# Bleeding in Patients Treated with Ticagrelor or Clopidogrel Before Coronary Artery Bypass Grafting

**Brief title:** Ticagrelor or clopidogrel before CABG

Manne Holm,[1] MD, PhD, Fausto Biancari,[2,3,4] MD, PhD, Sorosh Khodabandeh,[1,5] MD, Riccardo Gherli,[6] MD, Juhani Airaksinen,[2] MD, PhD, Giovanni Mariscalco,[7] MD, PhD, Giuseppe Gatti,[8] MD, Daniel Reichart,[9] MD, Francesco Onorati,[10] MD, PhD, Marisa De Feo,[11] MD, PhD, Giuseppe Santarpino,[12] MD, PhD, Antonino S. Rubino,[13] MD, PhD, Daniele Maselli,[14] MD, Francesco Santini,[15] MD, PhD, Francesco Nicolini,[16] MD, PhD, Marco Zanobini,[17] MD, Eeva-Maija Kinnunen,[4] MD, PhD, Vito G. Ruggieri,[18] MD, PhD, Andrea Perrotti,[19] MD, PhD, Stefano Rosato,[20] MSc, and Magnus Dalén,[1,5] MD, PhD.

[1]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden;
[2]Heart Center, Turku University Hospital, University of Turku, Turku, Finland;
[3]Department of Surgery, University of Turku, Turku, Finland;
[4]Department of Surgery, Oulu University Hospital and University of Oulu, Oulu, Finland;
[5]Department of Cardiac Surgery, Karolinska University Hospital, Stockholm, Sweden;
[6]Department of Cardiovascular Sciences, Cardiac Surgery Unit, S. Camillo-Forlanini Hospital, Rome, Italy;
[7]Department of Cardiovascular Sciences, Clinical Sciences Wing, University of Leicester, Glenfield Hospital, Leicester, UK;
[8]Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy;
[9]Hamburg University Heart Center, Hamburg, Germany;
[10]Division of Cardiovascular Surgery, Verona University Hospital, Verona, Italy;
[11]Department of Cardiothoracic Sciences, University of Caserta, Caserta, Italy;
[12]Cardiovascular Center, Paracelsus Medical University, Nuremberg, Germany and Città di Lecce Hospital GVM Care & Research, Lecce, Italy;
[13]Centro Clinico-Diagnostico "G.B. Morgagni", Centro Cuore, Pedara, Italy;
[14]Department of Cardiac Surgery, St. Anna Hospital, Catanzaro, Italy;
[15]Division of Cardiac Surgery, University of Genoa, Genoa, Italy;
[16]Division of Cardiac Surgery, University of Parma, Parma, Italy;
[17]Department of Cardiac Surgery, Centro Cardiologico – Fondazione Monzino IRCCS, University of Milan;
[18]Division of Cardiothoracic and Vascular Surgery, Robert Debré University Hospital, Reims, and Division of Cardiothoracic and Vascular Surgery, Pontchaillou University Hospital, Rennes, France;
[19]Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France;
[20]National Center of Global Health, Istituto Superiore di Sanità, Rome, Italy.

Word count: 4585

Funding: Magnus Dalén was financially supported by a research grant from Karolinska Institutet (grant number 2018-01278).

Conflict of interest**:** None

**Corresponding author:** Magnus Dalén, MD, PhD, Department of Cardiac Surgery, Karolinska University Hospital, SE-171 76 Stockholm, Sweden. Tel: +46 8517 708 37. Fax: +46 8 33 19 31. E-mail: magnus.dalen@sll.se

# Abstract

**Background:** We evaluated perioperative bleeding after CABG in patients preoperatively treated with ticagrelor or clopidogrel, stratified by discontinuation of these $P2Y_{12}$ inhibitors.

**Methods:** All patients from the prospective, European multicenter registry on Coronary Artery Bypass Grafting (E-CABG) treated with ticagrelor or clopidogrel undergoing isolated primary CABG were eligible. Primary outcome measure was severe or massive bleeding defined according to the Universal Definition of Perioperative Bleeding (UDPB), stratified by $P2Y_{12}$ inhibitor discontinuation. Secondary outcome measures included four additional definitions of major bleeding. Propensity score matching was performed to adjust for differences in pre- and perioperative covariates.

**Results:** 2311 patients were included, of whom 1293 (55.9%) received clopidogrel and 1018 (44.1%) ticagrelor preoperatively. Mean time between discontinuation and surgery was 4.5 ± 3.2 days for clopidogrel and 4.9 ± 3.0 days for ticagrelor. In the propensity score-matched cohort, ticagrelor-treated patients had a higher incidence of major bleeding according to UDPB when ticagrelor was discontinued 0-2 days compared with 3 days before surgery (16.0 vs. 2.7%, p=0.003). Clopidogrel-treated patients had a higher incidence of major bleeding according to UDPB when clopidogrel was discontinued 0-3 days compared with 4-5 days before surgery (15.6 vs. 8.3%, p=0.031).

**Conclusions:** In patients receiving ticagrelor 2 days before surgery and in those receiving clopidogrel 3 days before surgery, there was an increased rate of severe bleeding. Postponing non-emergent CABG for at least 3 days after discontinuation of ticagrelor and 4 days after clopidogrel should be considered.

**Abstract word count:** 234

**Clinical Trial Registration:** http://www.clinicaltrials.gov. Unique identifier: NCT02319083; European multicenter registry on Coronary Artery Bypass Grafting (E-CABG) registry.

**Key words:** Bleeding complications; Coronary artery bypass; Dual antiplatelet therapy.

# Introduction

Treatment of patients with acute coronary syndromes (ACS) includes dual antiplatelet therapy (DAPT) with acetylsalicylic acid and a $P2Y_{12}$ inhibitor to reduce the risk for thrombotic complications. Treatment with the $P2Y_{12}$ inhibitor ticagrelor has been increasingly used since it has been shown to reduce the rate of death from vascular causes, myocardial infarction, and stroke in comparison with clopidogrel [1]. Ticagrelor possesses a more potent and consistent platelet inhibition with faster onset and offset of action compared with clopidogrel [2]. Owing to these differences in pharmacodynamic and pharmacokinetic profiles, the two $P2Y_{12}$ inhibitors have different risks for procedure-related bleeding.

Patients with ACS who receive DAPT and urgently need coronary artery bypass grafting (CABG) have a high risk for severe perioperative bleeding complications [3]. There are few reports comparing CABG-related bleeding complications in patients preoperatively treated with ticagrelor or clopidogrel [4-6]. In order to reduce risk of bleeding complications, it is recommended that CABG should be postponed at least 3 days after discontinuation of ticagrelor and 5 days after clopidogrel [7], but the evidence on the optimal timing of discontinuation is limited. This issue has important clinical and economic implications as discontinuation of a $P2Y_{12}$ inhibitor before CABG may be associated with an increased risk of thrombotic complications [8] and delay of surgery increases the burden of resources. We sought to evaluate perioperative bleeding after CABG in patients preoperatively treated with ticagrelor or clopidogrel, stratified by discontinuation of these $P2Y_{12}$ inhibitors.

# Methods

## Study design

This is a study from the European multicenter registry on Coronary Artery Bypass Grafting (E-CABG), which is a prospective observational, multicenter study including patients undergoing isolated CABG. The detailed study protocol for the E-CABG registry has been published previously [9]. The study was approved by the regional or institutional review board according to national guidelines for approval of registry studies.

## Study population

Data were collected consecutively from 16 cardiac surgery centers in 6 European countries (Finland, France, Germany, Italy, Sweden, and United Kingdom). All adult patients who were preoperatively treated with ticagrelor or clopidogrel and underwent isolated primary CABG in one of the participating centers from January 2015 to May 2017 were eligible. Ticagrelor or clopidogrel treatment was initiated with a first day loading dose (ticagrelor: 180 mg, clopidogrel: 300-600 mg), followed by a maintenance dose (ticagrelor: 90 mg twice daily, clopidogrel: 75 once daily). Exclusion criteria were (1) patients with discontinuation of ticagrelor or clopidogrel >14 days prior to surgery; (2) patients without data on timing of ticagrelor/clopidogrel discontinuation; (3) patients treated preoperatively with both ticagrelor and clopidogrel; and (4) patients who had preoperatively received prasugrel.

## Outcomes

Primary outcome measure was severe or massive bleeding defined according to the Universal Definition of Perioperative Bleeding (UDPB) in adult cardiac surgery [10]. UDPB severe or massive bleeding is defined as including one or more of the following criteria: delayed sternal closure for bleeding, postoperative blood loss more than 1000 ml within 12 hours, 5 or more red blood cell (RBC) units transfused, 5 or more plasma units transfused, the use of recombinant factor VIIa, or reoperation

due to excessive bleeding. In the UDPB classification only RBC transfusions beginning at chest closure are counted.

Secondary outcome measures included four additional definitions of major bleeding (criteria specified in Supplemental material); (1) PLATelet Inhibition and Patient Outcomes (PLATO) life-threatening bleeding [1]; (2) Bleeding Academic Research Consortium(BARC) CABG-related bleeding [11]; (3) Blood conservation using Antifibrinolytics Randomized Trial (BART) massive bleeding [12]; (4) E-CABG severe or massive bleeding [13].

To investigate the impact of timing of discontinuation of $P2Y_{12}$ inhibitor on bleeding, we compared the incidence of the bleeding events described above within and between the ticagrelor and clopidogrel groups stratified by $P2Y_{12}$ inhibitor discontinuation (0-2 days, 3 days, 4-5 days, >5 days before surgery).

**Statistical analysis**

Variables are described using frequencies and percentages for categorical variables, and means and standard deviations or medians and interquartile range for continuous variables. In the overall cohort, outcomes were compared by independent samples t-test and $\chi^2$ test for binary and categorical variables, and analysis of variance for continuous variables. To reduce selection bias, a propensity score was calculated with ticagrelor/clopidogrel as the dependent variable (details in Supplemental material). Based on a previous study [4], a sample size of 500 patients in each group was chosen to achieve 80% power in finding a significant difference in the incidence of major bleeding complications between the two groups. A 2-sided p value of $<0.05$ was considered to indicate statistical significance. Analyses were performed using Stata v.15.1 (StataCorp LP, College Station, TX, USA).

# Results

### Study population and patient characteristics

The study flow chart is presented in Figure 1. 2311 patients who underwent isolated primary CABG and were treated with ticagrelor or clopidogrel within 14 days prior to surgery were included in the analysis. Of these, 1293 (55.9%) had received clopidogrel and 1018 (44.1%) ticagrelor preoperatively. Patient and procedural characteristics are listed in Table 1. In the propensity score-matched cohort (688 pairs), baseline characteristics were well balanced as shown in Table 1.

### Major bleeding

In the propensity score-matched cohort, the risk of major bleeding was similar between the ticagrelor and clopidogrel cohorts (Table 2). The incidence of UDPB severe or massive bleeding and other major bleeding definitions by day of discontinuation is shown in Figure 2 and Supplemental figure 1. In the overall series as well as in the propensity score-matched cohort, ticagrelor-treated patients had a higher incidence of major bleeding according to UDPB when ticagrelor was discontinued 0-2 days compared with 3 days before surgery (overall cohort: 17.7 vs. 7.7%, p=0.016, propensity score-matched cohort: 16.0 vs. 2.7%, p=0.003; Figure 3). Clopidogrel-treated patients had a higher incidence of major bleeding according to UDPB when clopidogrel was discontinued 0-3 days compared with 4-5 days before surgery (overall cohort: 15.4 vs. 8.8%, p= 0.006, propensity score-matched cohort: 15.6 vs. 8.3%, p=0.031). Even a short prolongation of the waiting time between ticagrelor intake and surgery was associated with a large reduction in bleeding complications (none vs. 1 day discontinuation of ticagrelor, 25.0 vs. 10.8%, p=0.033, in the propensity score-matched cohort). For clopidogrel, the risk of perioperative bleeding complications decreased more gradually over time (Figure 2). Patients with discontinuation of clopidogrel or ticagrelor 0-3 days before surgery more often received transfusions (Supplemental table 1).

# Discussion

We found that receiving ticagrelor 2 days before surgery and receiving clopidogrel 3 days before surgery was associated with an increased rate of severe bleeding. For ticagrelor, also a short prolongation of the waiting time between drug intake and surgery reduced bleeding complications, but for clopidogrel the risk decreased more gradually with increased discontinuation time.

For ticagrelor, these findings confirm the current guidelines, supporting postponing non-emergent CABG for at least 3 days after discontinuation of ticagrelor [7]. These guidelines are largely based on a previous study that showed no difference in major bleeding complications when ticagrelor was discontinued 3 days compared with 5 days before surgery [4]. In that study, the primary outcome was BARC CABG-related bleeding, a secondary outcome measure in our study. There are differences between bleeding definitions used in cardiac surgery trials and we chose UDPB severe or massive bleeding as the primary outcome measure since it has been validated in several studies and recommended for use as an outcome measure in clinical trials [10, 14, 15]. In our analysis, results were similar for UDPB and BARC CABG-related bleeding.

In a smaller cohort of patients with ACS undergoing CABG we have previously shown that preoperative treatment with ticagrelor until shortly before surgery was associated with an increased risk of major bleeding complications [16]. This bleeding risk, however, seemed to decrease substantially even with limited prolongation of the period between drug intake and surgery, which is in line with the present study.

For clopidogrel, the study by Hansson and coworkers showed that a discontinuation time of 5 days was associated with a slightly lower incidence of major bleeding complications compared with 3 days [4]. Our results suggest that the current recommendation to postpone surgery for at least 5 days after clopidogrel [7] might be reduced to 4 days, since only receiving clopidogrel 3 days before surgery was associated with an increased rate of severe bleeding. However, given the slow gradual decrease in bleeding risk with increased time of discontinuation of clopidogrel, it is difficult to define a time point beyond which bleeding risk is definitely decreased.

There are few reports comparing CABG-related bleeding complications in patients preoperatively

treated with ticagrelor or clopidogrel [4-6, 16]. Owing to their limitations, the findings of previous studies have been stated to require further confirmation [17]. The present study was conducted during more recent years than previous studies [4-6], which were largely retrospective analyses conducted when ticagrelor was a relatively new antiplatelet agent. During recent years physicians have gained improved knowledge of antiplatelet-related bleeding, thereby possibly decreasing the risk of bleeding when these agents are discontinued in close proximity to CABG. When compared to a previous study [4], in patients with 1 or 2 days postponing of surgery, the absolute incidence of BARC CABG-related bleeding seemed to be lower in the current study.

Interinstitutional differences in patient blood management, transfusion policy, and indication for reoperation for bleeding may exist, whilst this has not been adjusted for in previous studies. We attempted to adjust for such interinstitutional differences by including center in the propensity score model. We used multiple definitions of major perioperative bleeding which may more accurately describe major bleeding as incidence differs significantly depending on the bleeding definition used [11].

The present study has limitations. As in every observational study, the findings in our study may have been influenced by selection bias. We attempted to control for this by using propensity score matching. The fact that previous antiplatelet treatment and time since discontinuation were known by the treating physicians could have influenced transfusion decision. Furthermore, data regarding platelet function testing was not collected. Although debated, platelet function testing could prove to be beneficial in individualizing the timing of surgery after antiplatelet therapy.

In conclusion, postponing non-emergent CABG for at least 3 days after discontinuation of ticagrelor and 4 days after clopidogrel seems to be associated with a reduction in the risk of perioperative bleeding. These findings have clinical implications as CABG can be performed with a short period of discontinuation after exposure to ticagrelor or clopidogrel.

## References

1. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Investigators P, Freij A and Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045-57.
2. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS and Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009;120:2577-85.
3. Hansson EC and Jeppsson A. Platelet inhibition and bleeding complications in cardiac surgery: A review. Scand Cardiovasc J. 2016;50:349-354.
4. Hansson EC, Jideus L, Aberg B, Bjursten H, Dreifaldt M, Holmgren A, Ivert T, Nozohoor S, Barbu M, Svedjeholm R and Jeppsson A. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. Eur Heart J. 2016;37:189-97.
5. Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA, Horrow J, Husted S, James SK, Mahaffey KW, Nicolau JC, Scirica BM, Storey RF, Vintila M, Ycas J and Wallentin L. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol. 2011;57:672-84.
6. Schotola H, Brauer A, Meyer K, Hinz J, Schondube FA, Bauer M, Mohite PN, Danner BC, Sossalla S and Popov AF. Perioperative outcomes of cardiac surgery patients with ongoing ticagrelor therapy: boon and bane of a new drug. Eur J Cardiothorac Surg. 2014;46:198-205.
7. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, Group ESCSD, Guidelines ESCCfP and Societies ESCNC. 2017

ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2017.

8. Kedhi E, Stone GW, Kereiakes DJ, Serruys PW, Parise H, Fahy M, Simonton CA, Sudhir K, Sood P and Smits PC. Stent thrombosis: insights on outcomes, predictors and impact of dual antiplatelet therapy interruption from the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE trials. EuroIntervention. 2012;8:599-606.
9. Biancari F, Ruggieri VG, Perrotti A, Svenarud P, Dalén M, Onorati F, Faggian G, Santarpino G, Maselli D, Dominici C, Nardella S, Musumeci F, Gherli R, Mariscalco G, Masala N, Rubino AS, Mignosa C, De Feo M, Della Corte A, Bancone C, Chocron S, Gatti G, Gherli T, Kinnunen EM and Juvonen T. European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG registry): Study Protocol for a Prospective Clinical Registry and Proposal of Classification of Postoperative Complications. J Cardiothorac Surg. 2015;10:90.
10. Dyke C, Aronson S, Dietrich W, Hofmann A, Karkouti K, Levi M, Murphy GJ, Sellke FW, Shore-Lesserson L, von Heymann C and Ranucci M. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg. 2014;147:1458-1463 e1.
11. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG and White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736-47.
12. Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussieres JS, Cote D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R and Investigators B. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008;358:2319-31.
13. Mariscalco G, Gherli R, Ahmed AB, Zanobini M, Maselli D, Dalén M, Piffaretti G, Cappabianca G, Beghi C and Biancari F. Validation of the European Multicenter Study on

Coronary Artery Bypass Grafting (E-CABG) Bleeding Severity Definition. Ann Thorac Surg. 2016;101:1782-8.

14. Bartoszko J, Wijeysundera DN, Karkouti K, Callum J, Rao V, Crowther M, Grocott HP, Pinto R, Scales DC, Achen B, Brar S, Morrison D, Wong D, Bussieres JS, de Waal T, Harle C, de Medicis E, McAdams C, Syed S, Tran D, Waters T and Transfusion Avoidance in Cardiac Surgery Study I. Comparison of Two Major Perioperative Bleeding Scores for Cardiac Surgery Trials: Universal Definition of Perioperative Bleeding in Cardiac Surgery and European Coronary Artery Bypass Grafting Bleeding Severity Grade. Anesthesiology. 2018.
15. Kinnunen EM, Juvonen T, Airaksinen KE, Heikkinen J, Kettunen U, Mariscalco G and Biancari F. Clinical significance and determinants of the universal definition of perioperative bleeding classification in patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2014;148:1640-1646 e2.
16. Gherli R, Mariscalco G, Dalén M, Onorati F, Perrotti A, Chocron S, Verhoye JP, Gulbins H, Reichart D, Svenarud P, Faggian G, Santarpino G, Fischlein T, Maselli D, Dominici C, Musumeci F, Rubino AS, Mignosa C, De Feo M, Bancone C, Gatti G, Maschietto L, Santini F, Nicolini F, Gherli T, Zanobini M, Kinnunen EM, Ruggieri VG, Rosato S and Biancari F. Safety of Preoperative Use of Ticagrelor With or Without Aspirin Compared With Aspirin Alone in Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Grafting. JAMA Cardiol. 2016;1:921-928.
17. Weidinger F. Discontinuation of P2Y12 antagonists before coronary bypass surgery: is 5 days really required? Eur Heart J. 2016;37:198-9.

**Table 1** Patient and procedural characteristics

| | Overall cohort | | | Propensity score-matched cohort | | |
|---|---|---|---|---|---|---|
| | Clopidogrel n=1293 | Ticagrelor n=1018 | Standardized difference | Clopidogrel n=688 | Ticagrelor n=688 | Standardized difference |
| Age, years, mean (SD) | 67.9 ± 9.6 | 64.9 ± 9.7 | 0.3058 | 66.2 ± 10.1 | 66.0 ± 9.5 | 0.0197 |
| Female sex | 216 (16.7%) | 171 (16.8%) | -0.0025 | 114 (16.6%) | 116 (16.9%) | -0.0078 |
| Body mass index, kg/m$^2$, mean (SD) | 27.3 ± 4.0 | 27.4 ± 4.2 | -0.0211 | 27.4 ± 4.2 | 27.4 ±4.1 | 0.0166 |
| Transient ischemic attack | 27 (2.1%) | 16 (1.6%) | 0.0385 | 16 (2.3%) | 8 (1.2%) | 0.0889 |
| Stroke | 71 (5.5%) | 33 (3.2%) | 0.1102 | 19 (2.8%) | 24 (3.5%) | -0.0418 |
| Poor mobility | 31 (2.4%) | 19 (1.9%) | 0.0368 | 18 (2.6%) | 16 (2.3%) | 0.0187 |
| Extracardiacarteriopathy | 360 (27.9%) | 170 (16.7%) | 0.2706 | 142 (20.6%) | 148 (21.5%) | -0.0214 |
| Diabetes mellitus | 446 (34.5%) | 308 (30.3%) | 0.0906 | 221 (32.1%) | 228 (33.1%) | -0.0217 |
| Insulin-dependent diabetes mellitus | 200 (15.5%) | 138 (13.6%) | 0.0543 | 100 (14.5%) | 90 (13.1%) | 0.0421 |
| Dialysis | 24 (1.9%) | 1 (0.1%) | 0.1794 | 3 (0.4%) | 1 (0.1%) | 0.0540 |
| Chronic lung disease | 135 (10.4%) | 113 (11.1%) | -0.0213 | 72 (10.5%) | 75 (10.9%) | -0.0141 |
| Atrial fibrillation | 113 (8.7) | 52 (5.1) | 0.1434 | 44 (6.4%) | 47 (6.8%) | -0.0175 |
| Prior percutaneous coronary intervention | 445 (34.4%) | 302 (29.7%) | 0.1019 | 233 (33.9%) | 235 (34.2%) | -0.0061 |
| Left ventricular ejection fraction | | | 0.1405 | | | 0.0755 |
| >50% | 889 (68.8%) | 634 (62.3%) | | 443 (64.4%) | 451 (65.6%) | |
| 31-50% | 344 (26.6%) | 332 (32.6%) | | 205 (29.8%) | 208 (30.2%) | |
| <21% | 9 (0.7%) | 10 (1.0%) | | 7 (1.0%) | 6 (0.9%) | |
| 21-30% | 51 (3.9%) | 42 (4.1%) | | 33 (4.8%) | 23 (3.3%) | |
| Acute coronary syndrome | 774 (59.9%) | 887 (87.1%) | -0.6494 | 567 (82.4%) | 558 (81.1%) | 0.0339 |
| Emergent or salvage procedure | 70 (5.4%) | 79 (7.8%) | -0.0947 | 53 (7.7%) | 55 (8.0%) | -0.0108 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Critical preoperative state | 89 (6.9% | 65 (6.4%) | 0.0200 | 46 (6.7%) | 46 (6.7%) | 0 |
| EuroSCORE II, median (Q1, Q3) | 1.81 (1.10, 3.40) | 1.75 (1.10, 3.20) | 0.0358 | 1.83 (1.15, 3.24) | 1.85 (1.1, | 0.0142 |
| Number of diseased vessels, mean (SD) | 2.6 ± 0.6 | 2.6 ± 0.6 | 0.0084 | 2.62±0.6 | 2.6 ±0.6 | 0.0100 |
| Left main coronary artery stenosis | 526 (40.8%) | 369 (36.3%) | 0.0924 | 264 (38.4%) | 261 (37.9%) | 0.0090 |
| SYNTAX score, mean (SD) | 28.9 ±12.2 | 28.8 ±11.8 | 0.0077 | 29.3 ± 12.4 | 29.1 ± 12.4 | 0.0093 |
| Preoperative laboratory parameters | | | | | | |
| Hemoglobin, g/L, mean (SD) | 135 ± 18 | 136 ± 17 | -0.1065 | 135 ± 17 | 135 ± 17 | 0.0183 |
| Platelets, $x10^9$/l, mean (SD) | 229 ± 73 | 238 ± 69 | -0.1308 | 236 ± 78 | 234 ± 67 | 0.0211 |
| Estimated glomerular filtration rate, ml/min/1,73$m^2$, mean (SD) | 81.0 ± 28.1 | 84.6 ± 24.5 | -0.1351 | 84 ± 27 | 84 ± 26 | -0.0240 |
| Preoperative antithrombotic medications | | | | | | |
| Acetylsalicylic acid | 1144 (88.5%) | 956 (93.9%) | -0.1904 | 646 (93.9%) | 642 (93.3%) | 0.0238 |
| Acetylsalicylic acid within 24 hours before surgery | 963 (74.5%) | 856 (84.1%) | -0.2387 | 559 (81.2%) | 560 (81.4%) | -0.0037 |
| Low molecular weight heparin or fondaparinux | 590 (45.6%) | 559 (54.9%) | -0.1864 | 339 (49.3%) | 320 (46.5%) | 0.0553 |
| Unfractionated heparin | 22 (1.7%) | 21 (2.1%) | -0.0266 | 12 (1.7%) | 15 (2.2%) | -0.0314 |
| Warfarin | 15 (1.2%) | 6 (0.6%) | 0.0613 | 5 (0.7%) | 6 (0.9%) | -0.0163 |
| Novel oral anticoagulant | 3 (0.2%) | 2 (0.2%) | 0.0077 | 1 (0.1%) | 2 (0.3%) | -0.0311 |
| Glycoprotein IIb/IIIa inhibitor | 8 (0.6%) | 10 (1.0%) | -0.0408 | 6 (0.9%) | 6 (0.9%) | 0 |
| Days between discontinuation of ticagrelor or clopidogrel and surgery | | | -0.1393 | | | -0.0576 |
| None | 173 (13.4%) | 79 (7.8%) | | 87 (12.6%) | 56 (8.1%) | |
| 1 day | 140 (10.8%) | 179 (7.8%) | | 80 (11.6%) | 74 (10.8%) | |
| 2 days | 73 (5.6%) | 62 (6.1%) | | 36 (5.2%) | 45 (6.5%) | |
| 3 days | 87 (6.7%) | 117 (11.5%) | | 54 (7.8%) | 75 (10.9%) | |
| 4 days | 119 (9.2%) | 125 (12.3%) | | 61 (8.9%) | 83 (12.1%) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5 days | 198 (15.3%) | 125 (12.3%) | | 96 (14.0%) | 83 (12.1%) | |
| 6 or more days | 503 (38.9%) | 431 (42.3%) | | 274 (39.8%) | 272 (39.5%) | |
| WILL-BLEED bleeding risk score | | | 0.4454 | | | 0.1064 |
| Low risk (<4) | 496 (38.4%) | 191 (18.8%) | | 163 (23.7%) | 139 (20.2%) | |
| Medium risk (4-6) | 351 (27.1%) | 378 (37.1%) | | 240 (34.9%) | 231 (33.6%) | |
| High risk (>6) | 446 (34.5%) | 449 (44.1%) | | 285 (41.4%) | 318 (46.2%) | |
| Off-pump surgery | 326 (25.2%) | 174 (17.1%) | 0.1997 | 154 (22.4%) | 165 (24.0%) | -0.0379 |
| Bilateral internal mammary grafting | 423 (32.7%) | 368 (36.1%) | -0.0723 | 226 (32.8%) | 236 (34.3%) | -0.0308 |
| Number of distal anastomoses | 2.6 ± 1.0 | 2.8 ± 0.9 | -0.1622 | 2.7 ± 1.0 | 2.7 ± 1.0 | 0.0383 |
| Aortic cross-clamping time, minutes, mean (SD) | 56 ± 26 | 55 ± 26 | 0.0352 | 56 ± 26 | 56 ± 28 | 0.0075 |
| Cardiopulmonary bypass time, minutes, mean (SD) | 83 ± 34 | 83 ± 38 | -0.0031 | 83 ± 34 | 85 ± 42 | -0.0472 |

Data are n (%) unless otherwise noted. EuroSCORE = European System for Cardiac Operative Risk Evaluation, NSTEMI = non-ST-elevation myocardial infarction, SD = standard deviation, STEMI = ST-elevation myocardial infarction, SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery, Q = quartile.

**Table 2** Postoperative outcomes

| | Overall cohort | | | Propensity score-matched cohort | | |
|---|---|---|---|---|---|---|
| | Clopidogrel n=1293 | Ticagrelor n=1018 | p-value | Clopidogrel n=688 | Ticagrelor n=688 | p-value |
| Definitions of major bleeding | | | | | | |
| UDPB severe or massive bleeding | 143 (11.1%) | 87 (8.5%) | 0.045 | 77 (11.2%) | 60 (8.7%) | 0.14 |
| PLATO life-threatening bleeding | 474 (36.7%) | 381 (37.4%) | 0.70 | 258 (37.5%) | 279 (40.6%) | 0.26 |
| BARC CABG-related bleeding | 168 (13.0%) | 111 (10.9%) | 0.13 | 91 (13.2%) | 80 (11.6%) | 0.38 |
| BART massive bleeding | 61 (4.7%) | 44 (4.3%) | 0.65 | 32 (4.7%) | 32 (4.7%) | 1.0 |
| E-CABG severe or massive bleeding | 120 (9.3%) | 93 (9.1%) | 0.90 | 64 (9.3%) | 68 (9.9%) | 0.72 |
| 12 hours chest tube output, ml, mean (SD) | 490 ± 320 | 470 ± 280 | 0.17 | 500 ± 340 | 470 ± 300 | 0.11 |
| Resternotomy for bleeding | 46 (3.6%) | 33 (3.2%) | 0.82 | 24 (3.5%) | 23 (3.3%) | 0.88 |
| Delayed chest closure for bleeding | 6 (0.5%) | 4 (0.4%) | 0.80 | 4 (0.6%) | 3 (0.4%) | 0.71 |
| Decline in hemoglobin during the operation day, g/l, mean (SD) | 37 ± 19 | 38 ± 18 | 0.64 | 38 ± 19 | 37 ± 19 | 0.37 |
| Transfusions | | | | | | |
| Units of RBC transfused intraoperatively | | | 0.17 | | | 0.48 |
| 0 | 1040 (80.4%) | 849 (83.4%) | | 554 (80.5%) | 546 (79.4%) | |
| 1-2 | 202 (15.6%) | 132 (13.0%) | | 107 (15.6%) | 110 (16.0%) | |
| ≥3 | 51 (3.9%) | 37 (3.6%) | | 27 (3.9%) | 32 (4.7%) | |
| Units of RBC transfused during hospital stay | | | 0.003 | | | 0.89 |
| 0 | 659 (51.0%) | 594 (58.3%) | | 356 (51.7%) | 361 (52.5%) | |
| 1-2 | 381 (29.5%) | 249 (24.5%) | | 194 (28.2%) | 194 (28.2%) | |
| 5-10 | 240 (18.6%) | 161 (15.8%) | | 133 (19.3%) | 122 (17.7%) | |
| ≥11 | 13 (1.0%) | 14 (1.4%) | | 5 (0.7%) | 11 (1.6%) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Plasma transfused | 112 (8.7%) | 81 (8.0%) | 0.54 | 67 (9.7%) | 62 (9.0%) | 0.64 |
| Platelets transfused | 153 (11.8%) | 136 (13.4%) | 0.27 | 95 (13.8%) | 94 (13.7%) | 0.94 |
| Hemostatic drugs | | | | | | |
| Cryoprecipitate | 4 (0.3%) | 3 (0.3%) | 0.95 | 4 (0.6%) | 3 (0.4%) | 0.66 |
| Fibrinogen | 58 (4.5%) | 41 (4.0%) | 0.58 | 27 (3.9%) | 36 (5.2%) | 0.24 |
| Recombinant factor VIIa | 6 (0.5%) | 1 (0.1%) | 0.11 | 3 (0.4%) | 1 (0.1%) | 0.34 |
| Prothrombin complex concentrate | 25 (1.9%) | 20 (2.0%) | 0.96 | 16 (2.3%) | 17 (2.5%) | 0.86 |
| Atrial fibrillation | 373 (28.8%) | 250 (24.6%) | 0.021 | 185 (26.9%) | 170 (24.7%) | 0.34 |
| Maximum postoperative creatinine, µmol/l, mean (SD) | 119 ± 104 | 110 ± 67 | 0.020 | 110 ± 69 | 110 ± 70 | 0.97 |
| Dialysis | 52 (4.0%) | 22 (2.2%) | 0.012 | 22 (3.2%) | 16 (2.3%) | 0.32 |
| Stroke | 13 (1.0%) | 9 (0.9%) | 0.77 | 3 (0.4%) | 7 (1.0%) | 0.22 |
| ICU stay, days, mean (SD) | 3.0 ± 4.4 | 2.8 ± 4.0 | 0.28 | 3.1 ± 5.2 | 3.1±4.4 | 0.91 |
| Thirty-day mortality | 26 (2.0%) | 26 (2.6%) | 0.38 | 10 (1.5%) | 20 (2.9%) | 0.065 |

Data are n (%) unless otherwise noted. BARC CABG = Bleeding Academic Research Consortium, BART = Blood conservation using Antifibrinolytics Randomized Trial, E-CABG = European multicenter study on Coronary Artery Bypass Grafting, PLATO = PLATelet Inhibition and Patient Outcomes, RBC = red blood cells, SD = standard deviation,UDPB = Universal Definition of Perioperative Bleeding.

# Figure legends

**Figure 1**

Study flow chart.

**Figure 2**

Incidence of the primary outcome measure severe or massive bleeding according to UDPB stratified by days between discontinuation of clopidogrel or ticagrelor and surgery. UDPB = Universal Definition of Perioperative Bleeding.

**Figure 3**

Incidence of the primary outcome measure severe or massive bleeding according to UDPB stratified by days (0-2, 3, 4-5, >5 days) between discontinuation of clopidogrel or ticagrelor and surgery. UDPB = Universal Definition of Perioperative Bleeding.

**Supplemental figure 1**

Incidence of the secondary outcome measures major bleeding according to 4 definitions PLATO life-threatening bleeding, BARC CABG-related bleeding, BART massive bleeding, and E-CABG severe or massive bleeding stratified by days between discontinuation of clopidogrel or ticagrelor and surgery. Left panels: Overall cohort. Right panels: Propensity score-matched cohort. BARC CABG = Bleeding Academic Research Consortium, BART = Blood conservation using AntifibrinolyticsRandomizedTrial, E-CABG = European multicenter study on Coronary Artery Bypass Grafting, PLATO = PLATelet Inhibition and Patient Outcomes.

**Figure 1**

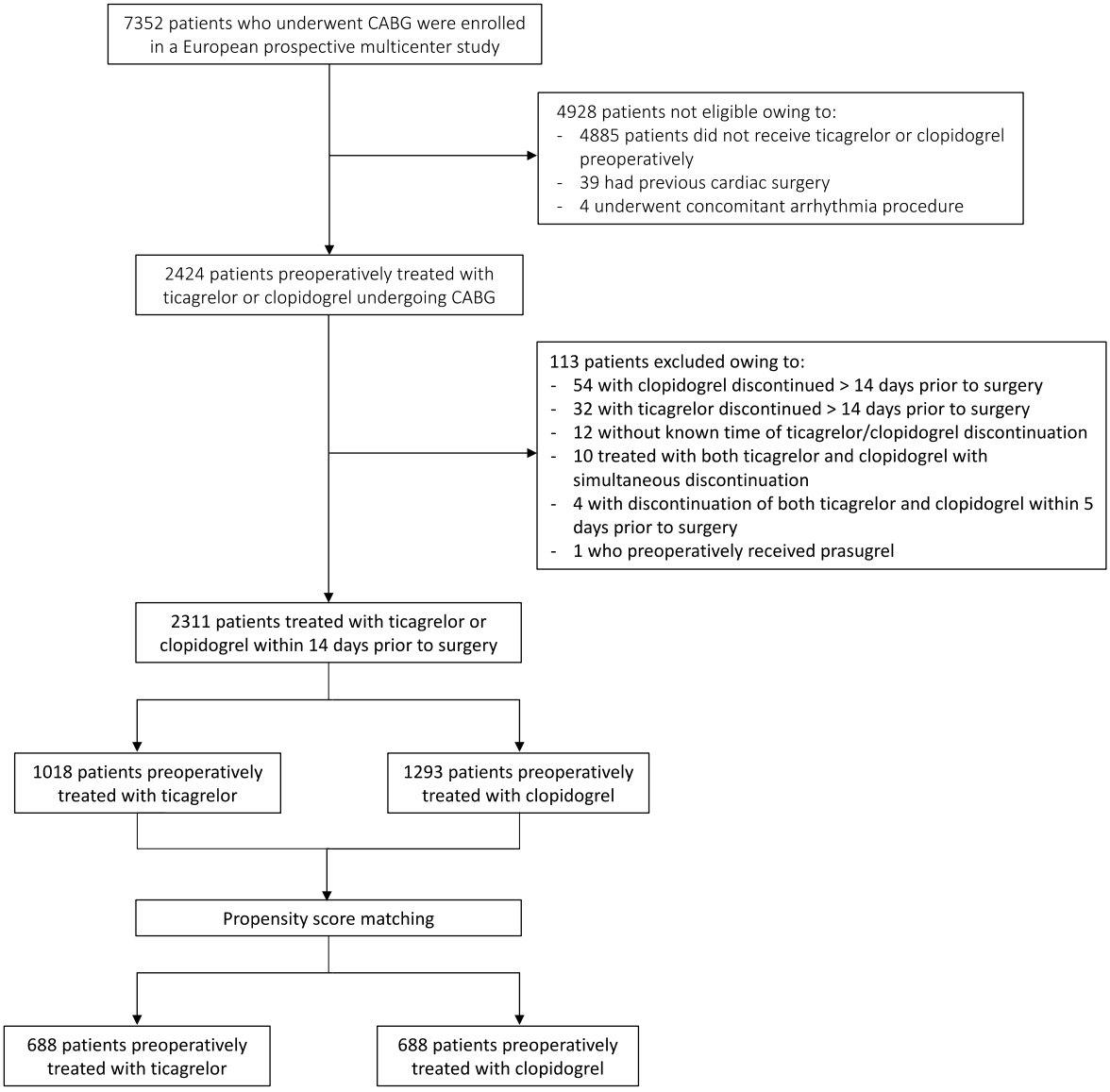


**Figure 2**

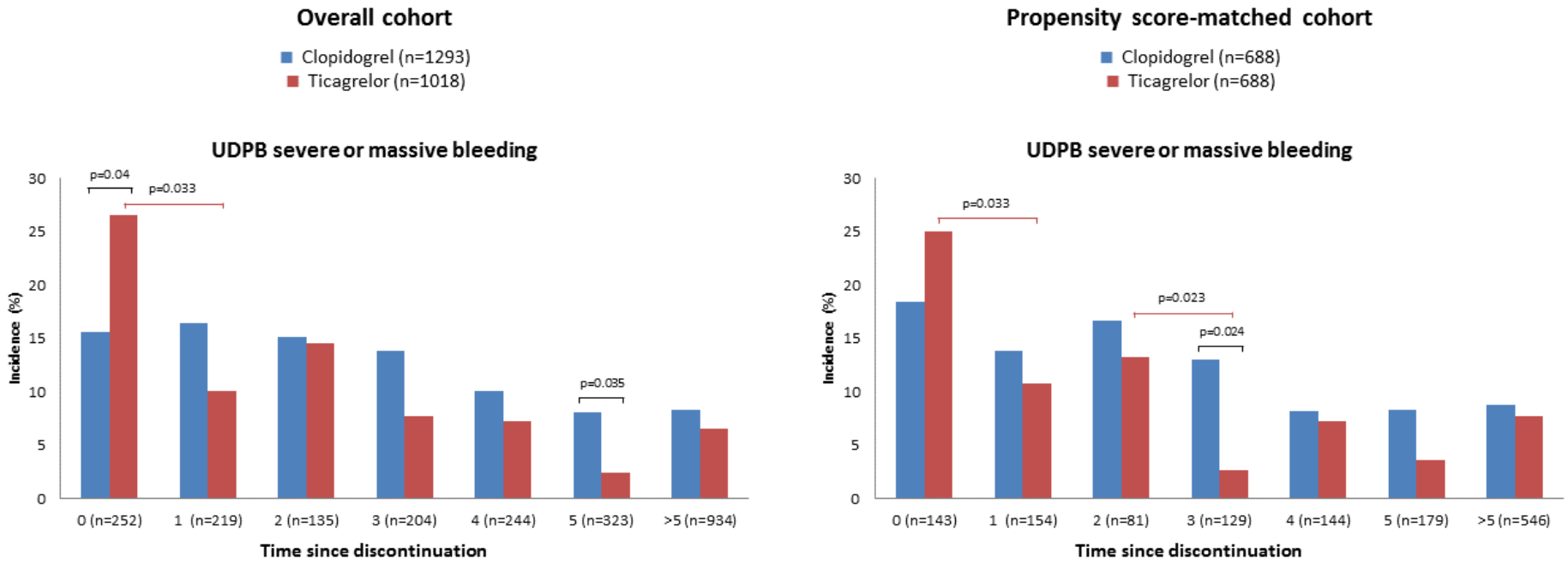
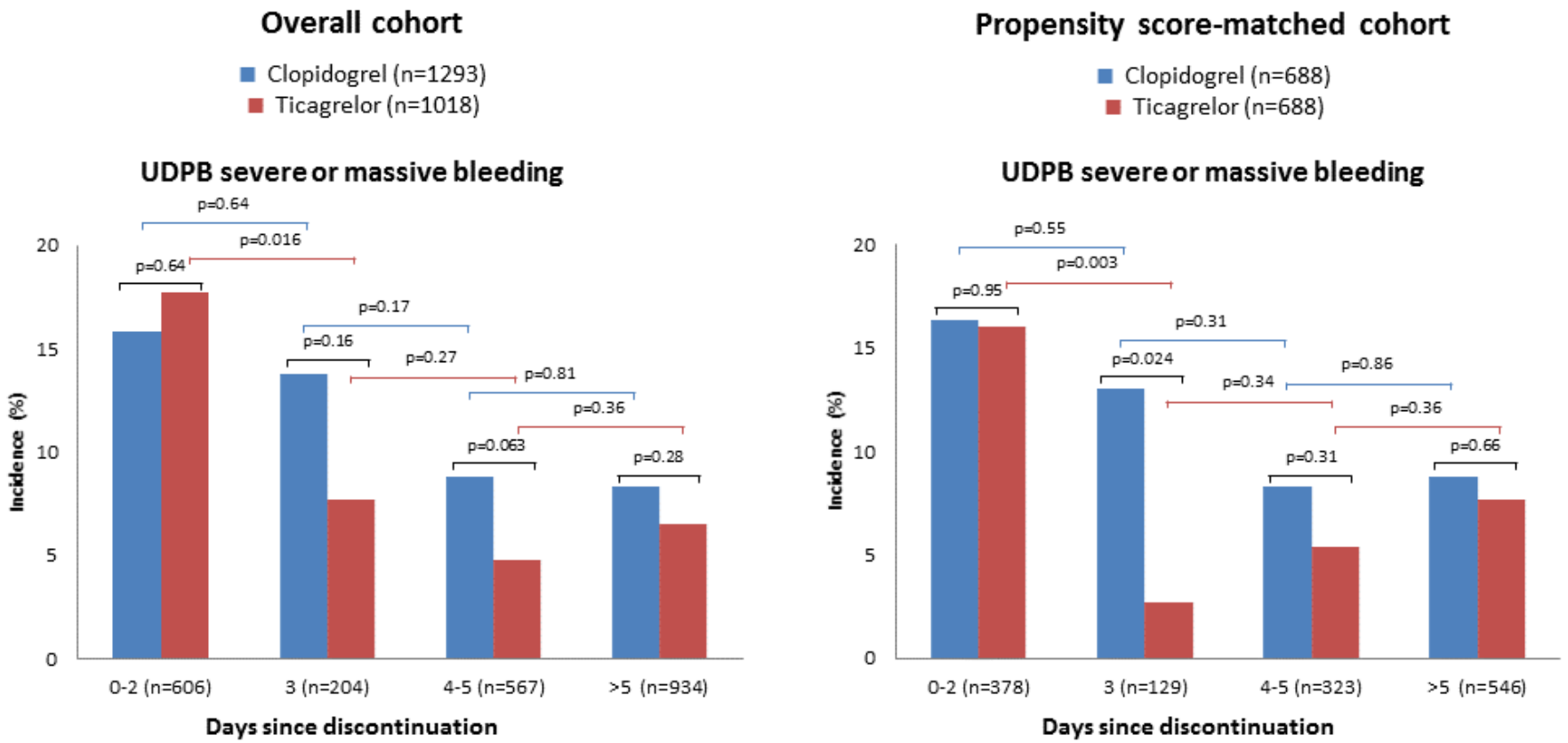


**Figure 3**



# Supplemental figure 1