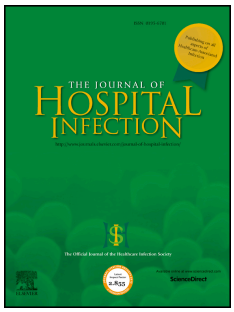

Infectious complications in patients receiving ticagrelor or clopidogrel before coronary artery bypass grafting

Magnus Dalén, MD, PhD, Fausto Biancari, MD, PhD.

PII: S0195-6701(19)30406-2

DOI: https://doi.org/10.1016/j.jhin.2019.09.018

Reference: YJHIN 5813

To appear in: *Journal of Hospital Infection*

Received Date: 14 August 2019

Accepted Date: 20 September 2019

Please cite this article as: Dalén M, Biancari F, Infectious complications in patients receiving ticagrelor or clopidogrel before coronary artery bypass grafting, *Journal of Hospital Infection*, https://doi.org/10.1016/j.jhin.2019.09.018.

Infectious complications in patients receiving ticagrelor or clopidogrel before coronary artery bypass grafting

Magnus Dalén,[1,2] MD, PhD and Fausto Biancari,[3,4,5] MD, PhD.

[1]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden;

[2]Department of Cardiac Surgery, Karolinska University Hospital, Stockholm, Sweden;

[3]Heart Center, Turku University Hospital, University of Turku, Turku, Finland;

[4]Department of Surgery, University of Turku, Turku, Finland;

[5]Department of Surgery, University of Oulu, Oulu, Finland.

Word count: 580

Summary word count: 150

Conflict of interest**:** None

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

Role of the Funder: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation or review of the manuscript; and decision to submit the manuscript for publication.

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

Summary

The antiplatelet agent ticagrelor has recently been found to have bactericidal activity demonstrated in vitro and in a in vivo mouse model, which warrant further clinical investigations. The aim of this study was to evaluate infectious complications after coronary artery bypass grafting in patients preoperatively treated with ticagrelor or clopidogrel. In a multicenter trial, all adult patients who were preoperatively treated with ticagrelor or clopidogrel prior to isolated primary coronary artery bypass grafting were eligible. Propensity score matching was used. Outcome measures were any sternal wound infection, deep sternal wound infection, and any in-hospital use of postoperative antibiotics. Of 2311 patients who were included, 1293 (55.9%) received clopidogrel and 1018 (44.1%) ticagrelor preoperatively. In both overall and propensity score matched analyses, ticagrelor was associated with a similar incidence of infectious complications compared to clopidogrel. Our findings do not support a clinically relevant bactericidal effect of ticagrelor in patients undergoing CABG.

Introduction

The antiplatelet agent ticagrelor has recently been found to have bactericidal activity demonstrated in vitro and in a in vivo mouse model [1]. Ticagrelor is a $P2Y_{12}$ receptor inhibitor approved for prevention of cardiovascular events in patients with coronary artery disease. In the Comparison of Ticagrelor and Clopidogrel in Patients with Acute Coronary Syndrome (PLATO) trial patients treated with ticagrelor had lower risk of infection-related death than clopidogrel patients [2] and in the Targeting Platelet-Leukocyte Aggregates in Pneumonia With Ticagrelor (XANTHIPPE) study improved lung function was seen among ticagrelor patients hospitalized for pneumonia [3]. These findings might be explained by the bactericidal effect of ticagrelor [1] and warrant further investigations comparing infectious complications in ticagrelor-treated patients compared with patients treated with other antiplatelet drugs. The aim of this study was to evaluate infectious complications after coronary artery bypass grafting (CABG) in patients preoperatively treated with ticagrelor or clopidogrel.

Methods

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 within 14 days prior to isolated primary CABG 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). The detailed study protocol has been published previously [4, 5]. The study was approved by the regional or institutional review board. Outcome measures were any sternal wound infection, deep sternal wound infection, and any in-hospital use of postoperative antibiotics. Wound complications were defined according to the Centers for Disease Control and Prevention definitions of surgical site infections [6]. To reduce selection bias, a propensity score was calculated with ticagrelor/clopidogrel as the dependent variable (details have been published previously [5]). Analyses were performed in the overall cohort as well as in patients

receiving ticagrelor or clopidogrel within 2 days before surgery. Analyses were performed using Stata v.15.1 (StataCorp LP, College Station, TX, USA).

Results and Discussion

Of 2311 patients who were included, 1293 (55.9%) received clopidogrel and 1018 (44.1%) ticagrelor preoperatively. Patient and procedural characteristics are listed in Table 1. Baseline characteristics were well balanced in the propensity score matched cohort (688 pairs). In all analyses, ticagrelor was associated with a similar incidence of infectious complications compared to clopidogrel (Table 2).

Our findings do not support a clinically relevant bactericidal effect of ticagrelor in patients undergoing CABG. Although bactericidal activity of ticagrelor have been demonstrated in vitro and in vivo in a mouse model [1], bactericidal concentrations are not reached systemically in patients receiving typical ticagrelor dosages. It has been suggested that antibacterial activity at infection sites may still be achieved through local drug accumulation [1], but this remains to be proved. As stated by Lancellotti and collaborators, the main limitation regarding their findings of bactericidal activity of ticagrelor is that in vivo demonstration of bactericidal activity of ticagrelor was obtained in a mouse model, which differs from humans in terms of ticagrelor pharmacokinetics [1]. This limitation was overcome in our study, where we studied the clinically relevant effect of ticagrelor in patients undergoing CABG.

The present analysis has limitations. We did not have data regarding bacteria cultures or type of antibiotics used in patients with documented infectious complications. Furthermore, diagnosis of infection was done by physicians at the treating hospital. However, definitions of infectious complications were stated in the study protocol [4] and participating center was included as a covariate in the propensity score model [5].

In conclusion, ticagrelor was associated with a similar incidence of infectious complications compared to clopidogrel. We did not find a clinically relevant bactericidal effect of ticagrelor in patients undergoing CABG.

References

1. Lancellotti P, Musumeci L, Jacques N, Servais L, Goffin E, Pirotte B, et al. Antibacterial activity of ticagrelor in conventional antiplatelet dosages against antibiotic-resistant gram-positive bacteria. *JAMA Cardiol.* 2019;4:596-599.
2. Storey RF, James SK, Siegbahn A, Varenhorst C, Held C, Ycas J, et al. Lower mortality following pulmonary adverse events and sepsis with ticagrelor compared to clopidogrel in the PLATO study. *Platelets*. 2014;25(7):517-525.
3. Sexton TR, Zhang G, Macaulay TE, Callahan LA, Charnigo R, Vsevolozhskaya OA, et al. Ticagrelor reduces thromboinflammatory markers in patients with pneumonia. *JACC Basic Transl Sci*. 2018;3(4):435-449.
4. Biancari F, Ruggieri VG, Perrotti A, Svenarud P, Dalén M, Onorati F, et al. 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.
5. Holm M, Biancari F, Khodabandeh S, Gherli R, Airaksinen J, Mariscalco G, et al. Bleeding in patients treated with ticagrelor or clopidogrel before coronary artery bypass grafting. *Ann Thorac Surg.* 2019;107:1690-1698.
6. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol. 1999;20:250–278.

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
Prior stroke	71 (5.5%)	33 (3.2%)	0.1102	19 (2.8%)	24 (3.5%)	-0.0418
Extracardiac arteriopathy	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
Chronic lung disease	135 (10.4%)	113 (11.1%)	-0.0213	72 (10.5%)	75 (10.9%)	-0.0141
Left ventricular ejection fraction >50%	889 (68.8%)	634 (62.3%)	0.1405	443 (64.4%)	451 (65.6%)	0.0755
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, 3.46)	0.0142
SYNTAX score, mean (SD)	28.9 ±12.2	28.8 ±11.8	0.0077	29.3 ± 12.4	29.1 ± 12.4	0.0093

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
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, SD = standard deviation, SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery, Q = quartile.

Table 2 Infectious complications in patients receiving clopidogrel or ticagrelor before coronary artery bypass grafting.

	Overall cohort			Propensity score-matched cohort		
Patients who received a P2Y12 inhibitor within 14 days before surgery						
	Clopidogrel n=1293	Ticagrelor n=1018	p-value	Clopidogrel n=688	Ticagrelor n=688	p-value
Any sternal wound infection	78 (6.0%)	62 (6.1%)	0.95	49 (7.1%)	50 (7.3%)	0.92
Deep sternal wound infection	35 (2.7%)	25 (2.5%)	0.71	25 (3.6%)	20 (2.9%)	0.45
Any postoperative use of antibiotics	333 (25.8%)	223 (22.0%)	0.035	192 (27.9%)	180 (26.3%)	0.49
Patients who received a P2Y12 inhibitor within 2 days before surgery						
	Clopidogrel n=386	Ticagrelor n=220	p-value	Clopidogrel n=161	Ticagrelor n=161	p-value
Any sternal wound infection	18 (4.7%)	13 (5.9%)	0.50	8 (5.0%)	10 (6.2%)	0.63
Deep sternal wound infection	8 (2.1%)	10 (4.5%)	0.085	4 (2.5%)	8 (5.0%)	0.24
Any postoperative use of antibiotics	121 (31.3%)	81 (37.0%)	0.16	58 (36.0%)	50 (31.2%)	0.37

Data are n (%).