Preoperative platelet function predicts perioperative bleeding complications in ticagrelor-treated cardiac surgery patients: a prospective observational study

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Abstract

Background: Treatment with P2Y12 receptor antagonists increases the risk for perioperative bleeding, but there is individual variation in the antiplatelet effect and time to offset of this effect. We investigated whether preoperative platelet function predicts the risk of bleeding complications in ticagrelor-treated cardiac surgery patients.

Methods: Ninety patients with ticagrelor treatment within <5 days of surgery were included in a prospective observational study. Preoperative platelet aggregation was assessed with impedance aggregometry using adenosine diphosphate (ADP), arachidonic acid (AA), and thrombin receptor-activating peptide (TRAP) as initiators. Severe bleeding complications were registered using a new universal definition of perioperative bleeding. The accuracy of aggregability tests for predicting severe bleeding was assessed using receiver operating characteristic (ROC) curves, which also identified optimal cut-off values with respect to sensitivity and specificity, based on Youden’s index.

Results: The median time from the last ticagrelor dose to surgery was 35 (range 4–108) h. The accuracy of platelet function tests to predict severe bleeding was highest for ADP [area under the ROC curve 0.73 (95% confidence interval 0.63–0.84, P<0.001); TRAP 0.61 (0.49–0.74); AA 0.53 (0.40–0.66)]. The optimal cut-off for ADP-induced aggregation was 22 U. In subjects with ADP-induced aggregation below the cut-off value, 24/38 (61%) developed severe bleeding compared with 8/52 (14%) when aggregation was at or above the cut-off value (P<0.001). The positive and negative predictive values for this cut-off value were 63 and 85%, respectively.

Conclusions: Preoperative ADP-induced platelet aggregability predicts the risk for severe bleeding complications in ticagrelor-treated cardiac surgery patients.

Key words: acute coronary syndrome; blood platelets; cardiovascular surgery; haemorrhage; platelet function tests
Editor’s key points

- Dual antiplatelet therapy (DAPT) increases risk of bleeding in cardiac surgery, but there is significant individual variation.
- Platelet aggregation was used to predict risk of bleeding in an observational study of 90 subjects treated before surgery with ticagrelor and aspirin.
- Preoperative platelet function testing was able to predict severe bleeding with reasonable sensitivity and specificity in DAPT patients.

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid and a P2Y12 receptor antagonist reduces the risk of thrombotic events in patients with acute coronary syndrome (ACS), but increases the risk of perioperative bleeding complications if acute or urgent surgery is necessary. Current international guidelines recommend discontinuation of the P2Y12 inhibitors ticagrelor and clopidogrel at least 5 days before surgery and 7 days before surgery for prasugrel. However, a significant proportion (30–50%) of patients on DAPT who undergo coronary artery bypass grafting (CABG) are operated on after a shorter discontinuation time. The recommended discontinuation times are based on the pharmacodynamic and pharmacokinetic properties of the P2Y12 inhibitors and experience from CABG subgroups in randomized trials. However, there is individual variation in the magnitude and duration of the antiplatelet effect of the P2Y12 inhibitors. An individualized assessment based on platelet function immediately before operation might thus be preferable to time since discontinuation to predict the risk for bleeding complications. This approach is endorsed in the latest European revascularization guidelines, which state that platelet function testing should be used to guide antiplatelet therapy interruption, rather than arbitrary use of a specified period of delay in patients undergoing CABG surgery. However, this statement is based on limited data, as indicated by a C level of evidence. Evidence in support of this approach has so far been published only for thienopyridine-treated CABG patients; no data are available for patients treated with the new, more efficient platelet inhibitor, ticagrelor, which is preferred over clopidogrel for most ACS patients according to current guidelines in the USA and Europe.

We designed a prospective observational study to test the hypothesis that preoperative platelet function testing can be used to predict the risk for major bleeding complications in ticagrelor-treated cardiac surgery patients when ticagrelor is discontinued <5 days before surgery.

Methods

Subjects

Ninety cardiac surgery patients [mean age 68 (SD 9), range (46–82) yr, 80% men] with ACS treated with acetylsalicylic acid and ticagrelor were included in the study from October 2012 to April 2015. In all patients, ticagrelor was discontinued <5 days before surgery, but acetylsalicylic acid was not stopped. Subject characteristics are presented in Table 1. The decision to operate despite ongoing or recently discontinued ticagrelor treatment was made by a heart team, including a senior cardiac surgeon and a senior cardiologist, according to guidelines. All subjects apart from two underwent CABG. These two patients had ACS treated with acute coronary stenting but required subsequent urgent valve surgery because of mitral regurgitation. The study was approved by the regional research ethics committee and was performed in accordance with the 1975 Declaration of Helsinki after written informed consent.

Clinical management

Subjects were operated on according to our standard protocol with cardiopulmonary bypass. Before cannulation, heparin (350 IU kg−1) was given and supplemented as required to maintain an activated clotting time of >480 s. The standard uncoated extracorporeal circuit was primed with 1 litre of Ringer-acetate (Fresenius-Kabi, Uppsala, Sweden), 0.2 litre of mannitol (150 mg/ml) (Fresenius-Kabi) and 10 000 IU of heparin. Cardiopulmonary bypass was performed with a phosphorylcholine-coated hollow-fibre membrane oxygenator (Sorin INSPIRE; Sorin, Mirandola, Italy) using standard non-pulsatile cardiopulmonary bypass technique with normothermia or mild hypothermia. Haemocrit was kept >20%, and a standard blood flow of 2.4 litre min−1 m−2 was maintained. Cardioprotection was achieved with cold blood cardioplegia. After decannulation, heparin was neutralized with protamine sulphate (1 mg protamine per 100 IU heparin). All subjects received bolus doses of 2 g tranexamic acid both at induction of anaesthesia and after skin closure; aprotilin was not used.

Bleeding and transfusions

Postoperative bleeding volume was defined as the total amount of chest tube drainage during the first 12 h after surgery or until re-exploration for bleeding. After surgery, the decision to transfuse red blood cells (RBCs) was based on clinical and haemodynamic status or signs of low oxygen delivery with mixed venous saturation <55%, or both, according to our institutional guidelines. Haemoglobin <70 g litre−1 was an absolute indication for RBC transfusion; with ongoing significant bleeding, a haemoglobin of 100 g litre−1 was the aim. Plasma was transfused for ongoing significant bleeding (>200 ml h−1) and prolonged coagulation time on thromboelastometry, in the absence of signs of a sustained effect of heparin on thromboelastometry or activated clotting time. Platelets were transfused for ongoing significant bleeding (>200 ml h−1) and for low platelet count (<100×109 litre−1) or suspected platelet dysfunction (i.e. ongoing or recently stopped antiplatelet therapy), or both. Both platelet concentrates produced by apheresis from one donor and from buffy coats from four regular blood donors were used. The final decision to transfuse or not was always at the discretion of the responsible physician.

Bleeding complications were defined according to the universal definition of perioperative bleeding (UDPb) in adult cardiac surgery. Severe bleeding occurred when one or more of these six criteria were met: chest drain loss >1000 ml in the first 12 h after surgery; delayed sternal closure; need for surgical re-exploration because of bleeding or tamponade; use of recombinant factor VIIa; transfusion of ≥5 units of RBCs within 24 h of chest closure; or transfusion of ≥5 units of plasma within 24 h of chest closure.

Platelet function testing

Whole blood samples were collected immediately before surgery (after induction of anaesthesia) and analysed using Multiplate whole blood aggregometry (Roche Diagnostics, Risch-Rotkreuz, Switzerland).
The following tests were performed: (i) ADP-HS (high-sensitivity) test with adenosine diphosphate (ADP) to assess P2Y12-dependent platelet aggregation; (ii) ASPI test with arachidonic acid (AA) to assess cyclooxygenase-dependent platelet aggregation; and (iii) TRAP test with thrombin receptor-activating peptide-6 (TRAP-6) to assess protease-activated receptor 1-dependent platelet aggregation.

Single analyses from one test cell (with two electrode pairs) were performed. The mean value from the two pairs of electrodes was presented as the result from the analysis. The manufacturer’s normal range with hirudin-test tubes for ADP-HS test is 43–100 U, for ASPI test 71–115 U, and for TRAP test 84–128 U.

The findings of the preoperative platelet function tests were available to the surgical and anesthetic team, but the analysis was always performed after the decision to operate, and consequently, not used as a decision tool for timing of surgery. Only platelet function measurements performed before surgery were included in the study.

### Statistical analysis

Data are presented as the mean (so) for continuous normally distributed variables, the median (range) for continuous non-normally distributed variables, and as a number and percentage for categorical variables. Normality was tested with the Shapiro-Wilk test. Categorical variables were compared using Fisher’s exact test. Continuous variables were compared with Student’s unpaired t-test or the Mann-Whitney U-test where appropriate. A P-value <0.05 was considered statistically significant for all the tests applied. Data for a formal sample size calculation were not available when the study was started. The sample size (n = 90) was based on a similar study with clopidogrel, in which 87 patients were studied.

The accuracy of aggregability tests for predicting severe bleeding was explored using a receiver operating characteristic (ROC) curve, which yielded an area under the curve (AUC) with its accompanying 95% confidence interval (CI). Youden’s index, J = (sensitivity + specificity) − 1, was defined for all points on the ROC curve. The maximal Youden’s index value was used as a criterion for selecting the optimal cut-off point. Positive predictive value (PPV) and negative predictive value (NPV) were calculated according to standard methods. The association between the preoperative ADP test value and the probability of severe bleeding was explored with logistic regression analysis. Computer software was used for all statistical calculations (Prism 6.0, GraphPad Software Inc., La Jolla, CA, USA; SPSS Statistics 22.0, IBM Corp., Chicago, IL, USA).

### Results

#### General

The median time from the last dose of ticagrelor to the start of surgery was 35 h (4–108 h). In 15 subjects (17%), treatment was stopped <24 h before surgery. The reasons for not waiting at least 5 days after the last dose of ticagrelor before surgery were as follows: alarming angiography (n = 45), clinical deterioration...
(n=22), recent coronary stenting (n=14), rescue CABG after percutaneous coronary intervention (n=4), logistical reasons (n=3), and intake of ticagrelor by mistake (when it should have been discontinued; n=2).

### Preoperative platelet aggregation

Median preoperative values for ADP-, AA-, and TRAP-induced platelet aggregation are shown in Table 1. There was a weak correlation between the time since discontinuation of ticagrelor and ADP-induced platelet aggregation ($R^2=0.30$, $P<0.001$; Fig. 1).

#### Bleeding and transfusions

The median postoperative bleeding volume during the first 12 h was 510 (200–1970) ml. Sixty-four of the 90 subjects (71%) were transfused with RBCs (66%), plasma (40%), or platelets (48%). Median values for transfusion were as follows: 2 units of RBCs (range 0–18); 0 units of plasma (0–17); and 0 units of platelets (0–14). Eight subjects (8.9%) underwent surgical re-exploration because of bleeding or tamponade. Severe bleeding according to the UDPB criteria occurred in 32 of the 90 subjects (36%).

#### Association between platelet function and bleeding complications

Subjects with severe bleeding according to the UDPB classification had a significantly lower preoperative ADP-induced platelet aggregation capacity compared with non-bleeders [17 (0–104) vs 32 (3–139) U, $P<0.001$; Table 1]. There was no significant difference between AA- and TRAP-induced aggregation in subjects with or without severe bleeding (Table 1). The accuracy of platelet function tests to predict severe bleeding was examined with ROC analyses. The AUC for ADP-induced aggregation was 0.73 (95% CI 0.63–0.84), $P<0.001$ (Fig. 2). The accuracy of TRAP- and AA-induced platelet aggregation to predict bleeding was markedly lower [TRAP AUC 0.61 (95% CI 0.49–0.74), AA AUC 0.53 (95% CI 0.40–0.66)].

Optimal cut-off values, sensitivity, specificity, and positive and negative predictive values are presented in Table 2. The optimal cut-off value for ADP-dependent aggregation was 22 U. Twenty-four of 38 (63%) subjects with ADP-induced aggregation below the cut-off value developed severe bleeding compared with 8/52 (15%) if the ADP aggregation was at or above the cut-off value ($P<0.001$; Fig. 3).

Subjects with ADP-induced aggregation below the cut-off (<22U) had a significantly shorter median time since discontinuation [24 (4–105) vs 72 (7–108) h, $P<0.001$], greater median postoperative bleeding time [660 (205–1970) vs 470 (470–1850) min (12 h)$^{-1}$, $P=0.004$], higher incidence of re-exploration for bleeding (16 vs 3.8%, $P=0.066$), and were more likely to receive RBCs (76 vs 58%, $P=0.076$), plasma (66 vs 21%, $P<0.001$), and platelets (76 vs 27%, $P<0.001$). The median transfused volume of RBCs [4.5 (0–18) vs 2 (0–14) units, $P=0.001$], plasma [2 (0–17) vs 0 (0–9) units, $P<0.001$] and platelets [2 (0–14) vs 0 (0–9) units, $P<0.001$] was higher in subjects with ADP-induced aggregation below the cut-off value. Median closure time (time from weaning off bypass to skin closure) was 88 (25–938) min in subjects with ADP-induced aggregation <22U, compared with 52 (26–200) min in subjects with ADP ≥22 U ($P<0.001$).

Figure 4 shows a univariate logistic regression analysis predicting the risk for severe bleeding complications in relation to

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**Table 2** Diagnostic properties of different preoperative platelet function tests. *Cut-off is the maximal Youden’s index value derived from the ROC curve. ADP, adenosine diphosphate; AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; TRAP, thrombin receptor-activating peptide

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<th>Specificity (%)</th>
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**Fig 1** Scatter plot of preoperative adenosine diphosphate (ADP)-induced aggregation and time since last dose of ticagrelor in ticagrelor-treated subjects. There was a linear correlation between the tested variables ($R^2=0.30$, $P<0.001$).

**Fig 2** Receiver operating characteristic curve for the precision of adenosine diphosphate (ADP)-induced aggregation to predict severe bleeding. The cut-off value (22U) had a sensitivity of 76% and a specificity of 75%.

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*Figures and Tables are from the original publication.*
platelet transfusion had a median preoperative ADP-dependent aggregation of 16 (range 0–72 U), with only one subject within the normal range (43–100 U). There was a trend towards lower ADP-induced aggregation in subjects with extreme bleeding compared with subjects with moderate bleeding [5–9 units; median 20 (0–84) U or low amounts of transfusions [0–4 units; median 39 (7–139) U].

Extreme bleeding

Twelve subjects with extreme bleeding (defined as transfusion of ≥10 units of RBCs, plasma, or platelets within 24 h of surgery) had a median ADP-induced aggregation of 16 (range 0–72 U), with only one subject within the normal range (43–100 U). There was a trend towards lower ADP-induced aggregation in subjects with extreme bleeding compared with subjects with moderate bleeding (P=0.006).

Discussion

The main finding of this study is that the preoperative ADP-induced platelet aggregation capacity predicted the risk for perioperative bleeding complications in cardiac surgery patients treated with ticagrelor ≤5 days before surgery.

Severe perioperative bleeding is associated with markedly increased mortality and morbidity after cardiac surgery. In a recent study (using the same bleeding definition as in the present study), the adjusted mortality risk was five- to eight-fold higher in patients with severe bleeding than in patients with insignificant or mild bleeding. The risk for bleeding complications is higher if treatment with a P2Y12 inhibitor is continued until operation or stopped shortly before. Thus, it is important when evaluating ACS patients on DAPT who need acute or subacute surgery to weigh the risk for bleeding complications against the risk of adverse ischaemic events if surgery is postponed.

The time required for recovery of platelet function is shorter after discontinuation of ticagrelor compared with clopidogrel. In the present study, a median ADP-dependent aggregation of 29 U was observed after a median discontinuation time of 35 h. This aggregation level is ~65% of the lower normal limit (44 U) and corresponds reasonably well to the approximate recovery to 50% of normal platelet function level observed 35 h after discontinuation in a previous study. Despite this seemingly predictable recovery after discontinuation, there is considerable variation in the speed of recovery in individual patients. The variation in offset of effect of ticagrelor is illustrated by the low goodness of fit between the time since discontinuation and ADP-dependent aggregation (Fig. 1). Some patients with a short time since discontinuation had high platelet aggregation and vice versa.

We observed that the accuracy of ADP-induced platelet aggregation immediately before cardiac surgery as a measure to predict risk for severe bleeding in patients with ticagrelor treatment ≤5 days before surgery was acceptable, but not perfect (AUC under the ROC curve 0.73, PPV 63%, and NPV 85%), underlining the multifactorial nature of perioperative bleeding complications. Our study confirms previous observations, mostly in clopidogrel-treated patients, of the value of preoperative assessment of platelet function and extends these earlier findings to patients treated with the more potent P2Y12 inhibitor, ticagrelor. The ability of platelet function tests to predict bleeding complications in ticagrelor-treated patients was in fact better than that previously reported in thienopyridine-treated patients.

A recent report by Ranucci and colleagues provided evidence for an association between preoperative platelet function and bleeding complications in patients with ongoing or recently halted treatment with clopidogrel, ticlopidine, or prasugrel, and identified the same optimal cut-off value (22 U) for ADP-dependent

![Fig 3 The distribution of the preoperative adenosine diphosphate (ADP)-induced aggregation values. The upper portion of the figure shows a scatter plot of the ADP-induced aggregation of the subjects with severe bleeding. The normal range of ADP-induced aggregation (43–100 U) is marked by a green background.](https://academic.oup.com/bja/article-abstract/117/3/309/2576174)

![Fig 4 Probability of severe bleeding in relation to the preoperative adenosine diphosphate (ADP)-induced aggregation. The grey area represents the 95% confidence interval.](https://academic.oup.com/bja/article-abstract/117/3/309/2576174)

preoperative value of ADP-induced platelet aggregation. Low preoperative ADP-induced aggregation was associated with a markedly increased risk of bleeding.

Large platelet transfusion

The UDPB criteria do not consider the use of platelet transfusion. As expected, there was a close correlation between severe bleeding and a large number of platelet transfusions. Fifteen of 90 subjects (17%) received ≥5 platelet units. Of these, all but one fulfilled the UDPB criteria for severe bleeding. Subjects with >5 units of platelet transfusion had a median preoperative ADP-dependent aggregation of 14 (0–72) U, compared with 37 (0–139) U in subjects with <5 units of platelet transfusion (P=0.006).
aggregability as in our study. However, there are important differences in the results of the two studies. Our study reported a greater area under the ROC curve for ADP-dependent aggregation (0.73 vs 0.62), a higher PPV (63 vs 20%), and a lower NPV (85 vs 94%). These disparities may be explained by differences in the study populations. All patients in the present study were treated with ticagrelor, and platelet testing was performed immediately before surgery. Furthermore, the mean time since discontinuation was markedly shorter (2 vs 4 days), mean ADP-dependent aggregation was lower (36 vs 49 U), and bleeding complications were more common (36 vs 7.5%). The higher incidence of bleeding complications can be explained by the more efficient platelet inhibition of ticagrelor and the shorter time since discontinuation; however, the lower responsiveness to platelet transfusion with ticagrelor compared with clopidogrel may also contribute.

As a result of individual variation in recovery of platelet function after discontinuation of P2Y₁₂ inhibitors, use of platelet function tests instead of time since discontinuation may help to optimize the timing of surgical procedures. However, platelet function tests could also be of value to establish the grade of platelet inhibition in patients in whom the time since discontinuation is unclear, such as unconscious or confused patients, and in patients with uncertain compliance to the treatment.

The present study has important limitations. Impedance aggregometry is dependent on platelet count, and concentrations <100\times10^9 \text{ litre}^{-1} can yield results that do not represent true platelet function. However, in the present study all patients had platelet count >100 (range 123–406)\times10^9 \text{ litre}^{-1} at the time of aggregometry. The limited sample size results in larger uncertainties around the estimates. The study was not blinded; therefore, knowledge of both the time since the last dose of ticagrelor and of the preoperative impedance aggregometry results might have influenced clinical handling, including surgical management and postoperative complications, especially regarding platelet transfusions. Furthermore, we used Youden’s index to define the optimal cut-off value. A limitation of this method is that a false negative (i.e. falsely predicted non-bleeder) and false positive (i.e. falsely predicted severe bleeder) are attributed the same statistical weight. In clinical practice, a false-negative value may confer greater risk in the management of patients, and a higher cut-off value may thus be considered. Finally, the results and conclusions of the present study are applicable only to the study population (i.e. ACS patients with ticagrelor treatment within 5 days before CABG). In other populations, other factor(s) may be as, or even more, important to predict bleeding complications.

In conclusion, we demonstrate that use of platelet function tests can predict severe bleeding complications in ticagrelor-treated cardiac surgery patients. In non-urgent conditions, surgery can be postponed until tests are satisfactory. In acute conditions, poor platelet function may motivate early use of pro-haemostatic drugs or blood products.

**Authors’ contributions**

Study supervision: AJ.
Study design: C.J.M., E.C.H., C.S.H., AJ.
Data interpretation: J.Å., C.H., AJ., C.J.M.
Writing of manuscript: C.J.M.

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**Declaration of interest**

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