

Coronary artery bypass grafting on clopidogrel or ticagrelor therapy: interval of discontinuation and risk of bleeding



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Abstract

Aim: To evaluate retrospectively the impact of ticagrelor or clopidogrel in patients taking dual antiplatelet aggregation therapy (DAPT, ASA + clopidogrel or ticagrelor) undergoing coronary artery bypass grafting (CABG) on postoperative bleeding complications and need for mediastinal surgical re-exploration, focusing on the interval of discontinuation of DAPT.

Material and methods: From January 2017 to January 2018, 190 patients underwent coronary artery bypass grafting with DAPT discontinuation 5 days (group 1, $n = 82$), 2–4 days (group 2, $n = 84$), or 0–1 days (group 3, $n = 24$) prior to CABG.

Results: As compared to group 1, blood loss from chest tube drainages at 24 hours was significantly higher in groups 2 and 3 (480 ± 238 vs. 512 ± 209 vs. 640 ± 253 ml; $p = 0.007$ and $p = 0.016$). Incidence of surgical re-exploration for bleeding was 1.2% in group 1, 2.4% in group 2, 12.5% in group 3 ($p = 0.014$). Independent predictors of surgical re-exploration were group 3 ($p = 0.05$; HR = 9.2) and preoperative increased value of creatinine serum level ($p = 0.02$; HR = 1.3). In group 3, the incidence of re-exploration was 5.6% (1/18) in patients taking ASA + clopidogrel, 33.3% (2/6) in those taking ASA + ticagrelor (HR=32), respectively ($p < 0.001$). Operative mortality was 1.2% in group 1, 1.2% in group 2, absent in group 3 ($p =$ not significant).

Conclusions: Continued DAPT intake until CABG shows a clear trend towards more bleeding complications when compared with its discontinuation. Major blood loss and surgical re-exploration were not associated with an increased risk of operative mortality. Ticagrelor intake confers a higher risk of bleeding in comparison with clopidogrel; by stopping its intake at least 2 days prior to surgery, an increased risk of bleeding complications is not observed.

Key words: clopidogrel, ticagrelor, coronary artery bypass, bleeding.

Streszczenie

Cel: Retrospektywna ocena wpływu klopidogrelu lub tikagreloru u pacjentów stosujących podwójną terapię przeciwplateletową (DAPT, ASA + klopidogrel lub tikagrelor) poddawanych zabiegowi pomostowania tętnic wieńcowych (CABG) na występowanie pooperacyjnych powikłań krwotocznych i konieczność ponownej interwencji chirurgicznej w śródpiersiu, ze szczególnym uwzględnieniem okresu odstawienia DAPT.

Material i metody: Od stycznia 2017 do stycznia 2018 r. łącznie 190 pacjentów przeszło operację pomostowania tętnic wieńcowych z odstawieniem DAPT przez okres 5 dni (grupa 1., $n = 82$), 2–4 dni (grupa 2., $n = 84$), 0–1 dnia (grupa 3., $n = 24$) przed CABG.

Wyniki: W porównaniu z grupą 1. utrata krwi przez drenaż w klatce piersiowej w czasie 24 godzin była istotnie większa w grupie 2. i 3. (480 ± 238 vs 512 ± 209 vs 640 ± 253 ml; $p = 0,007$ i $p = 0,016$). Częstość ponownej interwencji chirurgicznej ze względu na krwawienie wyniosła 1,2% w grupie 1., 2,4% w grupie 2. oraz 12,5% w grupie 3. ($p = 0,014$). Niezależnymi predyktorami ponownej interwencji chirurgicznej były: przynależność do grupy 3. ($p = 0,05$; HR = 9,2) i przedoperacyjnie podwyższone stężenie kreatyniny w surowicy ($p = 0,02$; HR = 1,3). W grupie 3. częstość ponownej interwencji wyniosła 5,6% (1/18) u pacjentów stosujących ASA + klopidogrel oraz 33,3% (2/6) u osób przyjmujących ASA + tikagrelor (HR = 32) ($p < 0,001$). Śmiertelność operacyjna wyniosła 1,2% w grupie 1., 1,2% w grupie 2. oraz 0 w grupie 3. ($p =$ brak istotności).

Wnioski: Kontynuowanie przyjmowania DAPT aż do przeprowadzenia CABG wykazuje wyraźny trend do zwiększonej liczby powikłań krwotocznych w porównaniu z odstawieniem DAPT. Nie stwierdzono zależności między istotną utratą krwi i koniecznością ponownej interwencji chirurgicznej a zwiększonym ryzykiem śmiertelności operacyjnej. Stosowanie tikagreloru wiąże się z wyższym ryzykiem krwawienia w porównaniu z klopidogrelem; przy odstawieniu preparatu co najmniej 2 dni przed zabiegiem nie obserwuje się zwiększonego ryzyka wystąpienia powikłań krwotocznych.

Słowa kluczowe: klopidogrel, tikagrelor, pomostowanie naczyń wieńcowych, krwawienie.

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Introduction

Dual antiplatelet therapy is often obligatory in patients after acute coronary syndrome with or without ST elevation, to avoid recurrence. Accordingly, acetylsalicylic acid (ASA) and thienopyridines, i.e. clopidogrel, are currently administered to prevent cardiovascular death and myocardial infarction or stroke [1]. Another platelet aggregation inhibitor is ticagrelor (Brilique, AstraZeneca PLC, London, UK), which was approved for use in the European Union in 2010 and in the United States in 2011. Ticagrelor is an antiplatelet agent analogous to the thienopyridines group, and inhibits the adenosine diphosphate P2Y₁₂ platelet receptors. In contrast to active substances of the same category, such as clopidogrel, ticagrelor allows the blockage of the ADP receptor in a reversible way. Moreover, ticagrelor does not need hepatic activation, and therefore is independent of the activity of cytochrome enzymes with a half-life of 7–8.5 hours, and, as compared with clopidogrel, after discontinuation allows a faster offset of platelet inhibition [2–4]. In 2012, Varenhorst *et al.* [5] analyzing data from the Platelet inhibition and patient Outcomes (PLATO) study in 1,261 patients undergoing coronary artery bypass grafting (CABG) showed that as compared with clopidogrel, ticagrelor was associated with fewer deaths from cardiovascular, bleeding, and infection complications. Based on these effective results, ticagrelor was implemented in the Guidelines of the European Society of Cardiology and is now recommended as standard therapy in patients with ACS and those at moderate-to-severe risk of ischemic events for 12 months.

The ESC and EACTS Guidelines on myocardial revascularization recommend stopping thienopyridines intake 5 days prior to elective surgery [5–7]. However, not for all patients it is possible to wait for a period of 5–7 days after the interruption of the double antiplatelet therapy (DAPT) including ticagrelor or clopidogrel, to carry out CABG. Moreover, unstable patients, presenting an anatomical picture of the coronary arteries at high risk of adverse events, are operated on after initial ticagrelor or clopidogrel loading and/or ongoing treatment.

The first cause of early mediastinal re-exploration after cardiac surgery is bleeding, with rates ranging from 2% to 6%. Excessive bleeding may require massive blood transfusion and lead to life-threatening complications such as low output cardiac syndrome, respiratory failure and pneumonia, deep sternal wound infections, and cardiac tamponade, and the mortality rate seen in the literature after re-exploration for bleeding reaches up to 8–25%.

Aim

The objective of our study was to evaluate the impact of ticagrelor or clopidogrel in patients taking DAPT on postoperative bleeding complications, such as blood loss from thoracic drainage tubes within 24 hours, and the need for mediastinal re-exploration in patients undergoing CABG, in particular focusing on the time interval of discontinuation of DAPT. The need for blood unit transfusions and postoperative length of stay were also assessed.

Material and methods

From January 2017 to January 2018, 190 patients (mean age: 67 ± 9.5, range: 39–58, years; 160 males) affected by multivessel coronary artery disease underwent isolated surgical myocardial revascularization at the Cardiac Surgery Division of the Tor Vergata University Hospital. On-pump CABG was performed in 171 (90%) patients, off-pump CABG techniques in 19 (10%). The study was approved by our local Institutional Review Board, which waived the need for patient consent. The study was designed to be a retrospective one.

Antiplatelet therapy protocol and study groups

Our antiplatelet therapy protocol included for the cases operated on in election of the interruption of ASA (100 mg *per os*, daily) and other antiplatelet agents once admitted to our ward substitution with enoxaparin sodium, subcutaneously administered on the basis of the subject's weight and renal function. For patients undergoing urgent CABG, single or double antiplatelet therapy could not always be interrupted, such as in presence of high-risk anatomic conditions of the coronary arteries, recently implanted stents, or the acute phase of coronary artery syndrome. When possible, only the single administration was maintained, for example ASA, with suspension of Plavix or Brilique. For patients on therapy, the dosage of clopidogrel was 75 mg *per os* daily, or 300–600 mg as a loading dose, while the dosage of ticagrelor was 90 mg every 12 hours, or 90–180 mg as a loading dose.

To assess the risk of bleeding complications we retrospectively divided the patients into three study groups. The first group (1, control group) ($n = 82$) consisted of patients in whom it was possible to suspend the antiplatelet aggregation therapy at least 5 days before CABG; the second group (2) ($n = 84$) consisted of patients in whom DAPT (ASA plus clopidogrel or ticagrelor) was administered up to 2–4 days before CABG and then suspended; the last group (3) ($n = 24$) consisted of patients in whom DAPT (ASA plus clopidogrel or ticagrelor) had not been discontinued within 24 hours or was being taken.

Criteria to choose off-pump-CABG or on-pump CABG

Off-pump CABG techniques were performed by an expert surgeon (C.B.). Exclusion criteria to perform off-pump CABG were left ventricular ejection fraction less than 0.30, left ventricular end-diastolic diameter greater than 60 mm, distal diffuse narrowing of coronary arteries, intra-myocardial course of the left descending coronary artery, emergency or urgency surgery in presence of perioperative hemodynamic instability. In these cases, on-pump CABG was the only surgical treatment performed.

Surgical strategy and safety measures

The access to the heart was obtained through a complete longitudinal sternotomy in all patients. On-pump

CABG was performed by means of normothermic cardiopulmonary bypass and intermittent antegrade warm blood cardioplegia (600 ml the first dose, 400 ml the others) administered every 16–25 minutes, or cold crystalloid St. Thomas cardioplegic solution (8–10 ml/kg the first dose, followed by doses of 5 ml/kg) administered every 30–35 minutes. Cardiopulmonary bypass was performed by means of a Sorin Monolyth-Pro (Sorin Biomedica; Turin, Italy) or Capiiox (Terumo Cardiovascular System; Borken, Germany) membrane oxygenator and a Stockert roller pump (Stockert Instrumente; Munich, Germany).

In off-pump CABG patients, left anterior descending artery and its diagonal branches were bypassed as first vessel, followed by the right coronary artery and finally the left circumflex artery system. Stabilization was obtained with the aid of suction stabilizers (Octopus and Starfish; Medtronic Inc; Minneapolis, MN; USA in the early phase, and Acrobat and X-pose; Guidant Co; Boston Scientific, Boston, MS, USA later on). Distal perfusion was maintained after arteriotomy by means of intravascular shunts (Clearview, Medtronic Inc; Minneapolis, MN; USA).

Monitoring of cardiac function was obtained with trans-oesophageal echocardiography and insertion of a Swan-Ganz pulmonary artery catheter. Other safety measures included perfusionist's stand-by on a ready-dry state (mounted, non-primed cardiopulmonary bypass circuit).

The internal thoracic artery as an in situ graft was the conduit of choice for the left anterior descending artery revascularization in the majority of cases.

Data collection and definitions

In the three groups of patients we evaluated the incidence of surgical re-exploration for bleeding, the average blood loss from the thoracic drainage tubes, calculated at 6 and 24 hours after CABG, respectively, and the need for blood cell and platelet transfusions. Perioperative myocardial infarction was defined as an increase of post-operative troponin I higher than 20 ng/ml associated with CK-MB above normal values and more than 10% of total CK, and the onset of ECG new anomalies.

Major non-cardiac complications were also analyzed: a pulmonary complication was defined as an episode of primary lung failure requiring mechanical ventilation for more than 48 hours, re-intubation, or intermittent application of positive end-expiratory pressure by mask; a neurological complication was defined as an episode of stroke due to a focal or general cerebral lesion; renal insufficiency was defined as a two-fold increase of preoperative serum creatinine level or oliguria necessitating continuous venovenous hemo-diafiltration. Operative mortality included death in hospital after an operation at any time or within 30 days after discharge.

In the perioperative period, the indication for the transfusion of red blood cell units was given for hemoglobin values less than 9.0 g/dl; that for platelet transfusion was based on mediastinal bleeding or on the platelet count value.

Statistical analysis

Analysis was performed with Stat View 4.5 (SAS Institute Inc, Abacus Concepts, Berkeley, CA). Student's *t* test for continuous data and the χ^2 or Fisher's exact test for categorical data were used. Twenty-six preoperative and perioperative variables were analyzed, including age, gender, EuroSCORE II Risk Stratification System expressed and percent risk of death plus or minus 1 standard deviation, previous myocardial infarction, smoking habit, co-morbidity (arterial hypertension, diabetes mellitus, chronic renal dysfunction, chronic obstructive pulmonary disease, hyperlipemia, carotid and peripheral vascular disease, obesity), previous stroke or hemorrhagic events, Canadian Cardiovascular Society grade of angina, preoperative left ventricular ejection fraction, number of diseased coronary artery vessels, the three groups of study defined by the time interval of DAPT discontinuation, antiplatelet aggregation drugs administration, need for urgent CABG. Intraoperative variables examined were number of grafts per patient, cardiopulmonary bypass and aortic cross-clamp times, off-vs. on-pump surgery, the use of bilateral internal thoracic artery. Risk factor analysis to detect independent predictors for the need for mediastinal re-exploration for bleeding was performed using univariate and logistic regression analyses. All other continuous values were expressed as mean plus or minus one standard deviation of the mean. All *p*-values less than 0.05 were considered statistical significant.

Results

Preoperative characteristics of the three study groups are reported in Table I. Significant differences were found for the lower mean age at the operation of patients of group 3, for the length of stay, that was, as expected, markedly shorter before performing CABG in group 3, due to the urgent CABG required for unstable angina and or high-risk anatomy of the coronary artery vessels ($p < 0.0001$, for all comparisons). The preoperative laboratory analysis did not show important differences regarding coagulation and blood cell count parameters (Table II). No statistically significant difference was detected among the intraoperative analyzed variables (Table III). In-hospital outcomes and bleeding complications are reported in Tables IV and V, respectively. Operative mortality was 1.1%: in group 1 one female patient aged 60 years died due to low output cardiac syndrome, in group 2 another one male patient aged 80 years, affected preoperatively by severe chronic renal dysfunction, died due to acute kidney failure (Table IV).

There were no bleeding complication-related deaths in the whole study population (Table V). The overall incidence of mediastinal re-exploration for bleeding was 3.2% (6/190); 1.2% in group 1, 2.4% in group 2, 12.5% in group 3 ($p < 0.05$, group 3 versus groups 1 and 2) (Table V). In groups 2 and 3 blood loss from chest tube drainages was significantly higher in comparison with group 1 ($p < 0.05$, for both measurements) (Table V).

Table I. Preoperative characteristics

Characteristic	Group 1 (n = 82)	Group 2 (n = 84)	Group 3 (n = 24)	P-value
Age [years]	67 ±8.9	68 ±10.4	63 ±11.3	0.06* 0.05°
Male gender, n (%)	70 (85.4)	68 (80.9)	22 (91.7)	0.463
EuroSCORE II, (%)	2.4 ±2.0	2.5 ±2.0	2.8 ±1.8	NS
CCS class, mean ± SD	2.7 ±1.4	2.9 ±0.8	2.9 ±1.5	NS
Hypertension, n (%)	50 (60.9)	62 (73.8)	15 (62.5)	0.207
Smoking habit, n (%)	47 (57.3)	42 (58.3)	13 (54.2)	0.962
Diabetes mellitus, n (%)	32 (39.0)	15 (36.9)	5 (41.7)	0.797
Hyperlipemia, n (%)	53 (64.6)	57 (67.9)	16 (66.7)	0.523
Obesity, n (%)	15 (18.3)	16 (19.0)	5 (20.8)	0.638
Chronic renal dysfunction, n (%)	40 (48.8)	44 (52.4)	10 (41.7)	0.926
Chronic obstructive pulmonary disease, n (%)	10 (12.2)	9 (10.7)	2 (8.3)	0.912
Peripheral vascular disease, n (%)	9 (11.0)	7 (8.3)	1 (4.2)	0.667
Carotid artery disease, n (%)	7 (8.5)	7 (8.3)	1 (4.2)	0.867
Previous stroke or hemorrhage, n (%)	3 (3.7)	5 (5.9)	0	0.463
Previous myocardial infarction, n (%)	22 (26.8)	25 (29.8)	7 (29.2)	0.807
Left ventricular ejection fraction, mean ± SD	0.56 ±0.09	0.54 ±0.11	0.52 ±0.07	0.627
Recent (< 30 days) myocardial infarction, n (%)	9 (11)	4 (4.8)	1 (4.2)	0.285
Unstable angina and/or high-risk anatomy of coronary artery vessels, n (%)	29 (35.4)	43 (51.2)	24 (100)	0.0110** < 0.0001°°
Preoperative length of stay [days]	7.3 ±6.5	3.0 ±1.8	1.0 ±1.2	< 0.0001§ < 0.0001†

CCS – Canadian Cardiovascular Society, NS – not significant, for all measurements. *p value significant (group 1 vs. group 2); °p-value significant (group 2 vs. group 3); **p-value significant (group 1 vs. groups 2, 3); °°p-value significant (group 2 vs. group 3); §p-value significant (group 1 vs. groups 2, 3); †p-value significant (group 2 vs. group 3).

In the logistic regression analysis, group 3 ($p = 0.05$; HR = 9.2; 95% CI: 0.866–97.98) and the preoperative increased value of creatinine serum level ($p = 0.02$; HR = 1.3; 95% CI: 0.927–1.832) were the only independent predictors of mediastinal surgical re-exploration. In group 3, the incidence of re-exploration was 5.6% (1/18) in patients taking ASA plus clopidogrel, and 33.3% (2/6) in those taking ASA plus ticagrelor (HR = 32) ($p < 0.001$). In patients taking ticagrelor a higher number of transfused platelets units per patient was required (0.8 ± 3.8 vs. 0.1 ± 0.9 U), with a borderline level of statistical significance ($p = 0.05$).

Discussion

In this study, we presented the effect of perioperative DAPT administration in patients undergoing coronary artery bypass grafting surgery, focusing on the time of discontinuation of the antiplatelet aggregation therapy and on the use of ticagrelor in comparison with clopidogrel. The main findings of our study were that non-discontinuation of DAPT at least 5 days before CABG led to significantly higher blood loss at 24 hours after surgery; and patients operated on in group 3, but not group 2, were at a significantly higher risk of surgical re-thoracotomy for bleeding. Surgical re-exploration required more blood transfusions

and a longer postoperative stay. Moreover, in group 3, ticagrelor administration in comparison with that of clopidogrel was significantly associated with a substantial higher risk of bleeding requiring re-thoracotomy (33.3% vs. 5.6%).

However, higher blood loss and the need for re-thoracotomy were not associated with an increased risk of operative mortality or of bleeding complication-related deaths.

Ticagrelor administration was initially discussed in 2009 in the PLATO study trial, demonstrating the superior effect of ticagrelor in 18,624 patients with acute coronary syndromes in comparison with clopidogrel; ticagrelor led to a significant decrease of cardiovascular events, i.e. deaths from cardiovascular causes, myocardial infarction and stroke at 12 months (9.8% vs. 11.7%, $p < 0.001$) [4]. However, ticagrelor was significantly associated with a higher rate of major bleeding, i.e. intracranial bleeding (4.5% vs. 3.8%) ($p = 0.03$) [4]. A sub-study of PLATO, performed on 1,261 patients with acute coronary syndromes undergoing CABG within 7 days after stopping the study drugs, showed a reduction of operative mortality without an increased risk of bleeding in patients treated with ticagrelor in comparison with those who took clopidogrel. Indeed, the risk of numerous episodes of bleeding with the use of ticagrelor was lower (9 vs. 27 patients, $p < 0.01$) [5].

Table II. Preoperative coagulation and blood cell count parameters

Parameter	Group 1 (n = 82)	Group 2 (n = 84)	Group 3 (n = 24)	P-value
INR	1.1 ±0.1	1.2 ±1.0	1.1 ±0.1	0.414 0.273 0.586
PT (%)	90 ±13	93 ±10	93 ±7.8	0.110 0.335 0.993
PT [s]	12.6 ±2.2	12.3 ±1.03	12.2 ±0.68	0.170 0.356 0.683
PTT, ratio	1.1 ±0.5	1.1 ±1.5	1.1 ±0.4	0.265 0.603 0.983
PTT [s]	37.1 ±18	34.9 ±5.1	34.9 ±10	0.293 0.616 0.980
Fibrinogen [mg/dl]	424.3 ±200	398.5 ±126	442.4 ±196	0.314 0.714 0.225
Anti-thrombin III (%)	93.4 ±14.4	95.7 ±14.4	96.2 ±16.1	0.333 0.471 0.899
Hemoglobin [g/dl]	13.2 ±1.8	13.3 ±1.9	13.3 ±1.7	0.839 0.756 0.871
Hematocrit (%)	41.0 ±5.4	41.0 ±5.6	40.8 ±5.4	0.937 0.877 0.920
Erythrocytes [$\times 10^6/\mu\text{l}$]	4.6 ±0.7	4.5 ±0.7	4.6 ±0.7	0.576 0.929 0.786
White cells [$\times 10^3/\mu\text{l}$]	8.6 ±4.3	7.5 ±2.1	8.9 ±4.1	0.036* 0.745 0.023°
Platelets [$\times 10^3/\mu\text{l}$]	231 ±65	238 ±69	233 ±85	0.495 0.912 0.760

INR – international normalized ratio, PT – prothrombin time, PTT – partial thromboplastin time. *P-value significant (group 1 vs. group 2); °p-value significant (group 2 vs. group 3).

Several reasons were discussed in this study because of better results with the use of ticagrelor compared to clopidogrel. Clopidogrel is an irreversible platelet inhibitor, and normal platelet activity is not recovered until 5 to 10 days

Table III. Intraoperative variables

Variable	Group 1 (n = 82)	Group 2 (n = 84)	Group 3 (n = 24)	P-value
Cardiopulmonary bypass time [min]	90 ±44	101 ±50	114 ±61	0.458 0.063 0.666
Aortic cross-clamp time [min]	54 ±28	56 ±37	69 ±36	0.696 0.043 0.149
Off-pump techniques, n (%)	9 (10.9)	8 (9.5)	2 (8.3)	0.922
Bilateral internal thoracic artery, n (%)	0	3 (3.6)	2 (8.3)	0.188
No. bypass grafts per patient, mean ± SD	2.7 ±0.8	2.7 ±0.8	2.6 ±0.9	NS

after its discontinuation. Cessation of clopidogrel is therefore recommended at least 5–7 days before CABG in order to limit the risk of bleeding. Ticagrelor, on the other hand, is a reversible binder of P2Y₁₂ inhibitor with a faster offset of platelet inhibition after drug discontinuation compared with clopidogrel. Moderate-to-poor responders to clopidogrel have a similar time of recovery of platelet function compared with ticagrelor-treated patients after cessation of the treatment. On the other hand, about one third of patients on clopidogrel therapy have a high level of platelet inhibition, thus explaining why these patients may be particularly vulnerable to bleeding complications. Several studies have documented an increased rate of bleeding when clopidogrel is administered within 5 days before surgery, and therefore the current guidelines recommend stopping clopidogrel at least 5 days before surgery [8–11]. A meta-analysis by Nijjer *et al.* [12] suggested that patients requiring urgent CABG should undergo surgery without delay for a clopidogrel-free period. However, this proposal does not take into consideration the variable levels of platelet inhibition in patients taking clopidogrel and the potentially greater risk of bleeding in the presence of an adequate level of platelet inhibition. This aspect could also have happened in our patient sample. In fact, in group 3 the incidence of bleeding requiring surgical re-exploration was 5.6% in patients taking clopidogrel, and therefore lower than in those taking ticagrelor. However, it may have happened that

Table IV. Postoperative results

Variable	Group 1 (n = 82)	Group 2 (n = 84)	Group 3 (n = 24)	P-value
Norepinephrine use > 24 hours, n (%)	11 (13.4)	11 (13.1)	4 (16.7)	0.817
Myocardial infarction, n (%)	0	0	0	> 0.90
Pulmonary complications, n (%)	0	4 (4.8)	0	0.088
Neurological damage, n (%)	1 (1.2)	0	0	> 0.90
Acute kidney injury, n (%)	0	2 (2.4)	0	0.307
Need for pacemaker implantation, n (%)	0	0	0	> 0.90
ICU stay [days]	2.8 ±2.1	3.2 ±3.4	2.8 ±1.6	NS
Postoperative in-hospital stay [days]	12 ±9.4	10 ±8.3	10 ±4.6	NS
Operative mortality, n (%)	1 (1.2)	1 (1.2)	0	0.380

ICU – intensive care unit.

Table V. Postoperative bleeding complications

Variable	Group 1 (n = 82)	Group 2 (n = 84)	Group 3 (n = 24)	P-value
Bleeding-related deaths, n (%)	0	0	0	–
Mediastinal re-exploration, n (%)	1 (1.2)	2 (2.4)	3 (12.5)	0.014
Blood loss from pleural-mediastinal drainage tubes at 6 hours [ml]	190 ±139	205 ±157	280 ±206	0.512 0.018* 0.064
Blood loss from pleural-mediastinal drainage tubes at 24 hours [ml]	480 ±238	512 ±209	640 ±253	0.357 0.007° 0.016**
No. transfused red blood cell, mean ± SD	1.0 ±1.8	1.7 ±5.5	1.1 ±1.4	0.298 0.853 0.652
Red blood cells transfusion, n (%)	34 (41.5)	37 (44)	12 (50)	0.545
Platelets transfusion, n (%)	3 (3.7)	1 (1.2)	2 (8.3)	0.161

*P-value significant (group 1 vs. group 3); °p-value significant (group 1 vs. group 3); **p-value significant (group 2 vs. group 3).

some patients taking clopidogrel did not have an adequate level of anti-platelet aggregation. In the PLATO study the authors recommended ticagrelor discontinuation 24 to 72 hours before an operation, compared with 5 days for clopidogrel. Hansson *et al.* [13] in 25 patients accepted for urgent CABG showed that adenosine diphosphate-induced aggregation was acceptable after 72 hours of ticagrelor discontinuation, with a mean aggregation value of 38 ± 23 U, which is above the suggested cut-off of 22 U. The use of the CABG technique is also an important aspect, regardless of the presence of an anti-aggregating therapy in progress. From a recently published meta-analysis performed by Shaefi *et al.* [14] the off-pump CABG approach was found to require fewer blood transfusions, presumably secondary to decreased intraoperative bleeding from cannulation and hemodilution that are required, instead, during on-pump CABG. However, it is not always possible to carry out CABG off-pump (in 10% of cases in our series), due to the presence of possible clinical instability and/or hemodynamic compromise [15, 16]. Retrospective clinical studies in small patient samples have examined the risk of ticagrelor use during cardiac surgery. Schotola *et al.* [17] in 32 patients receiving ticagrelor plus ASA and in 49 patients receiving clopidogrel plus ASA found that in the first 24 hours median blood loss, red blood cell and platelet transfusions, use of prothrombin complex concentrate and fibrinogen were significantly higher in the ticagrelor patients ($p \leq 0.01$, for all comparisons). The tendency towards more re-thoracotomies due to bleeding was greater with the use of ticagrelor ($p = 0.063$), but the mortality rate was similar in both groups. Hansson *et al.* [18] in a larger sample of patients (173 treated with DAPT-clopidogrel, 232 with DAPT-ticagrelor), did not find a significant difference in the incidence of major bleeding complications before CABG in both groups of patients when either drug was discontinued at 5 days (9.9% vs. 6.8%) or 2–4 days (25% vs. 6.3%). However, when drugs were discontinued under 24 hours, there was a non-significantly higher incidence of major bleeding in-

cagrelor-treated patients (41% vs. 21.7%, $p = 0.063$). Schaefer *et al.* [19] in 28 consecutive CABG patients on DAPT with ticagrelor therapy in comparison with 28 cases on DAPT with clopidogrel therapy observed higher rates of blood loss and need for red blood cell transfusion, and significantly longer in-hospital stay in ticagrelor-treated patients, recommending its discontinuation at least 3 days before CABG. Similar results to those cited above were found in our series. In fact, in group 3, without ticagrelor discontinuation, we found a 30-fold increased risk of surgical re-thoracotomy (2 cases out of 6 patients), in comparison with groups 1 and 2. This difference, in comparison with the rate of 1 case of bleeding out of 18 patients of the counterpart of DAPT patients who were taking clopidogrel, is most likely due to the fact that the time of withdrawal of the P2Y12 inhibitor is of marked importance in the ticagrelor-treated patients. In particular, ticagrelor, having a more direct action without the need for liver activation, has more powerful anti-aggregation action than clopidogrel, which can also have non-responder patients; but at the same time, it has a short half-life and reversible binding, beyond which its effect is limited more easily than clopidogrel. Therefore, the possibility of suspending this drug at least 2 days before CABG can significantly reduce the risk of bleeding.

The present study has several limitations: because of the retrospective nature, the conclusion that preoperative treatment predicts outcomes is limited by the small sample of patients; the number of patients in group 3 undergoing CABG without discontinuation of ticagrelor was only six; thus any conclusions should be drawn with caution. However, all patients consecutively undergoing isolated CABG were included during a study period of 12 months of observation.

Conclusions

With continued DAPT intake until CABG, there was observed a clear trend towards more bleeding complications when compared with its discontinuation. Major blood loss from drainages and surgical re-exploration due to active

bleeding were not associated with increased risk of operative mortality. Ticagrelor intake confers a higher risk of bleeding in comparison with clopidogrel; by stopping this intake at least 2 days prior to CABG surgery, an increased risk in major bleeding complications is not observed.

Disclosure

The authors report no conflict of interest.

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