International Journal of Cardiology 207 (2016) 84–86

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Correspondence

Efficacy of $P2Y_{12}$ receptor antagonists in patients with atrial fibrillation according to the CHA_2DS_2VASc score

Martina Ondrakova [a], Jiri Knot [a], Jaroslav Ulman [a], Marek Maly [b], Zuzana Motovska [a,*]

[a] University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic
[b] The National Institute of Public Health, Prague, Czech Republic

ARTICLE INFO

Article history:
Received 1 December 2015
Accepted 2 January 2016
Available online 6 January 2016

Keywords:
Atrial fibrillation
Percutaneous coronary intervention
$P2Y_{12}$ receptor antagonists
High on treatment platelet reactivity
CHA_2DS_2VASc score

Atrial fibrillation (AF) is the most common arrhythmia amongst adult population. It has been reported that 5.0–10.0% of the patients undergoing percutaneous coronary intervention (PCI) have concomitant AF [1–3]. Furthermore, AF is associated with a prothrombotic or hypercoagulable state [4]. It has been proven that the patients with AF had had far higher amounts of the platelet microparticles and the soluble P-selectin than the healthy controls in sinus rhythm. The abnormalities of the coagulant factors, including tissue factor, von Willebrand factor, factor IX and X, thrombin and fibrinogen were detected [5]. Patients with a history of AF who undergo PCI represent a group of patients where balancing between risks of thromboembolism and bleeding complications is accented. The combination of anticoagulant and antiplatelet therapy, particularly triple oral antithrombotic therapy (vitamin K antagonist/VKA + aspirin + clopidogrel), significantly increases the risk of bleeding complications [6,7]. Only sparse data are currently available on the combination of VKA with newer $P2Y_{12}$ inhibitors, which have been proven to reduce coronary endpoints, however, at the expense of more bleeding [8].

The aim of presented study was to verify whether the presence of AF impacts the efficacy of $P2Y_{12}$ receptor antagonists in the group of patients after stent-PCI, and to investigate whether there is a correlation between CHA_2DS_2VASc score and the efficacy of $P2Y_{12}$ receptor antagonists in this group of patients.

The prospective LAPCOR (Laboratory AntiPlatelet efficacy and Clinical Outcome Registry; ClinicalTrials.gov Identifier: NCT02264912) registry was analyzed. The consecutive patients who underwent stent-PCI were included. The registry protocol was approved by the Ethics Committee of the University Hospital Kralovske Vinohrady in Prague (Czech Republic). Patients were included after signing an informed consent for participation. No exclusion criteria were applied. The population of presented analysis consisted of 896 patients who underwent stent-PCI between June 2009 and June 2014.

The platelet reactivity was measured by phosphorylation of the protein VASP (vasodilator stimulated phosphoprotein) 24 ± 4 h after loading a dose of one of $P2Y_{12}$ receptor antagonists (clopidogrel 600 mg, prasugrel 60 mg, ticagrelor 180 mg) and it was expressed by Platelet Reactivity Index (PRI). The high on treatment platelet reactivity (HTPR) was defined by PRI ≥ 50. CHA_2DS_2VASc score was assessed in all patients.

Continuous data are presented as arithmetic means and standard deviations (SD). Two-sample t-test and Mann–Whitney test were used to examine differences between the groups. Categorical data were described using absolute and relative frequencies. Differences in proportions between the groups were analyzed using Fisher's exact test. Logistic regression model was used to compare study subgroups and to identify independent predictors of the HTPR. Variables included in the model were age, sex, body mass index, diabetes mellitus, hypertension and renal insufficiency. All statistical tests were evaluated as two-sided at a significance level of 0.05. Statistical analysis was performed by software Stata, release 9.2 (Stata Corp LP, College Station, TX).

Characteristics of the study population are presented in Table 1. Clopidogrel group consists 639 patients (16.28% with AF, 65.4% acute PCI), prasugrel group of 136 (5.15% with AF) and ticagrelor group of 121 patients (14.05% with AF).

We came to a conclusion that prasugrel and ticagrelor are significantly more effective than clopidogrel regardless of the presence of AF. Within the clopidogrel group, the median PRI was 44.9% (IQR 36.1) vs the prasugrel/ticagrelor group 12.6% (IQR 17.2) ($p < 0.001$). HTPR was detected in 42.8% of the patients with clopidogrel, while in the prasugrel/ticagrelor group, the proportion of the patients with HTPR was 7.5% ($p < 0.001$).

No difference in the efficacy of clopidogrel in patients with AF was observed, regardless of whether PCI was performed in a setting of ACS or electively. In patients who underwent elective PCI, the median PRI

* Corresponding author at: University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Srobarova 50, 10034 Prague, Czech Republic.
E-mail address: motovska.zuzana@gmail.com (Z. Motovska).

http://dx.doi.org/10.1016/j.ijcard.2016.01.039
0167-5273/

Table 1
Baseline characteristics of the study population in relation to presence of AF.

	Patients without AF		Patients with AF		p (value)
	n = 768		n = 128		
Age	65.6	(12.2)	74.6	(9.3)	<0.001
Sex (representation of male sex)	432	(67.2)	59	(51.8)	0.002
Body mass index (BMI)	28.5	(4.5)	27.6	(4.7)	0.043
Acute coronary syndrome	468	(72.8)	69	(60.5)	0.010
Hypertension	436	(67.8)	92	(80.7)	0.006
Diabetes mellitus	210	(32.7)	36	(31.6)	0.914
Dyslipidemia	240	(37.3)	45	(39.5)	0.676
Previous myocardial infarction	157	(24.5)	36	(31.6)	0.129
Previous *coronary* artery *bypass* grafting	65	(10.1)	13	(11.4)	0.738
Chronic ischemic limb disease	47	(7.3)	15	(13.2)	0.042
Previous stroke	41	(6.4)	21	(18.4)	<0.001
Smoking	250	(39.7)	26	(23.0)	0.001
Renal dysfunction	73	(11.4)	18	(15.9)	0.209
Glomerular filtration rate (GFR) before PCI	73.6	(56.6–89.4)	58.5	(44.8–77.3)	<0.001
GFR after PCI	73.1	(54.8–89.4)	59.0	(40.4–69.2)	<0.001
White blood count	9.7	(7.6–12.5)	8.6	(6.8–10.9)	0.003
Red blood count	4.6	(4.2–4.9)	4.4	(4.1–4.7)	0.020
Hemoglobin	13.9	(12.7–14.9)	13.7	(12.5–14.7)	0.200
Platelet	227	(190–270)	209.5	(175–273)	0.014
INR	1.11	(1.05–1.21)	1.19	(1.10–1.27)	<0.001
Clopidogrel	535	(83.7%)	104	(16.3%)	
Prasugrel	129	(94.6%)	7	(5.2%)	
Ticagrelor	104	(85.9%)	17	(14.1%)	

was 35.7% (IQR 42.3) in those with AF vs 42.8% (IQR 32.1) in those without AF (p = 0.643). HTPR was discovered in 42.2% of clopidogrel patients with AF and elective PCI and in 34.1% patients without AF (p = 0.384). Within the subpopulation of patients with ACS, the median PRI was 41.6% (IQR 38.5) in the group with AF vs 46.0% (IQR 36.1) without AF (p = 0.429). HTPR was assessed in 39.9% of the clopidogrel patients with ACS and AF, and in 43.4% patients without AF (p = 0.572).

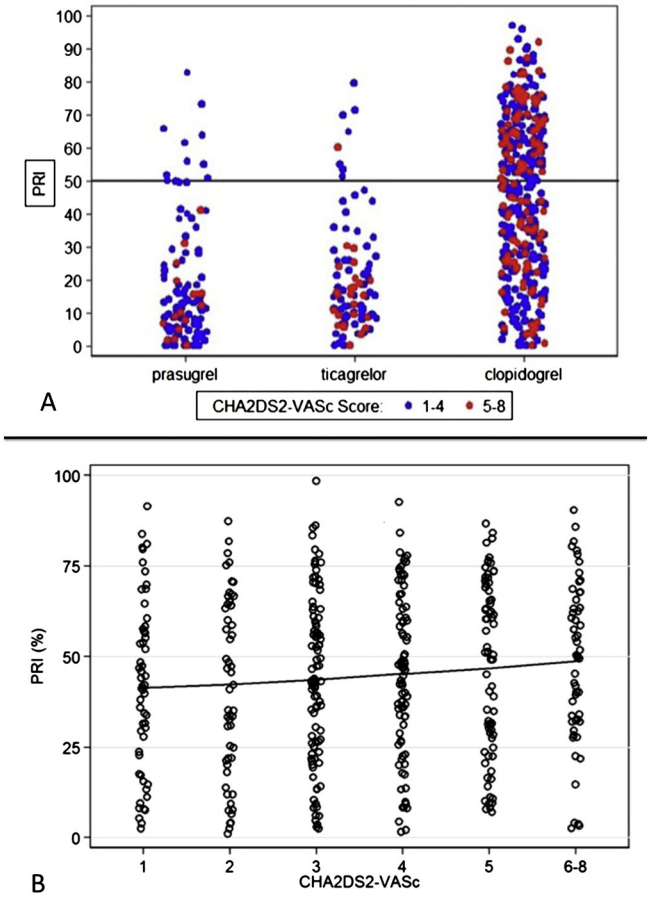

Fig. 1. The correlation between CHA_2DS_2VASc score and the efficacy of $P2Y_{12}$ receptor antagonists A/CHA_2DS_2VASc score and the efficacy of $P2Y_{12}$ receptor antagonists in patients with an acute coronary syndrome B/CHA_2DS_2VASc score and the efficacy of clopidogrel in patients with an acute coronary syndrome.

We did not demonstrate the impact of AF on the efficacy of prasugrel or ticagrelor. In this subpopulation, the median PRI was 11.6% (IQR 10.5) in the patients with AF vs 12.7% (IQR 18.0) in the patients without AF (p = 0.195). HTPR was revealed in 4.4% of prasugrel/ticagrelor patients with AF and in 7.9% without AF (p = 1.000).

The other finding was that periprocedural administration of glycoprotein IIb/IIIa inhibitors was associated with significantly higher efficacy of $P2Y_{12}$ receptor antagonists. In patients treated with GP IIb/IIIa inhibitors, the median PRI was 23.3% (IQR 40.5) in contrast to patients not treated with GP IIb/IIIa inhibitors, the median PRI was 35.3% (IQR 42.6) (p = 0.008).

The univariate and multivariate logistic regressions were used to test the correlation between CHA_2DS_2VASc score and the efficacy of $P2Y_{12}$ receptor antagonists. Using the univariate analysis, CHA_2DS_2VASc score was recognized as a significant predictor of the HTPR in the clopidogrel group of patients who underwent stent-PCI in setting of ACS (p = 0.015), primarily if CHA_2DS_2VASc score was ≥5 (odds ratio 1.72 [95% CI 1.13 to 2.63, p = 0.011]). This result became also significant after adjusting for confounding variables in the multivariate analysis (adjusted odds ratio 1.74 [95% CI 1.02 to 2.98, p = 0.041]). In clopidogrel group of patients undergoing elective PCI, CHA_2DS_2VASc score was not revealed as a predictor of the HTPR (p = 0.641). There was also no significant correlation between the efficacy of prasugrel and ticagrelor and CHA_2DS_2VASc score (p = 0.879) (Fig. 1).

The main finding of the presented study is that the presence of AF does not impact the efficacy of prasugrel or ticagrelor. For the replacement of clopidogrel one of prasugrel or ticagrelor should be considered in patients with AF who undergo stent-PCI in a setting of ACS and who are in a high risk of thrombotic events and low bleeding risk. Periprocedural administration of GP IIb/IIIa inhibitors in this high risk population increases the efficacy of clopidogrel.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

[1] A. Rubboli, M. Colletta, J. Valencia, A. Capecchi, N. Franco, L. Zanolla, et al., WARfarin and coronary STENTing (WAR–STENT) study group. Periprocedural management and in-hospital outcome of patients with indication for oral anticoagulation undergoing coronary artery stenting, J. Interv. Cardiol. 22 (2009) 390–397.

[2] S.J. Connolly, J. Pogue, R.G. Hart, S.H. Hohnloser, M. Pfeffer, S. Chrolavicius, et al., Effect of clopidogrel added to aspirin in patients with atrial fibrillation, N. Engl. J. Med. 360 (2009) 2066–2078.

[3] L.S. Wann, A.B. Curtis, C.T. January, K.A. Ellenbogen, J.E. Lowe, N.A.M. Estes III, et al., 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline). A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, Circulation 123 (2011) 104–123.

[4] D.S. Conway, P. Buggins, E. Hughes, G.Y. Lip, Relationship of interleukin-6 and C-reactive protein to the prothrombotic state in chronic atrial fibrillation, J. Am. Coll. Cardiol. 43 (2004) 2075–2082.

[5] A. Choudhury, G.Y. Lip, Atrial fibrillation and the hypercoagulable state: from basic science to clinical practise, Pathophysiol. Haemost. Thromb. 33 (2003/2004) 282–289.

[6] P. Karjalainen, P. Porela, A. Ylitalo, S. Vikman, K. Nyman, M.A. Vaittinen, et al., Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting, Eur. Heart J. 28 (2007) 726–732.

[7] Z. Khurram, E. Chou, R. Minutello, G. Bergman, M. Parikh, S. Naidu, et al., Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding, J. Invasive Cardiol. 18 (2006) 162–164.

[8] G. Montalescot, S.D. Wiviott, E. Braunwald, S.A. Murphy, C.M. Gibson, C.H. McCabe, Antman EM; TRITONTIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial, Lancet 373 (2009) 723–731.