.2	17.9–39.9
Postop-AA ($n = 29$)			
MA (mm)	43.1 ± 18.9	47.1	33.5–52.5
% Inhibition (%)	45.0 ± 33.4	35.2	19.2–68.8

SD standard deviation; *SP* split point; *MA* maximal amplitude; *ADP* adenosine diphosphate; *AA* arachidonic acid; *R* and *K* are standard TEG® parameters

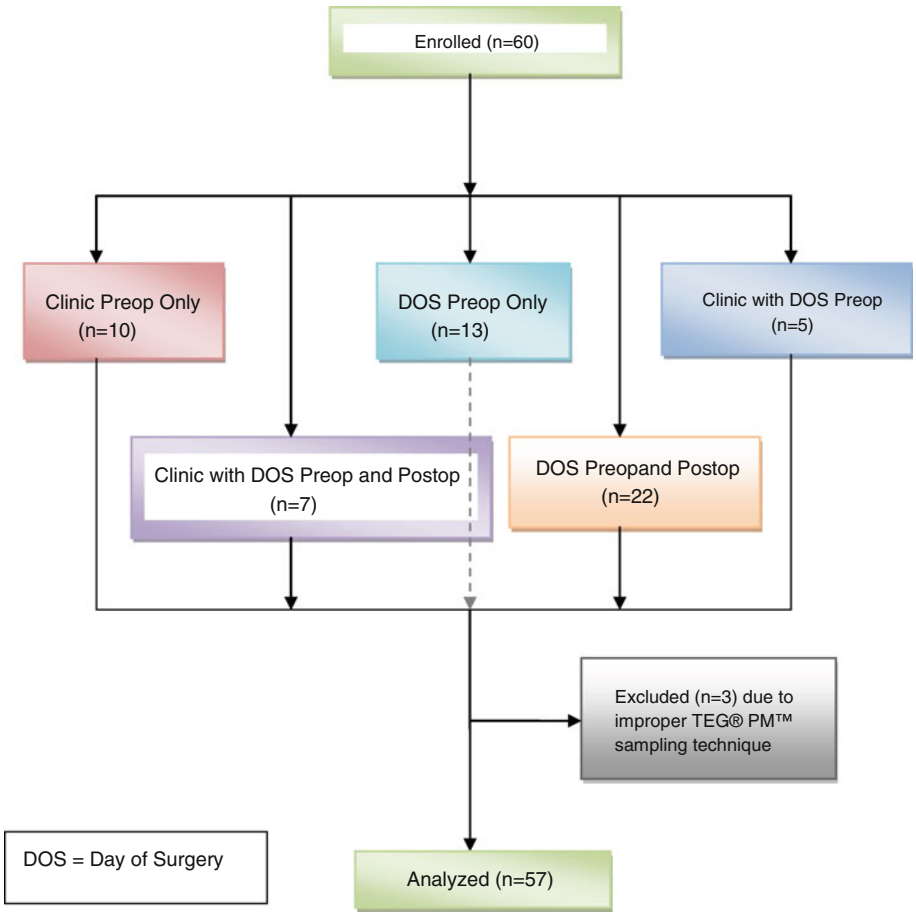

Fig. 1 This CONSORT flow diagram illustrates the enrollment and sample collection of patients involved in the study. *DOS* day of surgery

Measurements

In order to monitor platelet function, blood was immediately processed at the point-of-care and analyzed by using the TEG® analyzer. The following parameters were measured and graphically displayed: (1) the *R* value (Reaction time), i.e. the time from the start of a sample run until the first significant levels of detectable clot formation; (2) the *K* value (K Time), i.e. the time from the end of *R* time until the level of clot strength reaches an amplitude of 20 mm, representative of the speed of clot kinetics; (3) α angle, i.e. the measure of the acceleration of fibrin build-up and cross-linking (clot strengthening); (4) the SP value (Split Point), i.e. the time to initial amplitude when the tracing starts to split, indicating clotting; and (5) the maximal amplitude (MA), a direct function of the maximum clot strength [8].

The TEG® PM™ gives quantitative analysis of platelet function based on the formation, strength, and degradation of clots in whole blood. Maximal clot strength ($MA_{Thrombin}$) is the maximum amplitude and was achieved by transferring 1 mL of whole blood to a vial containing kaolin which was then mixed by inversion. The kaolin activated blood (360 µL) was transferred to the first TEG® cup as a standard TEG®. In order to detect the fibrin contribution to clot strength, blood (360 µL) from the heparinized tube was transferred to the second TEG® cup containing 10 µL Activator F, a mixture of reptilase and factor XIII, (MA_{Fibrin}). The P2Y12 receptor contribution to clot formation was assessed by the addition of 360 µL heparinized blood to the third TEG® cup along with 10 µl of 2 µM ADP (MA_{ADP}) and 10 µL Activator F. Likewise, the contribution of the COX-1 pathway to clot formation was assessed by transferring 360 µL heparinized blood to 10 µL of 1 mM AA (MA_{AA}) and 10 µL Activator F to the fourth TEG® cup. The addition of exogenous ADP and AA allows determination of the response of the ADP and thromboxane A2 (TXA2) receptors, respectively. The percentage platelet aggregation to agonist can be calculated by: $[(MA_{ADP/AA} - MA_{Fibrin})/(MA_{Thrombin} - MA_{Fibrin}) \times 100]$ and is calculated by the TEG® PM™ software. The raw MA data from the TEG® PM™ and percentage platelet inhibition were assessed and recorded.

The reference ranges for the kaolin TEG® parameters were $R = 4$–8 min, $K = 0$–4 min, $\alpha = 47-74°$, and MA = 54–72 mm. For the TEG® PM™, an MA greater than 50 was considered normal for both AA and ADP, as well as an

inhibition less than 30 % for aspirin (AA) and clopidogrel (ADP) [10, 11]. However, an interindividual variability is recognized especially for ADP, setting values of inhibition for ADP up to 40 % as normal [9, 10].

Statistical analysis

In this pilot, observational study, the results were analyzed utilizing STATA (STATA Corp., Version 10.0, College Station, TX). The outcome variables were presented as mean ± standard deviations, as well as the median and the 1st and 3rd quartiles. Preoperative and postoperative data were stratified per duration of therapy suspension (≤3, 3–7 and >7 days). Robust locally weighted polynomial regression was used to create a best fit on all patients based on the days off antiplatelet therapy. Comparison and p value was calculated from non-parametric Wilcoxon rank sum test. A p value <0.05 was considered significant.

Results

Demographics and laboratory data are presented in Table 1. Three subjects were excluded from analysis because of improper handling of samples or missing values precluding analysis. Average interruption was 5.3 ± 8.8 days for clopidogrel and 3.1 ± 4.9 days for aspirin. Preoperative baseline MA values were similar in both the clopidogrel and aspirin groups. Patients were distributed on a scatter plot depending on the duration off antiplatelet therapy (Figs. 2, 3). The mean and corresponding 25–75 interquartile for each day off antiplatelet therapy are also displayed for both the clopidogrel and aspirin groups.

Combined preoperative and postoperative data was available on 27 of the 57 patients who were receiving or had recently suspended clopidogrel (Table 2). These patients were divided into 3 groups, depending on the duration off clopidogrel (≤3, 3–7, and >7 days). Although all 3 groups showed decreased % inhibition in the postoperative samples, the only statistical significance ($p < 0.048$) was found when combining all the 3 groups together. These same patients were then distributed on a box-and-whisker plot with both their preoperative and postoperative values for comparison (Fig. 4). A difference seems to be noted on the plot for patients off clopidogrel ≤5 days, which is consistent with the grouping of the patients into two groups (0 ≤ 5 and >5 days) (Table 2), where a statistical difference ($p < 0.02$) was observed in the patients off clopidogrel from the 0 ≤ 5 days group.

Preoperative and postoperative data were available on 29 of the 57 patients who were currently on or had recently suspended aspirin, similarly divided into 3 groups this time depending on suspension of aspirin (≤3, 3–7, and >7 days) (Table 3). Distribution of preoperative to postoperative AA % inhibition showed similar patterns of decreasing inhibition with interruption of aspirin but did not reach significance (Fig. 5).

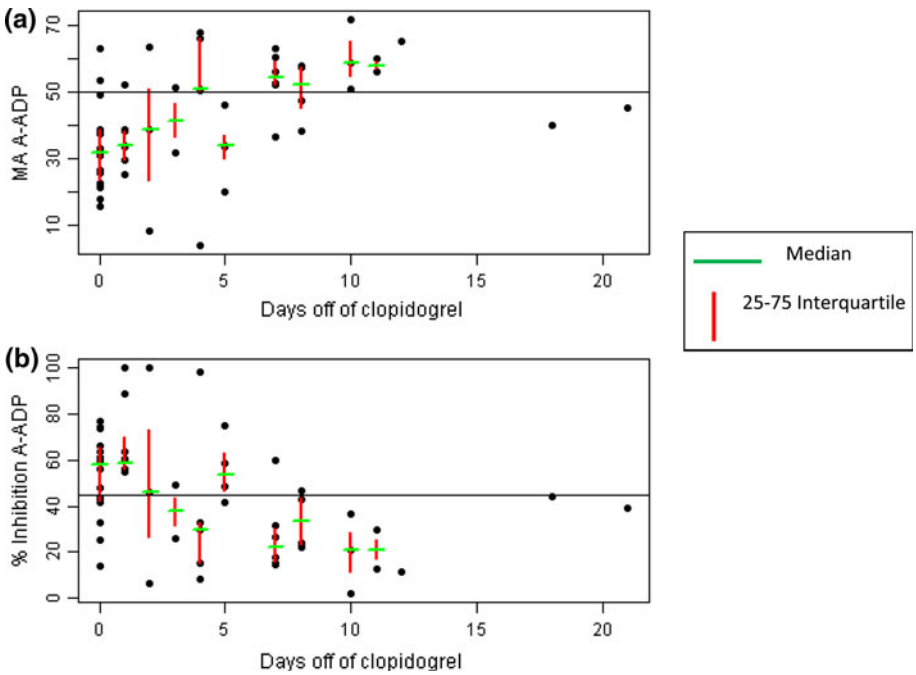

Fig. 2 The **a** preoperative MA ADP and **b** preoperative ADP % inhibition in the 57 patients are distributed on a scatter plot depending on the duration off clopidogrel. The median and corresponding 25–75 interquartiles for each day off clopidogrel are also displayed. *MA* maximum amplitude; *ADP* adenosine diphosphate. Test performed either in preanesthesia clinic or in day-surgery unit on day-of-surgery. The *solid line* represents the cut-off for normality (MA = 50 mm; % inhibition = 45)

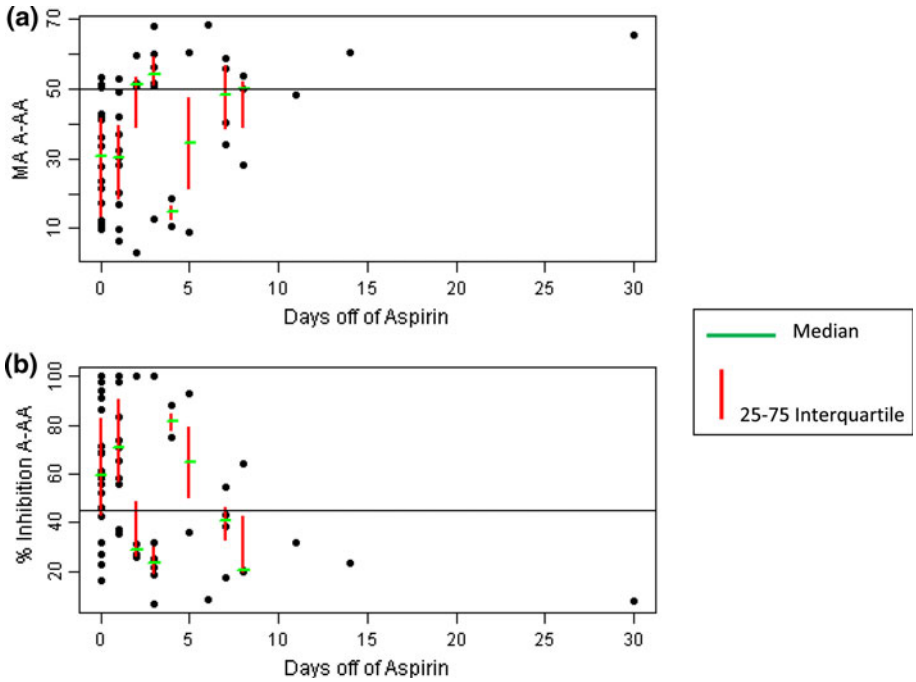

Fig. 3 The **a** preoperative MA AA and **b** preoperative AA % inhibition in the 57 patients are distributed on a scatter plot depending on the duration off aspirin. The median and corresponding 25-75 interquartiles for each day off aspirin are also displayed. *MA* maximum amplitude; *AA* arachidonic acid. Test performed in PACU after anesthesia team handed patient off to nursing staff. The *solid line* represents the cut-off for normality (MA = 50 mm; % inhibition = 45)

Table 2 Preoperative and postoperative percent (%) platelet inhibition in 27 patients separated into 3 groups by days off of clopidogrel ($0 \leq 3$, $3 \leq 7$ and >7 days) and into 2 groups by days off of clopidogrel ($0 \leq 5$ and >5 days)

Days off of clopidogrel	*N*	ADP % preop inhibition		ADP % postop inhibition		*p* value
		Mean	Median	Mean	Median	
$0 \leq 3$ days	11	51.9 ± 24.6	56 (33.7, 62.65)	37.6 ± 24.6	38.4 (18.5, 48.5)	0.13
$3 \leq 7$ days	11	39.5 ± 20	41.6 (22.15, 53.3)	29.2 ± 9.8	33.5 (21.9, 36.1)	0.25
>7 days	5	32.1 ± 10.3	29.4 (23.9, 38.8)	27.7 ± 17	27.2 (24.8, 38.6)	0.84
Total patients	27	43.2 ± 21.6	41.6 (25.6, 58.8)	32.3 ± 18.3	33.5 (21.25, 40.8)	0.048*
$0 \leq 5$ days	17	51.3 ± 21.2	49.3 (41.5, 61.4)	35.5 ± 20.6	35.9 (21, 45)	0.02*
>5 days	10	29.5 ± 14.7	25.2 (19, 36.5)	27 ± 12.6	26 (21.7, 35.6)	0.99

Data are presented as mean ± SD and median (1st and 3rd quartile). *p* value was calculated from non-parametric Wilcoxon rank sum test. *SD* standard deviation; *ADP* adenosine diphosphate

Discussion

This study has demonstrated that patients receiving or having recently suspended dual antiplatelet therapy (DAPT) presenting for non-cardiac surgery (NCS) at the anesthesia preoperative clinic or on the day of surgery have higher levels of preoperative platelet inhibition with respect to those patients that interrupted antiplatelet therapy most recently. A sequential decline that parallels longer interruption of clopidogrel or aspirin therapy was noted. This trend supports recent findings by Collyer et al. [9] and highlights the need for objective recommendations to guide decisions as to how long to safely suspend antiplatelet therapy prior to surgery. In addition, a trend to decreased platelet inhibition in postoperative samples especially for patients taking clopidogrel, although this did not reach significance, was noted. This may be related to effects of surgery on platelet reactivity, increased platelet aggregability [12] and increased activation of the sympatho-adrenal axis and catecholamine release [13]. By utilizing a patient population on combined antiplatelet therapy, this study distinguishes itself from previously published studies on the effects of antiplatelet therapy on platelet inhibition. Our findings are of more value to practitioners, who must frequently treat patients on DAPT in the clinical setting.

Timing of elective surgery is a major concern in patients with coronary artery stents who are receiving antiplatelet therapy. Low levels of preoperative platelet inhibition may be related to incomplete responsiveness to clopidogrel and/or aspirin therapy, an increasingly recognized concern

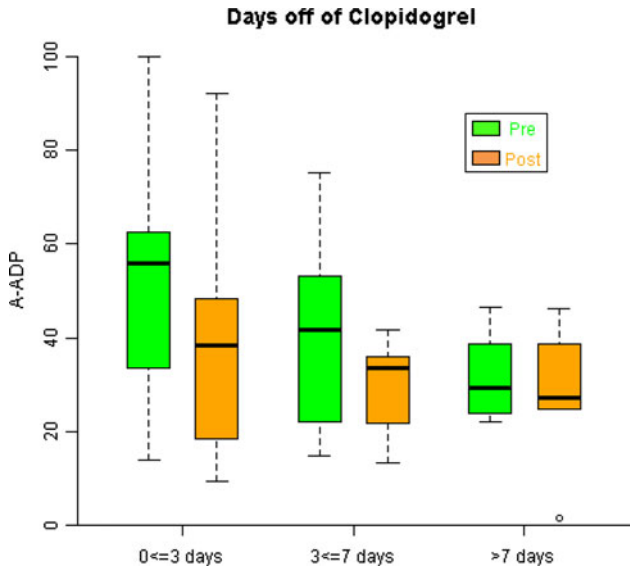

Fig. 4 Whisker plot distribution comparing preoperative and postoperative percent (%) inhibition in 27 patients based on days off clopidogrel. Preoperative values are expressed in *green* while postoperative values are expressed in *orange*

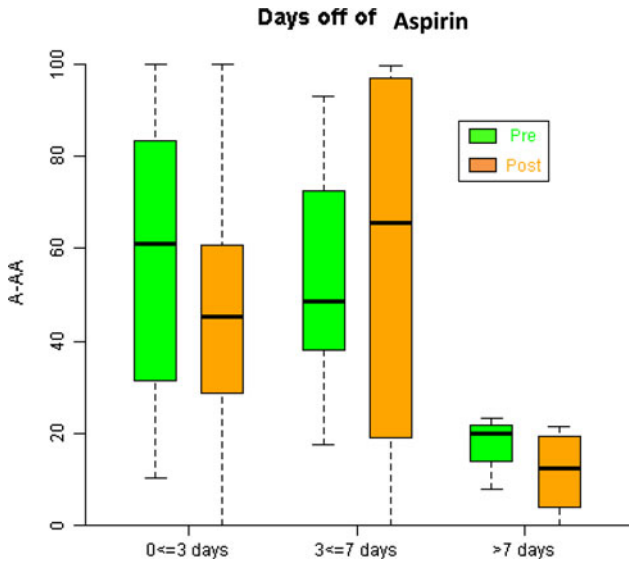

Fig. 5 Whisker plot distribution comparing preoperative and postoperative percent (%) inhibition in 29 patients based on days off aspirin. Preoperative values are expressed in *green* while postoperative values are expressed in *orange*

[13, 14]. Preisman et al. [15] comment on this lack of patient responsiveness to therapy by stressing the importance of measuring platelet function in patients undergoing cardio-thoracic surgery. We used prospective data from this present study to reiterate the need to measure platelet function in all patients on antiplatelet therapy [16].

A recent modification of the TEG® analysis that includes Platelet Mapping™ assay has generated interest. This assay facilitates not only the evaluation of the activation of arachidonic acid (AA) and adenosine diphosphate (ADP) pathways, allowing evaluation of the potential inhibition of those pathways by aspirin and clopidogrel, respectively [17, 18], but it may also permit assessment of the clotting status for the exclusion of a possible haemostasis imbalance toward a hemorrhagic status. The immediate availability of assessment of platelet function by point-of-care methodology may provide objective evidence of platelet inhibition and aid physician judgment in appropriate interruption of antiplatelet therapy for surgical procedures, facilitating personalized, data-driven management of antiplatelet therapy.

An important consideration is worth mentioning. While meaningful results have been seen in studies that document agreement between TEG® PM™ and platelet responsiveness due to thromboxane [19], inconsistencies have also been noticed between the ADP or the AA pathways measured by different point-of-care devices and compared to light aggregonometry [20]. Breet et al. [21] compared the predictive power of several well-known platelet function tests (the VerifyNow P2Y12 and PlateletWorks assays, and the IMPACT-R and the platelet function system [PFA-100]), with the exception of the TEG® PM™, and concluded all tests had about a 60 % sensitivity and 60 % specificity. Concerns about the low sensitivity of the TEG® PM™ stem from initial results by Tantry et al. [20]; however, Collyer et al. [9] and Bochsen et al. [10] have retested the TEG® and TEG® PM™ assays and found

Table 3 Preoperative and postoperative percent (%) platelet inhibition (mean ± SD) in 29 patients separated into 3 groups by their days off of aspirin (0 ≤ 3, 3 ≤ 7 and >7 days)

Days off of aspirin	*N*	AA % preop inhibition		AA % postop inhibition		*p* value
		Mean	Median	Mean	Median	
0 ≤ 3 days	18	58.7 ± 31.3	63.1 (31.5, 85.8)	50.2 ± 30	47.8 (28.8, 76.6)	0.44
3 ≤ 7 days	7	47.8 ± 28.1	43.1 (27.9, 63.4)	50.6 ± 41.8	62.3 (13.3, 83)	0.9
>7 days	4	17.9 ± 6.8	20 (16.8, 21.2)	11.5 ± 9.6	12.3 (5,7, 18.2)	0.34
Total patients	29	50.5 ± 31.1	42.5 (23.1, 72.4)	45 ± 33.4	35.2 (19.2, 68.8)	0.43

Data are presented as mean ± SD and median (1st and 3rd quartile). *p* value was calculated from non-parametric Wilcoxon rank sum test. *SD* standard deviation; *AA* arachidonic acid

them to be adequate in their sensitivity to platelet function. Indeed, the variability of reported TEG® PM™ data is in agreement with that showed by Collyer et al. [9]. This extreme variability in patient inhibition levels may be unrelated to antiplatelet therapy, due instead to different intrinsic patient factors (i.e. genetic polymorphisms, different TxA_2 or ADP receptor concentrations used, or the type of testing used [10]).

However a body of evidence indicates that cut off points to define effectiveness or "resistance" to one drug or the other may have been insufficiently investigated [9, 10]. Indeed, Madsen et al. [20] state "the effects of aspirin and clopidogrel on platelet function are not measured routinely, and no consensus has been reached regarding which laboratory criteria are the most clinically relevant to describe ALR [aspirin low response] and CLR [clopidogrel low response]". Our understanding of what cut-off values are appropriate has changed over the years. Originally, Tantry et al. [11] and Bochsen et al. [10] showed that values of MA <40 mm or % inhibition >50 % could have been considered as cut-off values for normal inhibition levels. However, Collyer et al. [9], Preisman et al. [15], and Mahla et al. [22] later showed how cut-off values are different depending on the drug used (aspirin vs. Clopidogrel), cross-over inhibition, time from suspension of medication(s), type of surgery, expected complication rate, and acceptable blood losses. Based on more complex or simple surgeries, we may want to reconsider the definition of what constitutes appropriate cut-off values. More investigation is necessary on this point.

Our preliminary data, together with others [9, 10], suggest that preoperative assessment of the antiplatelet effects of aspirin and clopidogrel is not only feasible but also necessary as the baseline level of inhibition (AA and ADP) was surprisingly low and decreased with longer interruption of therapy. This finding would support the rationale in maintaining aspirin therapy perioperatively. If these data are validated, it may lead to critical re-evaluation of the traditionally recommended continuation of aspirin and 5–7 days interruption for clopidogrel. Patients may be exposed to unnecessary risks of stent thrombosis if waning anti-platelet effects are demonstrated over a shorter period. This is of even greater significance given the subsequent additional decrease in platelet inhibition in postoperative samples, which coincides with the reported increased incidence of thrombotic events.

One potential limitation of this study is the use of patients receiving combined antiplatelet therapy of aspirin and clopidogrel, making it difficult to discriminate which effects are caused by which drug. However, dual therapy can be seen as providing the proper clinical context needed to evaluate the data. Patients frequently present on DAPT with aspirin and clopidogrel to treat cardiovascular disease, making studies like this one valuable to clinicians encountering such patients.

We recognize that another limitation to this study is the inconsistent availability either of platelet counts or of coagulation tests (PT, PTT, INR) in our patient population. However, a baseline kaolin TEG® was recorded for each patient and was considered a comprehensive test for the purposes of this study. Due to the varied surgical procedures undergone by the patients enrolled, only the general surgical area was included in Table 1. This lack of detailed reporting does pose a limitation as surgical procedures varied in duration and severity, which may have affected the results. Additionally, the variability of results produced by the TEG® makes determination of a normal range of inhibition difficult. Further research is needed to correlate the measured levels with outcomes, such as cardiac events during the perioperative period.

In conclusion, we documented low levels of preoperative platelet inhibition, suggesting that use of point-of-care platelet function testing may be a feasible and logical approach to objective evaluation of the effects of aspirin and clopidogrel on the AA and ADP pathways. Validation of these results in a larger prospective evaluation will likely provide evidence to guide physicians in the appropriate and personalized management of DAPT and potential interruption for elective surgical procedures.

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Conflict of interest Davide Cattano, M.D., Ph.D., is on the speaker bureau for Cadence, received research funding from Covidien, and Karl Storz Endoscopy, Germany. Carin A. Hagberg, M.D., has disclosed that she is a member of the speakers' bureaus for Ambu A/S, Cook Medical, Covidien, and LMA North America; and has received equipment support from Aircraft Medical, Ambu A/S, Cook Medical, Karl Storz Endoscopy, King Systems, LMA North America, Mercury Medical, and Verathon Medical.

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