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EFFICACY AND SAFETY OF PRASUGREL AND CLOPIDOGREL IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION IN PREHOSPITAL SETTING

Lukasz Szarpak, Assoc Prof. PhD, MBA[a,*] lukasz.szarpak@gmail.com, **Kurt Ruetzler,** Prof. MD[b], **Tomasz Figatowski**, MD[c], **Michal Pruc**, MS[d], **Aleksandra Gasecka**, PhD, MD[e], **Milosz J. Jaguszewski,** Prof, MD.[c]

[a]Institute of Outcomes Research, Maria Sklodowska-Curie Medical Academy in Warsaw, Warsaw, Poland; Maria Sklodowska-Curie Białystok Oncology Centre, Białystok, Poland; Polish Society of Disaster Medicine, Warsaw, Poland.

[b]Departments of General Anesthesiology and Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio, USA

[c]1st Department of Cardiology, Medical University of Gdansk, Gdansk, Poland.

[d]Polish Society of Disaster Medicine, Warsaw, Poland

[e]Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands; 1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland.

[*]Corresponding author at.: Institute of Outcomes Research, Maria Sklodowska-Curie Medical Academy, Solidarnosci Av. 12, 03-411 Warsaw, Poland

Keywords
Acute coronary syndrome; prehospital antiplatelet treatment; P2Y12; clopidogrel; prasugrel; outcome.

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To the Editor,

an early administration of dual antiplatelet therapy with acetylsalicylic acid and P2Y12 inhibitor is a gold standard in prehospital treatment of acute coronary syndromes (ACS) [1]. Compared to the well-established clopidogrel, prasugrel is a stronger P2Y12 inhibitor, which is currently preferred in the guidelines in ACS patients [2,3]. The TRITON-TIMI 38 trial showed the superiority of prasugrel to clopidogrel in reducing cardiovascular events in patients with ACS. However, prasugrel treatment was associated with higher rates of bleeding. An important aspect of this trial was that both P2Y12 inhibitors were administered in the perihospital setting [4]. In contrast to TRITON-TIMI 38, the results from the MULTIPRAC Registry where prasugrel was administered in the pre-hospital setting, revealed similar bleeding rates in prasugrel versus clopidogrel groups in ST-segment elevation myocardial infarction (STEMI) patients [5]. As a consequence, the preference of prasugrel over clopidogrel as a pre-hospital treatment of ACS remains still controversial. Therefore, we performed a systematic review and meta-analysis to

evaluate the efficacy and safety of prasugrel compared with clopidogrel for ACS in the prehospital setting.

We systematically reviewed randomized trials in accordance to the preferred reporting items for systematic review and meta-analysis (PRISMA) statement. We collected data from the following databases: Scopus, EMBASE, PubMed, Web of Science, and Cochrane Central Register and Controlled Trials (CENTRAL) up to March 21, 2021. Studies included in this meta-analysis fulfilled the following criteria (PICOS): (1) participants, adult patients with ACS; (2) intervention prasugrel in the pre-hospital setting; (3) comparison, clopidogrel in the pre-hospital setting; (4) outcomes, detailed information on survival; (5) study design, randomized controlled trials and observational trials. We presented all results as odds ratio (OR) with 95% confidence interval (CI). The fixed-effects model was used. The two-tailed $P < 0.05$ was considered statistically significant. We performed all statistical analyses with Review Manager Software 5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark).

According to the inclusion and exclusion criteria, three studies were included in the analysis [5-7], where 1,715 patients were treated with prasugrel, and 1,960 with clopidogrel. Two complementary manuscripts from the MULTIPRAC registry were included, with the study by Clemmensen et al. reporting short-term outcomes [5], and the study by Goldstein et al. reporting 1-year follow-up [7]. In all studies, the decision to administer the P2Y12 inhibitor (prasugrel or clopidogrel) was done by the coordinating doctor (mostly interventional cardiologist, who was about to perform the intervention in ACS), and the drug was administered either by the doctors or paramedics in the pre-hospital setting.

We presented the detailed characteristics of the included tests in Tables S1 and S2 (Supplementary File). In a 30-day observational period, major adverse cardiac events (MACE) rate was comparable in the prasugrel and clopidogrel group and amounted to 2.5% vs. 3.7% (OR=0.79; 95%CI: 0.54, 1.18; p=0.25). The 30-day cardiovascular mortality was also comparable between the groups (0.4% vs. 0.7% respectively; OR=0.51; 95%CI: 0.10, 2.55; p=0.41). There was a lower proportion of any in-hospital complications in the prasugrel group, compared to patients treated with clopidogrel (2.5% vs. 4.9%; OR=0.50; 95%CI: 0.27, 0.93; p=0.03; Table 1). Other complications, including major bleeding, were comparable between the groups (Table 1). At one year follow-up, prasugrel was associated with both lower cardiovascular mortality (0.5% vs. 2.6%, respectively; OR=0.18; 95%CI: 0.06, 0.58; p=0.004) and all-cause mortality (1.6% vs. 4.9%, respectively; OR=0.31; 95%CI: 0.15, 0.62; p=0.001), compared to clopidogrel.

In conclusions, the pre-hospital administration of prasugrel was associated with a lower mortality at one year follow-up and a lower risk of in-hospital complications, compared to clopidogrel.

Conflict of interest: None.

REFERENCES:

1. Gasecka A, Nieuwland R, van der Pol E, et al. P2Y12 antagonist ticagrelor inhibits the release of procoagulant extracellular vesicles from activated platelets. Cardiol J 2019; 26(6):782-789. doi: 10.5603/CJ.a2018.0045

2. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020 Aug 29:ehaa575. doi: 10.1093/eurheartj/ehaa575.
3. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur Heart J. 2018; 39(3):213-260. doi: 10.1093/eurheartj/ehx419.
4. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357(20):2001-15. doi: 10.1056/NEJMoa0706482.
5. Clemmensen P, Grieco N, Ince H, et al. MULTInational non-interventional study of patients with ST-segment elevation myocardial infarction treated with PRimary Angioplasty and Concomitant use of upstream antiplatelet therapy with prasugrel or clopidogrel--the European MULTIPRAC Registry. Eur Heart J Acute Cardiovasc Care. 2015; 4(3):220-9. doi: 10.1177/2048872614547449.
6. De Backer O, Ratcovich H, Biasco L, et al. Prehospital administration of P2Y12 inhibitors and early coronary reperfusion in primary PCI: an observational comparative study. Thromb Haemost. 2015; 114(3):623-31. doi: 10.1160/TH15-01-0026.
7. Goldstein P, Grieco N, Ince H, et al. Mortality in primary angioplasty patients starting antiplatelet therapy with prehospital prasugrel or clopidogrel: a 1-year follow-up from the European MULTIPRAC Registry. Vasc Health Risk Manag. 2016; 12:143-51. doi: 10.2147/VHRM.S95391.

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11. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357(20):2001-15. doi: 10.1056/NEJMoa0706482.
12. Clemmensen P, Grieco N, Ince H, et al. MULTInational non-interventional study of patients with ST-segment elevation myocardial infarction treated with PRimary Angioplasty and Concomitant use of upstream antiplatelet therapy with prasugrel or clopidogrel--the European MULTIPRAC Registry. Eur Heart J Acute Cardiovasc Care. 2015; 4(3):220-9. doi: 10.1177/2048872614547449.
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14. Goldstein P, Grieco N, Ince H, et al. Mortality in primary angioplasty patients starting antiplatelet therapy with prehospital prasugrel or clopidogrel: a 1-year follow-up from the European MULTIPRAC Registry. Vasc Health Risk Manag. 2016; 12:143-51. doi: 10.2147/VHRM.S95391.

Table 1. Polled analysis of outcomes in included studies

Trials	No of studies	Events/participants		Events		Heterogeneity between trials		P-value for differences across groups
		Prasugrel group	Clopidogrel group	OR	95%CI	P-value	I^2 statistic	
CLINICAL ENDPOINTS AT 30-DAYS FOLLOW UP								
MACE	*2*	*43/1,715 (2.5%)*	*72/1,960 (3.7%)*	*0.79*	*0.54, 1.18*	*0.63*	*0%*	*0.25*
In-hospital MACE	*1*	*22/883 (2.5%)*	*49/1,532 (3.2%)*	*0.77*	*0.46, 1.29*	*NA*	*NA*	*0.32*
CV death	*1*	*3/832 (0.4%)*	*3/428 (0.7%)*	*0.51*	*0.10, 2.55*	*NA*	*NA*	*0.41*
Death from any cause	*2*	*27/1,715 (1.6%)*	*49/1,960 (2.5%)*	*0.84*	*0.52, 1.37*	*0.77*	*0%*	*0.49*
Recurrent MI	*2*	*6/1,715 (0.3%)*	*11/1,960 (0.6%)*	*0.81*	*0.30, 2.23*	*0.73*	*0%*	*0.69*
Urgent revascularization	*2*	*15/1,715 (0.9%)*	*19/1,960 (1.0%)*	*0.85*	*0.42, 1.72*	*0.94*	*0%*	*0.65*
Stent thrombosis	*2*	*4/1,715 (0.2%)*	*13/1,960 (0.7%)*	*0.47*	*0.15, 1.45*	*0.44*	*0%*	*0.19*
Stroke	*1*	*2/832 (0.2%)*	*2/428 (0.5%)*	*0.51*	*0.07, 3.66*	*NA*	*NA*	*0.51*
Major bleeding	*2*	*29/1,715 (1.7%)*	*68/1,960 (3.5%)*	*0.64*	*0.41, 1.01*	*0.48*	*0%*	*0.05*
New renal impairment	*1*	*4/832 (0.5%)*	*7/428 (1.6%)*	*0.29*	*0.08, 1.00*	*NA*	*NA*	*0.05*
Any pre-hospital complication	*1*	*91/832 (10.9%)*	*38/428 (8.9%)*	*1.26*	*0.85, 1.88*	*NA*	*NA*	*0.25*
Any hospital complication	*1*	*21/832 (2.5%)*	*21/428 (4.9%)*	*0.50*	*0.27, 0.93*	*NA*	*NA*	***0.03***
MORTALITY AT ONE-YEAR FOLLOW UP								
CV death	*1*	*4/824 (0.5%)*	*11/425 (2.6%)*	*0.18*	*0.06, 0.58*	*NA*	*NA*	***0.004***
Death from any cause	*1*	*13/824 (1.6%)*	*21/425 (4.9%)*	*0.31*	*0.15, 0.62*	*NA*	*NA*	***0.001***

Table