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## Modified thromboelastography evaluation of platelet dysfunction in patients undergoing coronary artery surgery<sup>☆,☆☆</sup>

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### Abstract

**Objective:** Anti-platelet therapy is associated with increased perioperative bleeding. Although current guidelines call for its cessation 5–10 days prior to cardiac surgery, this could constitute an increased risk of preoperative myocardial infarction. The optimal safe period from discontinuation of anti-platelet therapy to surgery is as yet unknown for the individual patient. We investigated whether preoperative thromboelastography (TEG) with platelet mapping could predict bleeding tendency in patients (on recent anti-platelet therapy) undergoing coronary artery bypass grafting (CABG). **Methods:** We prospectively evaluated 59 patients on aspirin and clopidogrel therapy who underwent CABG. Of them, 25 patients received aspirin alone. TEG with platelet mapping was performed immediately prior to surgery in all 59 patients. **Results:** During the first 24 h post-surgery, 9/59 patients bled excessively ( $1216 \pm 310$  ml in excessive bleeding vs  $576 \pm 155$  ml in non-bleeding patients). Of the patients bled excessively, eight received clopidogrel treatment prior to surgery. However, 26 of the remaining 34 patients receiving clopidogrel did not bleed significantly. Clopidogrel-induced platelet dysfunction diagnosed by platelet mapping discerned between patients who demonstrated excessive bleeding and those who did not (78% – sensitivity, 84% – specificity,  $p = 0.004$ ). Aspirin-induced platelet dysfunction did not reflect a bleeding tendency. Of all patients, 85% did not respond to a standard dose of clopidogrel, whereas 44% did not respond to aspirin. **Conclusions:** TEG with platelet mapping is able to predict excessive postoperative blood loss among patients who underwent CABG and recent anti-platelet therapy. The prevalence of non-responsiveness to anti-platelet therapy, including clopidogrel, is higher in patients undergoing coronary artery bypass grafting than in the general population. In this study, aspirin-induced platelet dysfunction did not influence postoperative blood loss.

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**Keywords:** Thromboelastography; Blood loss, postoperative; Platelet aggregation inhibitors; Coronary artery bypass

### 1. Introduction

Anti-platelet therapy has become an integral part of cardiac surgery perioperative management, due mainly to the extensive use of implantable intravascular devices and the proven efficacy of anti-platelet therapy in patients with unstable coronary syndromes [1]. Aspirin and clopidogrel treatment during the perioperative period is associated with a substantial increase in re-exploration rates, chest drain blood loss and blood product usage. As a result, clinical guidelines currently call for the cessation of clopidogrel therapy 5–7 days prior to surgery even in urgent cases, and the withdrawal of aspirin administration 2–10 days prior to elective surgery [1,2]. It is recognised, however, that the

cessation of clopidogrel therapy in patients in need of urgent coronary revascularisation may constitute an increased risk of myocardial infarction while awaiting surgery [3]. This problem could stem from individual patient variability of response to anti-platelet therapy and elimination of the drug (manifested by profound platelet aggregation depression in one sector of the population, compared with lack of response in another). To date, there are no available data regarding the prevalence of aspirin and clopidogrel resistance in patients undergoing coronary revascularisation.

Quantification of patient response to anti-platelet therapy may help individualise the surgical approach, facilitating more precise timing of the operation and prediction of the risk of microvascular bleeding. The current ‘gold standard’ for platelet function evaluation is laboratory-based light transmittance aggregometry, which is labor intensive, operator dependent and expensive. Therefore, point-of-care platelet function tests, such as modified thromboelastography (TEG), could be both useful and

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beneficial. Results of platelet function assessment by this method correlate closely with light transmittance aggregometry [4]. TEG is able to predict percutaneous coronary intervention outcomes [5]. In addition to estimating the severity of platelet function inhibition, this method provides valuable information concerning the whole process of blood coagulation.

The authors hypothesised that modified TEG is able to predict clinically significant bleeding tendencies in patients, with a history of recent anti-platelet therapy, undergoing surgical myocardial revascularisation. An additional aim of the study was to examine the prevalence of aspirin and clopidogrel resistance in this patient population.

## 2. Materials and methods

The study was approved by the Institutional Human Research Review Committee and registered at the ClinicalTrials.gov website (Identifier NCT00778492). Given the non-interventional nature of the study, the Institutional Human Research Review Committee waived the need to obtain written consent from the patients participating in the study. We prospectively studied 60 patients from the Department of Cardiac Surgery of the Sheba Medical Center, with the following inclusion criteria: first-time elective or urgent coronary artery bypass grafting (CABG) and treatment with anti-platelet agents (aspirin and/or clopidogrel) within 1 week prior to surgery. Urgency was defined as the need for CABG during the same hospitalisation as coronary catheterisation. Emergency surgery was defined as an indication for CABG within 24 h of cardiac catheterisation. Exclusion criteria included: patients requiring emergent surgery and combined operations, those with grossly abnormal coagulation tests, including a history of coagulopathy, preoperative treatment with other anticoagulants, as well as enrollment in any other study.

Because of the high negative impact associated with re-exploration procedures resulting from postoperative bleeding during the perioperative period, the authors chose this event rate as the study's primary outcome. Patients were excluded from the study if a clear source of surgical bleeding was found during the exploration. The study's secondary outcomes were chest tube blood output during the first 24 postoperative hours and consumption of blood products during postoperative hospitalisation.

### 2.1. Power analysis

The decision to recruit 60 patients was based on the following assumptions: in the Medical Center's Department of Cardiac Surgery, the total rate of re-sternotomies for bleeding varies between 5% and 9%. Based on the assumption that in our patient population the event rate is 10% in those patients with grossly abnormal platelet function and 2% in those with normal and slightly abnormal platelet function, and accepting the clinically important difference in the event rates of 5%, it was necessary to recruit 24 patients from each group, thereby generating a significance level of 0.05 and a power of 80% [6]. However, since currently there is no information regarding the rate of response to anti-platelet agents in

patients undergoing cardiac surgery, it was decided to recruit 60 patients.

### 2.2. Anaesthesia and perfusion protocol

Our Medical Center's standard anaesthetic and perfusion management protocol was used for all patients. Anaesthesia was induced by midazolam, fentanyl and propofol and maintained by isoflurane. Analgesia was provided by fentanyl (total dose of 15–20  $\mu\text{g kg}^{-1}$ ). Muscle relaxation was induced by pancuronium. Arterial pressure was monitored through radial arterial cannula. Central venous or pulmonary artery catheters were used for haemodynamic monitoring and vasoactive drug infusions, based on the preference of the attending anaesthesiologist. Normal saline without heparin was used as a flush solution. Fluid replacement was in the form of a crystalloid infusion (Lactated Ringer's solution). Cardiopulmonary bypass was established following anticoagulation with 3–4  $\text{mg kg}^{-1}$  of heparin to achieve an activated clotted time of  $>500$  s. A dose of 50  $\text{mg kg}^{-1}$  tranexamic acid was given immediately following heparin administration. An additional 100 mg of heparin was added to the priming fluid of the cardiopulmonary bypass circuit which contained 1200 ml of Lactated Ringer's solution. Cardiopulmonary bypass circuit consisted of non-coated tubing and hollow fibre membrane blood oxygenator with biocompatible phosphorylcholine coating, hardshell venous reservoir and an integral heat exchanger (Apex Ph.I.S.I.O./M, Sorin, Italy). A roller blood pump was used. Boluses of heparin were given such that the activated clotted time values remained in the range of 450–500 s. Patients' temperatures were allowed to drift without active cooling. Cardiac arrest was induced by means of antegrade cold blood cardioplegia. If a patient's haemoglobin level decreased to  $<8 \text{ g dl}^{-1}$ , one unit of red blood cells was infused into the cardiopulmonary bypass circuit. At the end of the surgical procedure, patients were re-warmed to a nasopharyngeal temperature of 36.5 °C, and weaned from the cardiopulmonary bypass. Heparin was reversed with protamine at a ratio of 0.75–1.0:1.0. The dose of protamine sulphate and later the absence of residual heparin in patient's blood were determined by measuring free heparin concentrations in the blood (HepCon HMS Plus system, Medtronic Inc., Minneapolis, MN, USA). Complete blood count and coagulation panel, including prothrombin time, partial thromboplastin time, thrombin time and blood fibrinogen concentrations, were analysed immediately upon arrival at the intensive care unit, and in the morning of the first 3 postoperative days, or, more frequently, if microvascular bleeding was suspected. Transfusion of blood products and management of postoperative bleeding in the intensive care unit were determined by following institutional algorithm. Transfusion of packed red blood cells (PRBCs) was not performed if patient's blood haemoglobin level was  $>10 \text{ g dl}^{-1}$ . If patient's haemoglobin level decreased  $<8 \text{ g dl}^{-1}$ , one unit of PRBC was transfused. If this parameter remained between 8 and  $10 \text{ g dl}^{-1}$ , PRBCs were transfused under special circumstances (e.g., signs of myocardial ischaemia, ongoing bleeding with symptoms of hypovolemia and decreases of oxygen saturation in mixed venous or superior vena cava blood unrelated to problems with systemic oxygenation). Other blood components were

transfused only in the case of ongoing bleeding. If this situation was accompanied by increasing the activated clotting time (ACT) to  $>110\%$  of its initial preoperative value, 20 mg of protamine sulphate was administered. If patient's international normalised ratio (INR) was  $>1.3$ , patient received 10–15 ml  $\text{kg}^{-1}$  of fresh frozen plasma. If ongoing bleeding was accompanied by the decrease of blood fibrinogen levels below  $1.5 \text{ g dl}^{-1}$ , 10 units of cryoprecipitate were transfused. If bleeding continued despite normal ACT, INR and blood fibrinogen levels,  $0.1 \text{ unit kg}^{-1}$  of platelet concentrate was used. Indication for chest exploration was bleeding with the rate of  $500 \text{ ml h}^{-1}$ ,  $400 \text{ ml h}^{-1}$  for 2 consecutive hours or  $200 \text{ ml h}^{-1}$  for 3–4 consecutive hours.

### 2.3. Platelet mapping

Modified TEG [4] (Haemoscope Corporation, Niles, IL, USA) was used for platelet mapping based on the manufacturer's instructions. It was performed by an investigator not directly involved in patient care. A blood sample of 7 ml was drawn from the arterial line prior to induction of anaesthesia and was used for analysis within 20 min. An amount of 2.7 ml of blood was placed in a tube together with  $0.109 \text{ mol l}^{-1}$  of citrate, and 4 ml was kept in a heparinised tube. A citrated sample was used for routine kaolin-enhanced TEG in the first cuvette. In this test, platelets are activated by thrombin, the most potent platelet activator known. Maximum amplitude (MA) of this test was used as a control for estimating a patient's maximum platelet aggregation potential. Heparinised blood activated by reptilase and factor XIIIa (activator F) was used to produce a cross-linked fibrin clot in the second cuvette for estimating the fibrin contribution to MA (MAf). Activator F and platelet agonist (arachidonic acid (AA) or adenosine diphosphate (ADP)) were used for blood activation in two other cuvettes. The MA of samples in these cuvettes enabled the assessment of a whole-blood, cross-linked clot produced by interaction of fibrin with agonist-activated platelets (MAaa and MAadp). The degree of platelet activation is calculated by computerised software as  $((\text{MAaa} - \text{MAf}) / (\text{MA} - \text{MAf})) \times 100\%$  and  $((\text{MAadp} - \text{MAf}) / (\text{MA} - \text{MAf})) \times 100\%$ . Agonist resistance was defined as  $>50\%$  agonist activation [7]. Results of the platelet mapping were not available to the operating room staff, the intensive care unit team and the study outcome data-collecting investigator.

### 2.4. Statistical analysis

The Kolmogorov–Smirnov test was used for evaluating normality of distribution of all continuous variables. To define the group of patients with a tendency to bleeding, data concerning chest tube blood loss during the first 24 h post-surgery were analysed by a two-step cluster analysis. Differences between patients with a tendency to bleeding and those with normal blood loss were estimated by the Student *t*-test for variables with normal distribution. Fisher's exact test was used for dichotomous variables. The Mann–Whitney *U*-test was used if the distribution was not normal. Step-down Holm–Sidak procedure was used for the correction for multiple comparisons [8]. Receiver operating characteristic (ROC) curves were constructed to assess the

ability of TEG parameters to predict excessive postoperative blood loss [9]. Correlation between chest tube discharge during the first postoperative 24 h and TEG parameters was evaluated by Spearman's correlation coefficient. Value of  $p \leq 0.05$  was considered statistically significant.

### 3. Results

Data from predetermined patient sample were collected between 13 May 2008 and 24 November 2008. Fig. 1 illustrates the study flow. All patients from the sample were discharged from hospital. One patient, excluded from the analysis, was taken to the operating room for chest reopening due to excessive postoperative bleeding and was found to have a clear surgical source of bleeding that was easily corrected. There was one more patient who had undergone chest reopening for bleeding. This patient was treated with clopidogrel prior to surgery. A daily dose of 100 mg aspirin was administered to 57 patients, until its discontinuation 0–3 days (median, 1 day) prior to surgery. A daily dose of 75 mg clopidogrel was administered to 34 patients who underwent surgery during the first 4 days following its caesation (median, 1 day).

Analysis of data of 24-h chest tube discharge demonstrated that its distribution was not normal. Indeed, cluster analysis revealed two groups of patients (those with a tendency to bleeding and those without a bleeding tendency). Distribution of 24-h chest tube discharge within both of these groups was normal. The characteristics of both groups of patients are presented in Table 1. The amount of blood loss from chest drains during the first 24 h post-surgery was significantly greater in patients with bleeding tendency. Patients did not differ regarding most of their preoperative demographic and laboratory variables, intra-operative variables and postoperative blood coagulation test parameters. There were no differences in the amount of postoperative

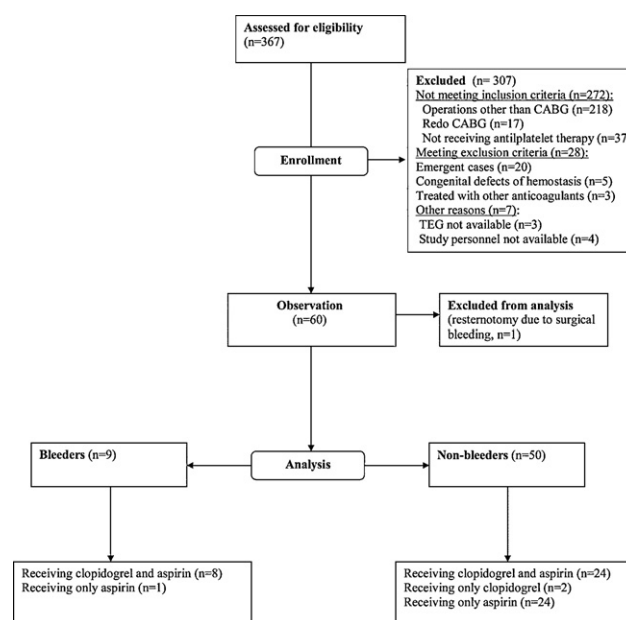


Fig. 1. Flow chart showing study protocol.

Table 1  
Patient characteristics and parameters of perioperative coagulation tests.

Patient characteristics/variables	Patients with bleeding tendency (n = 9)	Patients without bleeding tendency (n = 50)	Uncorrected p values	Values of p corrected for multiple comparisons
24-h chest tube blood loss (ml)	1216 ± 310	576 ± 155	<0.0001	0.0032
Age (years)	56.9 ± 4.0	63.9 ± 10.6	0.06	0.06
Weight (kg)	78.6 ± 11.2	82.5 ± 14.9	0.38	0.38
Height (cm)	172 ± 9	169 ± 8	0.42	0.42
Sex: M/F	9/0	41/9	0.33	0.33
Operation time (min)	249 ± 62	247 ± 44	0.91	0.91
Cardiopulmonary bypass time (min)	88 ± 20	87 ± 34	0.89	0.89
Aortic cross-clamp time (min)	66 ± 29	64 ± 34	0.90	0.90
Elective/urgent surgery	3/6	12/38	0.68	0.68
Left ventricular function:				
Good/moderate/severe dysfunction	7/1/1	32/6/2	0.27	0.27
Treated with clopidogrel	8 (89%)	26 (52%)	0.07	0.07
Treated with clopidogrel (surgery after caesation, days)	1–3 (median, 1)	0–4 (median, 1)	0.36	0.36
Preoperative coagulation tests:				
Platelet count	260 ± 41	225 ± 47	0.04	0.71
International normalised ratio	1.07 ± 0.12	1.02 ± 0.08	0.31	0.31
Partial thromboplastin time	33.7 ± 3.4	20–80 (median, 32; interquartile range, 7)	0.24	0.24
Intensive care unit coagulation (on arrival):				
Platelet count	206 ± 50	195 ± 41	0.56	0.56
International normalised ratio	1.19 ± 0.12	1.15 ± 0.10	0.38	0.38
Partial thromboplastin time	28.3 ± 3.0	28.5 ± 4.3	0.87	0.87
Thrombin time	17.4 ± 2.8	18.0 ± 9.8	0.78	0.78
Fibrinogen	251 ± 84	292 ± 65	0.2	0.2
Intensive care unit coagulations (POD1):				
Platelet count	201 ± 35	188 ± 50	0.35	0.35
International normalised ratio	1.14 ± 0.06	1.14 ± 0.11	0.96	0.96
Partial thromboplastin time	28.7 ± 3.7	27.0 ± 3.6	0.23	0.23
Thrombin time	16.6 ± 3.3	15.3 ± 1.9	0.36	0.36
Fibrinogen	282 ± 80	267 ± 64	0.62	0.62
Thromboelastogram parameters:				
Reaction time (min)	6.9 ± 2.0	7.9 ± 1.8	0.14	0.14
Maximum amplitude (mm)	66.2 ± 7.1	63.6 ± 6.8	0.30	0.30
K (min)	1.8 ± 0.7	2.1 ± 0.7	0.26	0.26
Angle	65.1 ± 8.6	60.2 ± 8.3	0.11	0.11
Platelet mapping:				
Fibrin contribution to maximum amplitude	11.8 ± 9.1	13.9 ± 8.6	0.51	0.51
MAAdp	39.1 ± 16.3	54.3 ± 13.5	0.004	0.117
MAAa	26.1 ± 21.4	36.9 ± 15.9	0.08	0.08

All data are presented as mean ± SD, except the interval between the caesation of therapy with clopidogrel and the operation, which is presented as range and median, and preoperative partial thromboplastin time of patients without bleeding tendency, which is presented as range with median and interquartile range. POD, postoperative day; K, time from reaction time to point of thromboelastographic curve with amplitude of 20 mm; MAAdp, maximum amplitude after stimulation of platelets with adenosine diphosphate; MAAa, maximum amplitude after stimulation of platelets with arachidonic acid.

blood loss during the first 24 h post-surgery between patients receiving and not receiving clopidogrel ( $p = 0.06$ ). No differences were found regarding the interval between caesation of clopidogrel or aspirin treatment and surgery in both patient groups.

Significant correlation existed between the use of platelet concentrate and MAAdp in patients with bleeding tendency (Spearman's  $\rho = -0.75$ ,  $p = 0.02$ ).

The only TEG parameter with significant ability to predict bleeding tendency was MAAdp (area under the ROC curve of 0.81,  $p = 0.004$ ; Fig. 2). According to coordinates of the ROC curve, MAAdp of <42.5 mm could predict bleeding tendency (bleeding vs non-bleeding group) with a sensitivity of 78% and specificity of 84%. Significant difference in the amount of

postoperative blood loss was found between those with normal (>42.5 mm) and abnormal MAAdp (Table 2). No significant correlation was found between any of the TEG-derived parameters and blood loss during the first 24 h post-surgery. Analysis of this population cohort's response to anti-platelet therapy revealed a high rate of non-responsiveness to clopidogrel. Indeed, 29 of 34 patients (85%) on clopidogrel exhibited platelet activation of >50% in response to ADP. The rate of non-responsiveness to aspirin was 44%, with 25 of 57 patients producing a response >50% to activation with AA. No significant correlation was found between time from clopidogrel caesation to surgery and MAAdp. Furthermore, no significant correlation was found between time from aspirin caesation to surgery and MAAa.

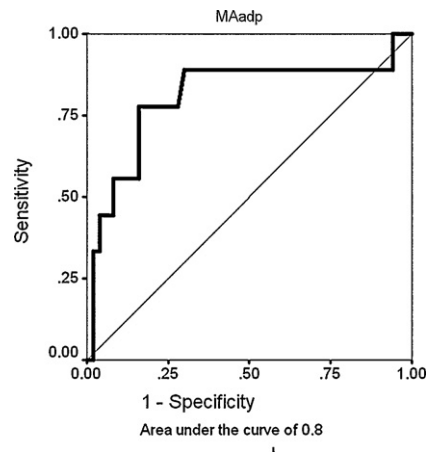


Fig. 2. Receiver operating characteristic curve for thromboelastogram maximum amplitude after platelet activation with adenosine diphosphate (MAadp), to predict bleeding tendency.

#### 4. Discussion

Postoperative bleeding remains one of the major complications of cardiac surgery. It is associated with a significant impact on perioperative morbidity, mortality and utilisation of healthcare resources. Perioperative blood loss demanding transfusion of more than 5 units of PRBCs was found to be associated with an 8.1-fold increase in the odds of death post-surgery [10]. Re-exploration for bleeding after cardiac surgery is an independent predictor of adverse events such as sepsis, renal failure, acute respiratory distress syndrome and prolonged mechanical ventilation [11]. Anti-platelet therapy, especially with clopidogrel, appears to significantly contribute to cardiopulmonary bypass-induced platelet dysfunction, causing an increase in chest drain blood loss, utilisation of blood products and incidence of re-explorations [1]. Despite the fact that some studies could not confirm these findings [12], guidelines accepted by international cardiac surgery societies recommend the cessation of clopidogrel 5–7 days, and aspirin 2–10 days prior to elective surgery, stressing, however, that this cessation may constitute an increased risk of myocardial infarction while awaiting surgery [1,2].

High variability of the response to anti-platelet therapy has been found in populations of healthy volunteers, as well as in patients with various clinical conditions, such as those following coronary stenting and stroke, and also in patients suffering from heart failure [13–15]. A recent study performed in patients receiving anti-platelet therapy who underwent

non-cardiac surgery also showed variability in patient response to these drugs [16]. Therefore, the degree of possible dysfunction of natural haemostatic mechanisms in those patients undergoing cardiac surgery who have a history of recent anti-platelet drug therapy, cannot be predicted solely on clinical grounds. The results of our study confirm that the patients undergoing cardiac surgery present with a wide range of responses to anti-platelet drugs. Although no common definition of resistance to anti-platelet drugs exists, we used the definition proposed by Tantry et al. [7] for aspirin resistance measured by TEG PlateletMapping™. These authors defined resistance to aspirin as more than 50% activation on TEG during ongoing aspirin therapy. Although our study included patients with different intervals after cessation of anti-platelet therapy, in majority of them this period was very short. Indeed, in 27 of 34 patients exposed to clopidogrel, and in 51 of 57 exposed to aspirin, this interval was equal or less than 24 h. Among these patients with a very recent history of anti-platelet drug use who underwent cardiac surgery, 85% of those exposed to clopidogrel and 44% of those exposed to aspirin exhibited activation of > 50% in response to either ADP or AA agonists. These results are consistent with those of Bochsén et al. [17], who also found higher platelet reactivity to ADP in patients undergoing cardiac surgery in comparison with healthy donors. The reasons for such a high rate of unresponsiveness to anti-platelet drug therapy in patients undergoing cardiac surgery compared with other patient populations are unclear. It is possible that currently the majority of potential cardiac surgery patients on anti-platelet therapy are those who may be considered ‘treatment failures’ following percutaneous coronary interventions. Poor responsiveness to standard dosages of clopidogrel was identified as a predictor of recurrent coronary events in patients undergoing percutaneous coronary intervention [18]. Since urgent cardiac surgery in patients with a history of percutaneous coronary intervention may be considered a recurrent coronary event, a poor response to standard doses of anti-platelet drugs should be more prevalent in this patient population. Not surprisingly, those in need of urgent surgery represented 75% of our study cohort.

The other possible explanations for high platelet reactivity of our patients are high variability in drug elimination and poor compliance to treatment, and not drug resistance *per se*. Since we did not assess actual levels of anti-platelet drugs in blood of our patients, these factors might have played certain role in observed wide spectrum of platelet reactivity to specific agonists at least in part of our study population. However, it does not change the fact that patients, considered being on anti-platelet therapy, may present for

Table 2  
Comparison between patients with normal and abnormal adenosine diphosphate response.

	Normal ADP response (n = 44)	Abnormal ADP response (n = 15)	Uncorrected p values	Values of p corrected for multiple comparisons
Explorations	0	1	0.25	0.25
24-h chest tube blood loss	595 ± 188	913 ± 433	0.000	0.007
Any blood product use	20	12	0.03	0.17
Total packed red blood cells (units)	0–5	0–7	0.04	0.18
Total fresh frozen plasma (units)	0–2	0–6	0.11	0.11
Total cryoprecipitate (units)	0–10	0–20	0.11	0.11
Total platelets (units)	0–8	0–20	0.08	0.08

their surgery with wide range of platelet activity poorly predicted on clinical grounds.

No correlation was found between the time interval from caesation of anti-platelet therapy till surgery, and the degree of inhibition of agonist-induced platelet activation. These facts cast doubt on the recommendation for a fixed safe waiting period following discontinuation of anti-platelet therapy, to avoid perioperative microvascular bleeding, which is associated with platelet dysfunction. In many patients this interval may be unnecessary and potentially unsafe due to the increased risk of ischaemic events, whereas in some patients it may not be adequate for platelet aggregation recovery. An individual flexible approach based on direct assessment of platelet function may be beneficial for the determination of the optimal timing of elective procedures and the prediction of bleeding potential in urgent cases.

Recently, several point-of-care methods for the evaluation of platelet function have become available for clinical practice. One of these methods is modified TEG with platelet mapping. Developed to specifically estimate the severity of aspirin- and clopidogrel-induced derangements in platelet function, this method has been favourably compared with conventional laboratory-based light transmittance aggregometry [4,7]. It was proved to be useful in risk evaluation of post-procedural ischaemic events in patients who had undergone percutaneous coronary interventions [18]. Standard TEG was useful in the management of postoperative bleeding in the patients undergoing cardiac surgery [19]. TEG-guided treatment protocols have been shown to decrease transfusion requirements, donor exposure, frequency of reoperations for bleeding and overall use of healthcare resources. However, the role of standard TEG in the prediction of perioperative bleeding is controversial. Although normal rotational thromboelastometry, a method similar to that of TEG, was found to have had significant negative predictive values for postoperative bleeding, a diagnosis of impaired haemostasis based on its results was a poor predictor of haemorrhage [20,21]. One possible explanation may be the dependence of the test's predictive ability on the prevalence of the condition in the tested population. Since the above-mentioned studies assessed the use of TEG in a population of cardiac patients who had a relatively low prevalence of significant bleeding, this finding was probably a foregone conclusion. Another possible explanation for the poor predictive ability of TEG to identify patients with significant postoperative bleeding may lie in its inadequate reflection of complex native haemostatic mechanisms by *ex vivo* coagulation tests. Blood coagulation and haemostasis undergo profound changes in response to extracorporeal circulation, haemodilution and surgical stress. Some of these changes may be reflected by TEG but not necessarily associated with increased blood loss. On the other hand, dysfunction of various receptors affecting platelet aggregation may be undetected by standard TEG, since this method uses direct activation of the platelet GPIIb/IIIa receptor by thrombin, bypassing platelet P2Y12 and thromboxane receptors. This problem could be solved by TEG PlateletMapping™, specifically designed to evaluate the ability of P2Y12 and thromboxane receptors to cause platelet aggregation in response to the respective agonist. In this test, thrombin activity in the blood sample is eliminated by the

use of heparin. A special activator, containing reptilase and factor XIIIa, is used to generate a cross-linked fibrin clot to isolate fibrin contribution to fibrin strength. Then, the contribution of P2Y12 or cyclooxygenase pathways of platelet aggregation to clot formation may be measured by the addition of the respective agonist, ADP or AA.

The present study describes for the first time the use of PlateletMapping™ for the evaluation of platelet reactivity to specific agonists in patients referred for coronary artery surgery. In order to estimate the ability of this method to predict the bleeding propensity of these patients, a subpopulation of patients with a high risk of microvascular bleeding (i.e., those on anti-platelet therapy) was included into the study.

The results of the present study show significant ability of TEG PlateletMapping™ to predict postoperative bleeding in patients receiving anti-platelet therapy. Although aspirin-induced dysfunction of the platelet thromboxane receptor was not associated with a bleeding tendency, dysfunction of the ADP receptor, found by preoperative PlateletMapping™, could predict postoperative bleeding with relatively high precision. MA<sub>ADP</sub> of <42.5 mm could predict abnormal postoperative bleeding with a sensitivity of 78% and specificity of 84%. There were significant differences in the amount of postoperative blood loss between patients with MA<sub>ADP</sub> of less than and more than 42.5 mm.

One of the findings of the present study was the lack of influence of aspirin-related depression of the platelet thromboxane receptor on postoperative bleeding tendency. Although the Perioperative Blood Conservation Guidelines of the Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists call for discontinuation of aspirin treatment in elective patients [2], several studies have failed to find increased perioperative blood loss or transfusion requirements in patients undergoing first-time or even repeated coronary artery surgery [22,23]. In a large retrospective study demonstrating the effect of aspirin on transfusion requirements, this effect was observed in only one quintile of patients (namely, those with the longest cardiopulmonary bypass times, greater number of women, repeated operations and more prevalent preoperative renal dysfunction) [24]. The majority of patients in our study were suffering from acute coronary syndromes, demanding urgent surgical intervention. In this population of patients with potent activation of the coagulation system, the effect of such a low-intensity anti-platelet drug as aspirin may have become over-ridden by the more potent triggers of platelet aggregation, and therefore lost its clinical relevance in respect to surgical haemostasis.

The present study proves the value of PlateletMapping™ in predicting bleeding tendency in patients treated with clopidogrel who need to undergo coronary surgery. This method may influence the development of new perioperative strategies for use in this patient population. However, further studies are needed to show whether a specific treatment protocol based on this or any other point-of-care method for assessment of haemostasis could improve patient outcome.

One limitation of the present study is its lack of power to detect differences in the measures of primary outcome, namely the incidence of chest re-explorations for bleeding. The authors planned the present study based on their department's relatively high incidence of 5–9% of chest re-

explorations for bleeding, and low rate of poor clopidogrel response. Currently, however, patients undergoing coronary artery surgery do not comprise the major part of everyday practice in our department. In the present study, patients receiving anti-platelet medication had a relatively low incidence of re-explorations for bleeding, which was similar to that of patients receiving no anti-platelet drugs in other studies [25,26]. The possible explanation for this may be the greater attention displayed by surgeons performing meticulous surgical haemostasis in a group of patients with a very high perceived risk of perioperative bleeding.

A further limitation of the present study is its relatively high trigger level for transfusion based on an algorithm for the use of blood products. This algorithm is in current use in our department and was not changed for use in this study so that it could reflect everyday clinical practice.

No significant correlation was found between any of the TEG-derived parameters and blood loss during the first 24 h post-surgery. One possible reason for this might be the relatively low incidence of significant postoperative bleeding in our study cohort. In a recent multicentre study, Berger et al. examined the impact of clopidogrel on the postoperative period in a similar patient population, that is, those with acute coronary syndromes requiring coronary artery bypass surgery [25]. They found a 35% incidence of major bleeding in patients receiving clopidogrel. Although the definition of major bleeding used by Berger et al. was different from ours, the incidence of re-exploration for postoperative bleeding was similarly much higher (6.4% vs 1.7% in our study). Another reason for the differences between these two studies could be the multifactorial nature of postoperative haemorrhaging, which is also influenced by patient, surgeon and procedure-related factors [2].

In conclusion, results of the present prospective observational study suggest that maximal amplitude of TEG in response to the activation by ADP (parameter characterising the degree of depression of platelet function in response to clopidogrel therapy) may predict significant postoperative bleeding in patients receiving perioperative therapy with this drug. Whether specific treatment protocol based on this point-of-care method of quantification of platelet dysfunction could lead to an improved clinical outcome remains to be shown in a randomised controlled trial. No correlation was found between the depression of thromboxane receptor by aspirin and postoperative bleeding tendencies. In our study, a subpopulation of patients on recent anti-platelet therapy undergoing coronary artery surgery demonstrated a relatively high incidence of unresponsiveness to this treatment.

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## Appendix A. Conference discussion

**Dr J. Pepper (London, United Kingdom):** Obviously to be able to accurately predict excessive postoperative blood loss after coronary bypass surgery is very helpful. And the authors report 78% sensitivity and 84% specificity in patients receiving clopidogrel. We're moving into a new era of personalized anti-platelet treatment.

What surprised me though was the degree of drug resistance in your patients. The incidence of 85% clopidogrel resistance is very high. Recent papers by Wang and colleagues in the *European Heart Journal* in 2006, Snoep and colleagues in the *American Heart Journal* in 2007, and more recently Ang and colleagues in *JACC* in 2008, give resistant figures or treatment failure rates of 21%. And furthermore, the quoted aspirin resistance of 44% is also high compared to others. In a recent study in our own unit the figure was 23%.

So in your discussion of your manuscript you say the figures are in line with others, but the reference you give deals with general platelet activity in cardiac patients and not specifically drug resistance. So I'd just like to have an explanation for these rather high figures.

**Dr Preisman:** I think it's a question of selection of our patients. Patients who present for cardiac surgery were already treated by cardiologists. And we all know that after percutaneous coronary intervention, unresponsiveness to anti-platelet therapy predicts treatment failure. Cardiac surgery may be viewed as treatment failure actually, because most of our patients were urgent patients – 75% of urgent patients in our population.

So a patient who had coronary stenting and after that presents with acute coronary syndrome might be considered as treatment failure. So in this population we expect a high rate of resistance to anti-platelet therapy. That is my explanation. It might be right and wrong, I don't know.

**Dr Pepper:** I just wondered if others, maybe the chairmen, have similar experiences. It just seems to us very high in our experience.

**Dr R. Siebenmann (Zurich, Switzerland):** Have you any data about the individual observations of the surgeon during the operation? As we all know, we have some impression if it's bleeding more or less. I know this is not very scientific criteria, but sometimes it seems to work better than any test.

**Dr Preisman:** Yes. But we try to avoid things that we cannot quantify. We didn't try to ask surgeons for their impression during the operation. So I don't know, I can't say.

**Dr M. Grabenwoger (Vienna, Austria):** From the conclusions you have drawn and your high predictive failure of the measurement, in the daily routine in your hospital what are you doing now? What's your protocol?

**Dr Preisman:** Usually we map patients for response to clopidogrel before the operation. Now it is part of our routine.

**Dr Grabenwoger:** And when they are responders?

**Dr Preisman:** If they are responders, then we see the performed inhibition of platelet response to ADP, we prepare for dealing with coagulopathy. That means we have to get platelets in OR and use them. It means we know that probably we will have to use them after the operation.

**Dr Grabenwoger:** All right. You have to select a surgeon who is used to operating dry.