

Cite this article as: Kremke M, Gissel MS, Jensen MJ, Thomassen SA, Jakobsen C-J. The association between a three-day ticagrelor discontinuation and perioperative bleeding complications. Eur J Cardiothorac Surg 2018; doi:10.1093/ejcts/ezy355.

The association between a three-day ticagrelor discontinuation and perioperative bleeding complications

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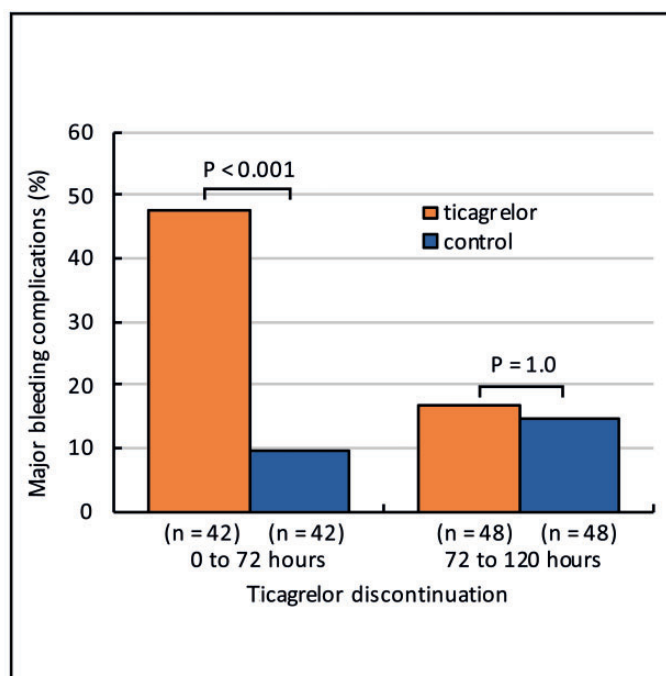
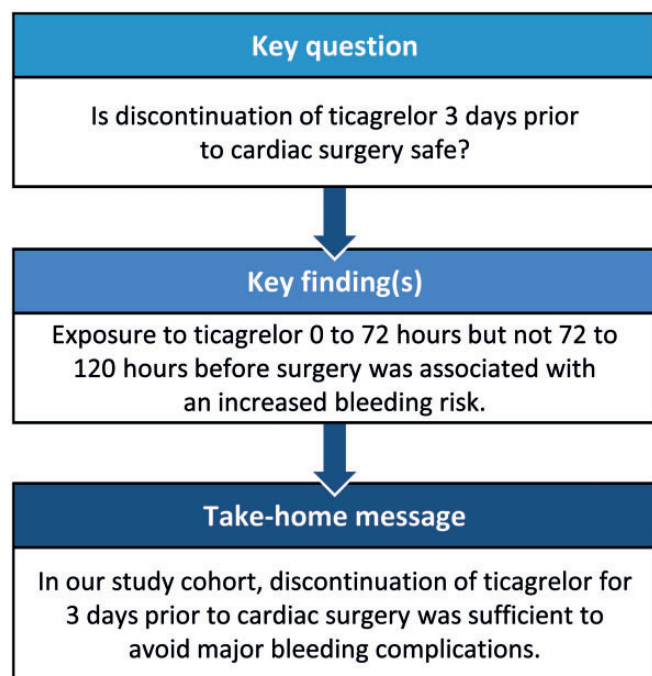
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Received 5 May 2018; received in revised form 17 August 2018; accepted 20 September 2018



Abstract

OBJECTIVES: Dual antiplatelet therapy at the time of cardiac surgery is associated with excessive perioperative bleeding. International guidelines, therefore, recommended discontinuing oral adenosine diphosphate receptor antagonists prior to non-emergency surgery. In this study, we analysed whether a 3-day ticagrelor discontinuation was sufficient to avoid major bleeding complications.

METHODS: This study is a retrospective cohort analysis of 3377 patients undergoing coronary artery bypass or single-valve surgery from January 2013 to September 2017. Patients exposed to ticagrelor prior to surgery were compared with control patients exposed to aspirin only. Outcome measures included transfusion requirements, bleeding volumes, the need for re-exploration and the composite outcome major bleeding complication. Data were retrieved from the the Western Denmark Heart Registry.

RESULTS: During the study period, 101 patients were preoperatively exposed to ticagrelor, whereas 3276 patients were exposed to aspirin only. Propensity-score matching resulted in 90 pairs of patients. Overall, ticagrelor exposure was associated with a greater risk of major

bleeding complications compared with control patients [31 vs 12%, relative risk 2.6, 95% confidence interval (CI) 1.4–4.8]. While ticagrelor exposure within 0–72 h before surgery ($n = 42$) was associated with a substantially increased risk of major bleeding complications (48 vs 10%, relative risk 5.0, 95% CI 1.9–13.4), ticagrelor exposure 72–120 h before surgery ($n = 48$) showed no statistically significant association (17 vs 15%, relative risk 1.1, 95% CI 0.4–2.9).

CONCLUSIONS: In our historical cohort, ticagrelor exposure 0–72 h prior to cardiac surgery was associated with an increased risk of major bleeding complications. On the other hand, ticagrelor exposure 72–120 h prior to surgery was not associated with a clinically relevant increase in major bleeding complications.

Keywords: Bleeding • Blood transfusion • Coronary artery bypass grafting • Dual antiplatelet therapy • Ticagrelor

INTRODUCTION

After acute coronary syndrome (ACS) or stent implantation, dual antiplatelet therapy with aspirin and an oral adenosine diphosphate (ADP) receptor antagonist can prevent the occurrence of new ischaemic events [1–3]. However, ongoing dual antiplatelet therapy at the time of cardiac surgery is associated with an increased bleeding risk [4].

Ticagrelor, a direct-acting and reversible ADP receptor antagonist, was introduced in Denmark in 2013 and is now the most commonly used ADP receptor antagonist in the treatment of ACS. Compared to its predecessor clopidogrel, the pharmacokinetic profile of ticagrelor is more predictable, demonstrating a faster onset of action and a more consistent platelet inhibition [5].

Until recently, international guidelines have recommended the discontinuation of both clopidogrel and ticagrelor 5 days prior to non-emergency cardiac surgery [6, 7]. However, pharmacological and clinical studies have suggested that platelet function recovery after ticagrelor discontinuation was faster as compared to clopidogrel, resulting in acceptable platelet function 3 days after ticagrelor discontinuation [5, 8–11]. As a consequence, the European Society of Cardiology, the European Association for Cardio-Thoracic Surgery and the European Association of Cardiothoracic Anaesthesiology recently updated their guidelines and now recommend to discontinue ticagrelor at least 3 days prior to non-emergency cardiac surgery [12–14].

Platelet function recovery after ticagrelor discontinuation, however, is subject to marked individual variability, and one-fourth of all patients still have significantly impaired platelet function 72 h after ticagrelor discontinuation [5, 9].

The objective of this analysis was to describe the relationship between the time of ticagrelor discontinuation and the risk of perioperative bleeding complications. We hypothesized that a 72-h ticagrelor discontinuation was sufficient to avoid excessive perioperative bleeding in the majority of patients.

METHODS

Study design and patients

This retrospective cohort study included patients from January 2013 to September 2017. Three cardiothoracic centres (Aalborg, Aarhus and Odense University Hospital) participated in the analysis. These hospitals cover the Western Denmark region, comprising about half of the total Danish population.

Patients exposed to ticagrelor within 5 days prior to surgery were identified and compared with matched control patients exposed to aspirin only (Fig. 1). Eligible procedures were coronary artery bypass grafting (CABG) surgery (on-pump or

off-pump), aortic valve replacement, mitral valve repair/replacement or a combination of CABG with single-valve repair/replacement. Patients not exposed to antiplatelet agents within 5 days prior to cardiac surgery and patients treated with platelet inhibitors other than ticagrelor and aspirin (e.g. clopidogrel and glycoprotein IIb/IIIa inhibitors) were not eligible. Subjects with missing data on key baseline covariates were excluded, as were patients with a serum creatinine level above 200 $\mu\text{mol/l}$.

Study patients and procedures were identified in the Western Denmark Heart Registry, a web-based clinical registry, which gathers detailed information of all patients undergoing cardiac surgery at the participating hospitals [15]. Patients and procedures were primarily characterized using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) variables [16]. The time from ticagrelor discontinuation to surgery was determined from patient records and electronic drug charts. Access to these documents was granted by the Danish Patient Safety Authority (number 3-3013-1991/1). The study was approved by the regional Data Safety Authority (number 1-16-02-636-16).

End points

Outcome measures were perioperative transfusion requirements, postoperative bleeding volumes and re-exploration for bleeding or cardiac tamponade. These outcomes were determined from the Western Denmark Heart Registry.

Perioperative transfusion requirements were reported in millilitres and measured from the beginning of the primary operation until discharge from the intensive care unit. Postoperative bleeding volumes were defined as overall mediastinal and pleural chest tube drainage volumes until chest tube removal or discharge from the intensive care unit, depending on which occurred first. Re-exploration for bleeding, cardiac tamponade and cardiac ischaemia were uniquely coded in the Western Denmark Heart Registry.

Major bleeding complication was a composite outcome, defined as the occurrence of at least one of the following dichotomous outcomes: the intraoperative transfusion of more than 1000 ml red blood cells, a postoperative bleeding volume greater than 2000 ml or the need for re-exploration for bleeding or cardiac tamponade.

Perioperative management

Patients were treated in accordance with local hospital guidelines. Treatment with ticagrelor was typically initiated with an oral 180-mg loading dose followed by a 90-mg maintenance dose twice daily. According to previous international guidelines, cardiac surgeons aimed to discontinue ticagrelor 5 days prior to

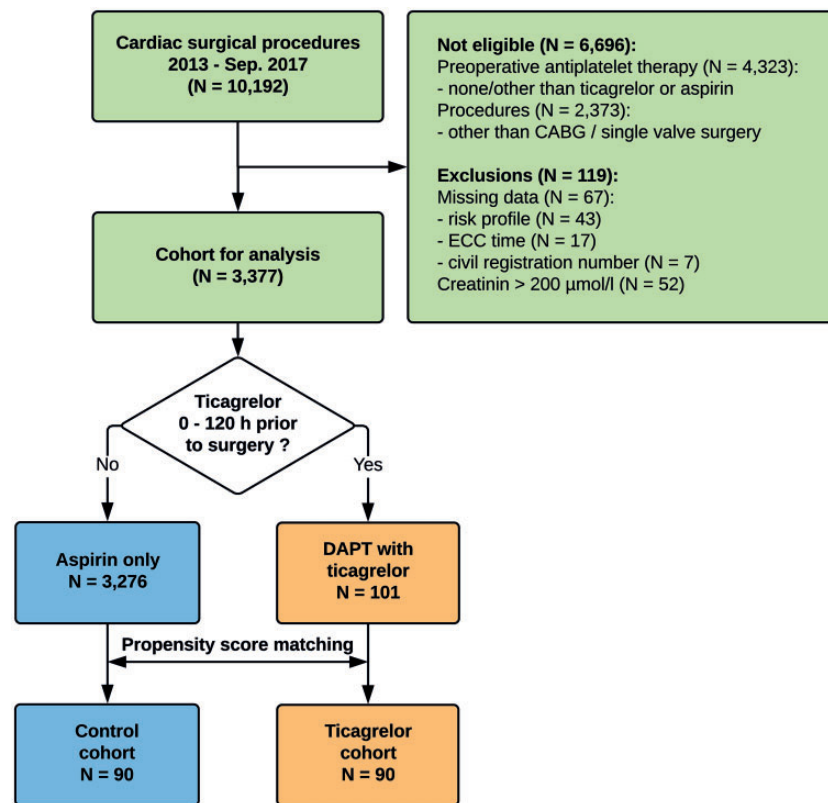


Figure 1: The study design and cohort allocation. CABG: coronary artery bypass grafting; DAPT: dual antiplatelet therapy; ECC: extracorporeal circulation.

surgery, if clinically feasible. Patients with stable coronary artery disease were usually treated with low-dose (75 mg) aspirin monotherapy once daily. Prior to CABG surgery, treatment with aspirin was usually not discontinued. Prior to elective cardiac surgery other than CABG, patients were advised to discontinue aspirin 5 days preoperatively. Oral vitamin K-antagonists, i.e. warfarin, were usually discontinued 2 days prior to surgery. Fondaparinux and a low-molecular-weight heparin were typically withheld 12 h before surgery.

Routine surgical and cardioprotective techniques were used. Most patients were maintained normothermic or mildly hypothermic during cardiopulmonary bypass. The majority of patients received either tranexamic acid or, less frequently, aprotinin as part of a blood conservation strategy. Autotransfusion systems designed for blood salvage (Cell Saver®) were available at all centres.

Transfusions of allogeneic blood components were given at the discretion of the attending anaesthesiologist or surgeon. The decision for transfusion was based on clinical assessment of the patient and supported by laboratory results. A standardized transfusion protocol existed at one of the participating centres. Haemoglobin thresholds for the transfusion of red blood cells varied and ranged from 7.5 to 9.0 g/dl. All centres had access to thromboelastometry (ROTEM®) measurements and platelet function tests (Multiplate® or VerifyNow®).

Statistical analysis

Continuous data from non-Gaussian distribution were described as sample median with respective 25th and 75th percentiles and

compared with the Wilcoxon signed-rank test. Categorical, dichotomous variables were reported as counts and percentages. They were compared using the McNemar's test. Relative risks (RRs) and the respective 95% confidence intervals (CIs) were calculated according to Altman. A *P*-value <0.05 was considered to be statistically significant. Statistical analyses were performed using the MedCalc Statistical Software version 13.2.0 (MedCalc Software, Ostend, Belgium).

Ticagrelor treatment was not randomly assigned in the study population. Therefore, we used propensity score matching to reduce the risk of bias due to confounding. A propensity score is a single score that represents the probability of receiving a treatment, conditional on a set of covariates. The included covariates were thought to be related to both preoperative ticagrelor exposure and perioperative bleeding. The aim of creating a propensity score was to balance these covariates between patients in the ticagrelor and the control cohort. We aimed to match each patient preoperatively exposed to ticagrelor with one control patient with a similar propensity score [17, 18].

The propensity score was computed using multivariable logistic regression. The included covariates were sex, age, history of insulin-dependent diabetes, chronic obstructive pulmonary disease, peripheral artery disease, preoperative central nervous disease, previous cardiac surgery, critical preoperative state, unstable angina, reduced left ventricular function, recent myocardial infarction, acute surgery (all values above EuroSCORE criteria), surgery type (CABG, aortic valve or mitral valve surgery), extracorporeal circulation time (off pump, ≤120 min, 121–180 min, >180 min) and perioperative aprotinin use. We performed a one-to-one pair matching without replacement. We aimed to match each patient in the ticagrelor cohort with a

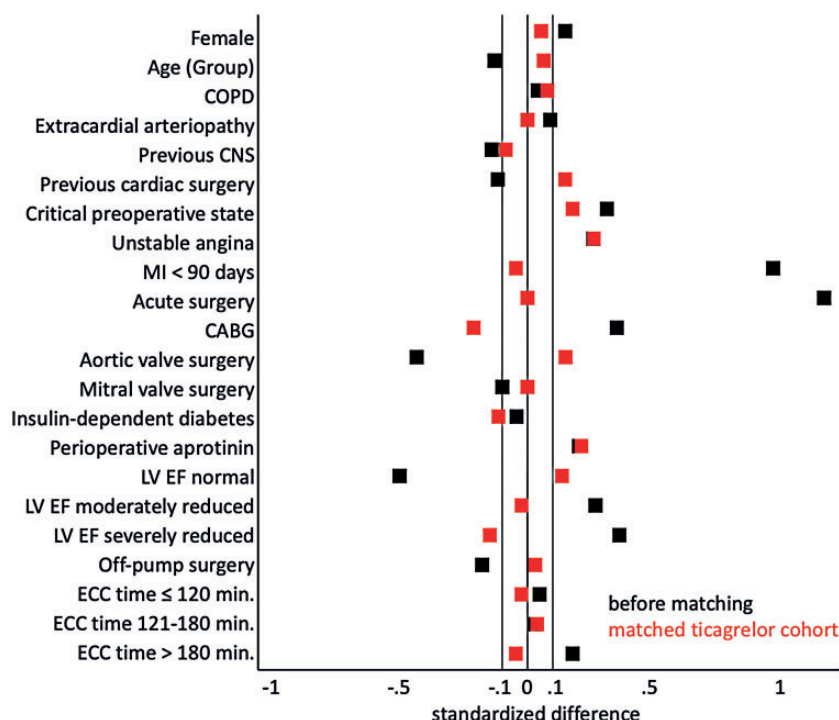


Figure 2: Standardized differences in all matching criteria, the ticagrelor cohort versus the control cohort, before and after propensity score matching. The included covariates were EuroSCORE I and II criteria. CABG: coronary artery bypass grafting; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; ECC: extracorporeal circulation; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

control patient with the nearest propensity score and with an absolute caliper width of 0.025 on the propensity score. Propensity score matching was done using the statistical software package Stata® 14.0 (StataCorp LP, TX, USA).

RESULTS

During the study period, 3377 patients were exposed to ticagrelor or aspirin within 5 days prior to CABG, single-valve surgery or a combination of CABG and single-valve surgery. While the majority ($n=3276$) had been treated with aspirin only, 101 patients had been exposed to dual antiplatelet therapy with ticagrelor and aspirin.

Before matching, there were considerable baseline differences between the 2 cohorts (Fig. 2, [Supplementary Material, Table S1](#)). Patients exposed to ticagrelor were more often in a critical post-operative state, had an increased rate of recent myocardial infarction or unstable angina pectoris and presented more frequently with a severely reduced left ventricular function. Additionally, ticagrelor-exposed patients more often underwent acute and urgent CABG surgery, had a lower rate of off-pump surgery and longer cardiopulmonary bypass times. Likewise, they were more frequently treated with the antifibrinolytic aprotinin. Extracardiac comorbidities, such as insulin-dependent diabetes mellitus or chronic lung disease, were evenly balanced in both cohorts.

Propensity score matching resulted in 90 pairs of patients. After matching, most covariates were reasonably balanced (Fig. 2, [Supplementary Material, Table S1](#)).

The majority of patients in the ticagrelor cohort ($n=85$) underwent isolated CABG, 14 of whom underwent off-pump CABG. Three patients underwent a combination of CABG with valve

surgery and 2 patients underwent isolated valve surgery. Approximately one-third of all operations ($n=33$) were performed at day 4 (72–96 h) after ticagrelor discontinuation ([Supplementary Material, Fig. S1](#)).

Overall, perioperative transfusion requirements were greater in the ticagrelor than in the control cohort (Table 1). More patients received red blood cells, plasma and platelet concentrates and the volumes of plasma and platelet concentrates given to transfused patients were greater in the ticagrelor cohort. However, we could not demonstrate a statistically significant difference in bleeding volumes between the 2 cohorts.

The risk of re-exploration for bleeding or cardiac tamponade was greater in the ticagrelor cohort (Table 1). In the subgroup of patients who had discontinued ticagrelor less than 72 h before surgery ($n=42$), we observed a substantially increased risk of re-exploration compared to the respective control patients (29 vs 5%, RR 6.0, 95% CI 1.4–25.2; Fig. 3). However, when ticagrelor was discontinued 72–120 h before surgery ($n=48$), the risk of re-exploration was not increased (10 vs 10%, RR 1.0, 95% CI 0.3–3.2).

The risk of major bleeding complications was greater in the ticagrelor cohort than in the control cohort (31 vs 12%, RR 2.6, 95% CI 1.4–4.8). This effect was driven by a markedly increased risk of major bleeding complications in patients who had discontinued ticagrelor less than 72 h before surgery (48 vs 10%, RR 5.0, 95% CI 1.9–13.4; Fig. 3). However, we could not demonstrate a statistically significant increased risk of major bleeding complications in the study patients exposed to ticagrelor within 72–120 h before cardiac surgery (17 vs 15%, RR 1.1, 95% CI 0.4–2.9).

The greater risk of major bleeding complications in the ticagrelor cohort was not, however, accompanied by an increased 30-day mortality or a greater need for postoperative dialysis (Table 1).

Table 1: Perioperative bleeding complications in the ticagrelor cohort and control cohort

Outcomes	Ticagrelor cohort (n = 90)	Control cohort (n = 90)	P-values
Patients transfused, ^a n (%)			
Red blood cells	35 (39)	18 (20)	0.006
Plasma	29 (32)	12 (13)	0.003
Platelets	44 (49)	12 (13)	<0.001
Transfusion volume ^b (ml), median (IQR)			
Red blood cells	784 (455–1500)	600 (300–1200)	0.38
Plasma	1200 (600–2167)	600 (572–750)	0.007
Platelets	900 (600–1800)	300 (300–384)	<0.001
Bleeding volume (ml), median (IQR)	503 (300–1300)	510 (348–881)	0.69
Re-exploration, n (%)			
For bleeding	15 (17)	7 (8)	0.070
For tamponade	4 (4)	1 (1)	0.18
Overall, n (%)	17 (19)	7 (8)	0.029
New need for dialysis, n (%)	1 (1)	3 (3)	0.31
30-Day mortality, n (%)	0 (0)	2 (2)	0.16

^aPatients who received at least 1 unit of red blood cell concentrate, fresh frozen plasma or platelet concentrate during surgery or until discharge from the intensive care unit.

^bTransfusion requirements of patients who had received at least 1 unit of red blood cells, plasma or platelets.

IQR: interquartile range.

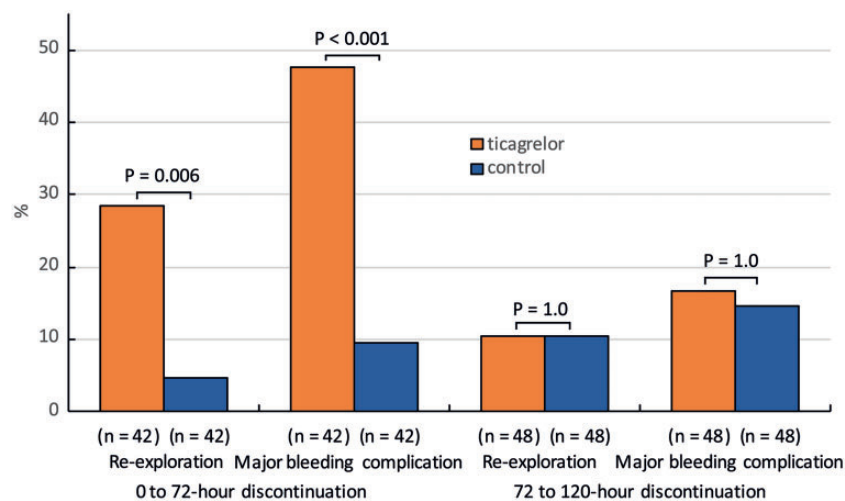


Figure 3: Re-exploration for bleeding or cardiac tamponade and major bleeding complications in the ticagrelor and control cohorts. Patients in the ticagrelor cohort were stratified by the time of ticagrelor discontinuation and compared with their respective control patients. Statistics: McNemar's test.

DISCUSSION

The main finding of this analysis was that exposure to ticagrelor less than 72 h prior to cardiac surgery was associated with a substantially increased risk of major bleeding complications. However, we could not demonstrate a statistically significant increased risk of major bleeding complications in the study patients exposed to ticagrelor 72–120 h before cardiac surgery. This finding suggests that most study patients had regained sufficient platelet function 72 h after ticagrelor discontinuation.

Previous analyses that described the relationship between the time of ticagrelor discontinuation and bleeding-related complications have yielded similar results.

In the ONSET/OFFSET study, Gurbel *et al.* [5] used platelet aggregometry to compare the onset and offset of platelet

inhibition in ticagrelor- or clopidogrel-treated patients. The authors showed that platelet function recovered faster after ticagrelor withdrawal compared with clopidogrel. Despite ticagrelor's stronger platelet inhibition during maintenance therapy, residual platelet inhibition was similar in the ticagrelor and the clopidogrel group 24 h after drug withdrawal. Residual platelet inhibition at 3 days after ticagrelor discontinuation was less than in the clopidogrel group yet comparable to platelet inhibition 5 days after clopidogrel withdrawal. However, the ONSET/OFFSET study did not address whether impaired platelet function tests were associated with a clinically significant bleeding risk.

In a nationwide Swedish study, Hansson *et al.* [8] analysed bleeding risks in 2244 ACS patients treated with either ticagrelor or clopidogrel prior to CABG. The authors demonstrated the greatest incidence of major bleeding in the subgroup of patients

who had discontinued ticagrelor less than 24 h before surgery, a finding consistent with ticagrelor's more potent antiplatelet effect during maintenance therapy.

When both study drugs were discontinued less than 5 days prior to surgery, however, the overall incidence of major bleeding was less in ticagrelor-treated patients, an effect mainly driven by a low risk of major bleeding in patients who had discontinued ticagrelor 3–5 days prior to surgery. The bleeding risk in these patients was not different from patients who had discontinued ticagrelor 5 days or longer, indicating a low level of residual platelet inhibition 3 days after ticagrelor discontinuation. The authors concluded that CABG surgery 3 days after ticagrelor discontinuation posed no risk of increased bleeding.

In a later pharmacological study, however, Hansson *et al.* [9] yielded different results. Using ADP-induced aggregometry to assess platelet function recovery after ticagrelor withdrawal, the authors found rapid platelet function recovery after ticagrelor discontinuation. The mean ADP-induced aggregation at 72 h after ticagrelor discontinuation was 38 U and thereby clearly above the suggested cut-off level for the risk of major bleeding (22 U), demonstrating a sufficient platelet function recovery in most patients. There was, however, a marked individual variability. Although half of the study patients reached the suggested cut-off level for the risk of major bleeding at 48 h after ticagrelor withdrawal, one-fourth of patients still remained below that cut-off level even at 72 and 96 h after ticagrelor withdrawal. Hansson *et al.* concluded that a substantial number of patients were at an increased risk of bleeding even 72–120 h after ticagrelor withdrawal, a finding that we could not reproduce with our analysis.

Overall, a comparatively small fraction of patients in our historical cohort underwent cardiac surgery within 5 days after ticagrelor exposure. We assume that cardiac surgeons at our institutions, in accordance with the international revascularization guidelines, aimed to postpone non-emergency cardiac surgery in patients exposed to ticagrelor. The peak of performed procedures at day 4 after ticagrelor discontinuation suggests that cardiac surgeons regarded a 72-h ticagrelor discontinuation as a reasonable compromise between bleeding and ischaemic risks in many patients (Supplementary Material, Fig. S1).

Currently, limited treatment options for ticagrelor-exposed patients requiring emergency cardiac surgery are available. Many anaesthesiologists and surgeons tend to administer platelet concentrates to prevent or treat perioperative bleeding, although platelet transfusions have shown no or minimal ability to reverse platelet inhibition in healthy volunteers exposed to clopidogrel or ticagrelor [19]. We could demonstrate that patients in the ticagrelor cohort received more platelet concentrates than the control patients, although it remained unclear whether platelets were administered prophylactically or to actively bleeding patients.

Although transfusion requirements were greater in the ticagrelor cohort, we could not demonstrate an increased 30-day mortality compared to the control patients. Previous analyses, however, demonstrated an association between perioperative blood transfusion and greater mortality after cardiac surgery [20–21].

In the future, new treatment options may become available. Recently, a group of researchers has developed an antibody against ticagrelor, reversing ticagrelor's potent antiplatelet effect [22]. The introduction of this antibody in clinical practice could lead to a profound change of treatment strategies in ACS patients requiring urgent or emergency cardiac surgery.

Limitations

Our study has several limitations. First, although the study period extended over several years, we were only able to identify a limited number of patients who were preoperatively exposed to ticagrelor. Because of the small sample size, the resulting CIs were relatively wide. Therefore, it is difficult to draw more general conclusions about the bleeding risk associated with ticagrelor. In our historical cohort, patients exposed to ticagrelor within 72–120 h prior to cardiac surgery were not at an increased risk of major bleeding complications compared to the control patients. This finding cannot, however, exclude an increased bleeding risk in the general population of patients.

Second, although ticagrelor and control cohort were matched on propensity scores, differences in certain baseline covariates remained due to the small sample size. An exact balance requires a large sample, even in randomized controlled trials.

Third, observational analyses of registry data may be prone to bias introduced by unmeasured confounders and depend, to a large extent, on the validity of the registry data. The quality of the Western Denmark Heart Registry data has, however, been demonstrated in a recent analysis [13].

Finally, our definition of major perioperative bleeding, which was in some aspects similar to previous definitions, was somewhat arbitrary, and a standardized transfusion protocol was lacking at two of the participating centres. This makes comparisons with other studies difficult.

However, our study also has strengths. It is a real-life analysis that directly compared ticagrelor-exposed patients with matched-control patients not exposed to ticagrelor, whereas most previous analyses were pharmacological studies or analyses that compared ticagrelor with other ADP-receptor antagonists. The observed bleedings risks are, therefore, most likely attributable to ticagrelor exposure itself and not to the confounding factors.

CONCLUSION

In our historical cohort, the risk of major bleeding complications was substantially increased when ticagrelor was discontinued 0–72 h before cardiac surgery. We could not, on the other hand, demonstrate an increased bleeding risk in the study patients exposed to ticagrelor 72–120 h before surgery. Our results support the recently revised recommendations of the European Society of Cardiology and of the European Association for Cardio-Thoracic Surgery to discontinue ticagrelor at least 3 days before non-emergency cardiac surgery.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

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