Učinkovitost i sigurnost individualizirane primjene antagonista P2Y12 receptora temeljem agregometrije u odnosu na fiksne doze u bolesnika nakon akutnog infarkta miokarda s elevacijom ST-segmenta

Efficacy and safety of individualized P2Y12 receptor antagonists treatment in patients after acute myocardial infarction with ST-segment elevation

Hrvoje Jurin*, **Jure Samardžić**, **Saša Pavasović**, **Mia Dubravčić**, **Marijan Pašalić**, **Boško Skorić**, **Maja Čikeš**, **Daniel Lovrić**, **Jana Ljubas Maček**, **Dora Fabijanović**, **Ivo Planinc**, **Nina Jakuš**, **Davor Miličić**

Medicinski fakultet Sveučilišta u Zagrebu, Klinički bolnički centar Zagrebu, Zagreb, Hrvatska

University of Zagreb School of Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

RECEIVED:
October 28, 2018

ACCEPTED:
November 5, 2018

KLJUČNE RIJEČI: antiagregacijska terapija, akutni koronarni sindrom.

KEYWORDS: antiaggregational therapy, acute coronary syndrome.

CITATION: Cardiol Croat. 2018;13(11-12):441. | https://doi.org/10.15836/ccar2018.441

***ADDRESS FOR CORRESPONDENCE**: Hrvoje Jurin, Klinički bolnički centar Zagreb, Kišpatićeva 12, HR-10000 Zagreb, Croatia. / Phone: +385-98-525-002 / E-mail: hrvoje.jurin@gmail.com

ORCID: Hrvoje Jurin, https://orcid.org/0000-0002-2599-553X • Jure Samardžić, https://orcid.org/0000-0002-9346-6402
Saša Pavasović, https://orcid.org/0000-0002-3705-0226 • Mia Dubravčić, https://orcid.org/0000-0003-0441-4772
Marijan Pašalić, https://orcid.org/0000-0002-3197-2190 • Boško Skorić, https://orcid.org/0000-0001-5979-2346
Maja Čikeš, https://orcid.org/0000-0002-4772-5549 • Daniel Lovrić, https://orcid.org/0000-0002-5052-6559
Jana Ljubas Maček, https://orcid.org/0000-0001-7171-2206 • Dora Fabijanović, https://orcid.org/0000-0003-2633-3439
Ivo Planinc, https://orcid.org/0000-0003-0561-6704 • Nina Jakuš, https://orcid.org/0000-0001-7304-1127
Davor Miličić, https://orcid.org/0000-0001-9101-1570

Uvod: Postoji niz studija koje su ukazale na postojanje povišene ostatne trombocitne aktivnosti (mjerene testovima trombocitne agregacije) u pojedinih bolesnika liječenih klopidogrelom ovisno o stupnju biotransformacije lijeka.[1-3] Također je pokazano kako se povišenjem doze klopidogrela može nadvladati navedena povišena aktivnost, a time ujedno i utjecati na kliničke ishode liječenja. Ovdje donosimo rezultate skupine bolesnika koji su dovršili jednogodišnje praćenje, a koji su uvršteni u randomiziranu kliničku studiju ispitivanja učinkovitosti i sigurnosti individualizirane primjene antagonista P2Y12 receptora temeljem nalaza testova agregometrije u odnosu na fiksne doze tikagrelora u bolesnika nakon akutnog infarkta miokarda s elevacijom ST-segmenta (STEMI).

Bolesnici i metode: U analizu je uključeno 51 uzastopnih bolesnika (9 žena, srednja dob 58,9 godina) nakon preboljelog STEMI-a. Svi su bolesnici tijekom prvih mjesec dana liječeni standardnom dozom tikagrelora uz acetilsalicilatnu kiselinu, a potom su randomizirani u dvije skupine. Prva skupina je nastavila postojeću antiagregacijsku terapiju tijekom godine dana, a u drugoj je skupini tikagrelor zamijenjen klopidogrelom uz individualnu titraciju doze ovisno o nalazima agregometrije mjerenih Multiplate® analizatorom. Primarni ishod studije bila je incidencija velikih kardiovaskularnih događaja (kardiovaskularna smrt, infarkt miokarda, moždani udar i ponovna revaskularizacija), a sekundarni učestalost velikih i malih krvarenja definiranih BARC klasifikacijom.

Rezultati: Tijekom praćenja nije zabilježen niti jedan primarni ishod kao niti jedan slučaj velikog krvarenja. Zabilježena je statistički značajno manja incidencija malih krvarenja u skupini bolesnika liječenih individualiziranom primjenom P2Y12 antagonista (p=0,027) što odgovara 4,8 puta većoj šansi razvoja krvarenja u bolesnika liječenih fiksnom dozom tikagrelora u odnosu na bolesnike liječene individualiziranim pristupom (OR 4,8; 95% CI 1.118 to 20.611; p=0,035).

Zaključak: Rezultati ukazuju kako bi individualizirana primjena P2Y12 antagonista mogla predstavljati jednako učinkovitu, a sigurniju opciju liječenja bolesnika nakon preboljelog STEMI-a u odnosu na terapiju fiksnim dozama tikagrelora.

Introduction: Several studies have reported high residual platelet activity (measured using platelet aggregation tests) in patients treated with clopidogrel depending on the grade of drug biotransformation in liver via cytochrome P450 system.[1-3] It is also known that this high on-treatment activity as well as clinical outcomes may be improved by increasing clopidogrel dose. We report the results of a group of patients who have completed 1-year follow-up and who were included in a randomized clinical trial investigating efficacy and safety of individualized P2Y12 receptor antagonists treatment based on aggregometry tests versus fixed dose ticagrelor regimen in patients after acute myocardial infarction with ST-segment elevation (STEMI).

Patients and Methods: We analyzed the data of 51 consecutive patients (9 female, mean age 58.9 years) treated for STEMI. During the first month after STEMI all the patients were treated using fixed dose ticagrelor with aspirin. Afterwards the patients were randomized into two groups. First group continued with the aforementioned therapy during one-year period. Patients in the second group were switched from ticagrelor to clopidogrel and treated during the one-year period by individualizing clopidogrel dose based on aggregometry tests using Multiplate® analyzer. Primary outcome was the incidence of major cardiovascular events (cardiovascular death, myocardial infarction, stroke and repeat revascularization). Secondary (safety) outcome was the incidence of minor and major bleeding defined using BARC classification.

Results: During one-year follow-up we haven't observed primary outcome or major bleeding event. We found statistically significantly lower incidence of minor bleeding in the group of patients treated with individualized P2Y12 antagonists dose tailoring (p=0.027) which transfers to 4.8 times higher chance of having minor bleeding while treated with fixed dose ticagrelor in comparison to patients treated with individualized approach (OR 4.8; 95% CI 1.118 to 20.611; p=0.035).

Conclusion: These results show that individualized P2Y12 antagonists treatment using aggregometry tests may represent equally effective but safer treatment approach in comparison to fixed dose ticagrelor regimen in patients after STEMI.

LITERATURE

1. Samardzic J, Krpan M, Skoric B, Pasalic M, Petricevic M, Milicic D. Serial clopidogrel dose adjustment after platelet function testing improves outcome of acute coronary syndrome patients undergoing percutaneous coronary intervention with high on-treatment platelet reactivity. J Thromb Thrombolysis. 2014 Nov;38(4):459-69. https://doi.org/10.1007/s11239-014-1087-0
2. Horenstein RB, Madabushi R, Zineh I, Yerges-Armstrong LM, Peer CJ, Schuck RN, et al. Effectiveness of clopidogrel dose escalation to normalize active metabolite exposure and antiplatelet effects in CYP2C19 poor metabolizers. J Clin Pharmacol. 2014 Aug;54(8):865-73. https://doi.org/10.1002/jcph.293
3. Muslimova EF, Afanasiev SA, Rebrova TY, Sergienko TN, Repin AN. [Association of ITGB3, P2RY12, and CYP2C19 gene polymorphisms with platelet functional activity in patients with coronary heart disease during dual antiplatelet therapy]. Ter Arkh. 2017;89(5):74-78. https://doi.org/10.17116/terarkh201789574-78