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Selection of $P2Y_{12}$ antagonist, treatment initiation, and predictors of high on-treatment platelet reactivity in a "Real World" registry

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

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

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ABSTRACT

Objective: The present study aimed to compare characteristics related to selection of a $P2Y_{12}$ antagonist, investigate initiation of therapy with new-generation drugs, and identify predictors of high on-treatment platelet reactivity (HTPR) in patients with acute coronary syndrome treated with stent percutaneous coronary intervention (PCI).

Methods and Results: Data from 589 patients in the LAPCOR (Laboratory AntiPlatelet efficacy and Clinical Outcome Registry; ClinicalTrials.gov Identifier: NCT02264912) registry was analyzed. $P2Y_{12}$ receptor antagonist efficacy was measured by VASP phosphorylation 24 ± 4 hours after a loading dose of clopidogrel (600 mg, N = 407), prasugrel (60 mg, N = 106), or ticagrelor (180 mg, N = 76) and expressed by platelet reactivity index (PRI). HTPR was defined as PRI ≥ 50%. Patients treated with prasugrel were significantly younger and had significantly higher hemoglobin levels than those who received clopidogrel or ticagrelor, while chronic kidney disease was significantly more prevalent in the ticagrelor group. Almost all invasively managed patients given new-generation drugs received a loading dose after coronary angiography. Mean residual PRI and HTPR were significantly higher after clopidogrel (44.2 ± 23.1% and 42.2%, respectively) vs. prasugrel (17.7 ± 18.0% and 9.4%, respectively) or ticagrelor (18.8 ± 17.0% and 7.9%, respectively; all $p < 0.001$). Among multiple variables tested, HTPR in patients treated with the new agents significantly related only to platelet count ($p = 0.014$) and mean platelet volume ($p = 0.03$).

Conclusion: Safety is the most important aspect under consideration in choosing new agents for an individual patient. Other than platelet count and mean platelet volume, factors known as predictors of higher platelet reactivity, did not influence the efficacy of new-generation $P2Y_{12}$ receptor antagonists.

Introduction

Dual antiplatelet therapy, aspirin plus $P2Y_{12}$ receptor antagonist, is a cornerstone of medical therapy for acute coronary syndromes (ACS) resulting from atherothrombosis [1,2]. The second-generation thienopyridine clopidogrel was used for more than a decade almost exclusively (with a small contribution of ticlopidin) as the $P2Y_{12}$ antagonist for combination antiplatelet therapy. Millions of treated patients have confirmed the drug benefits while exposing its limitations: slow onset of action and significant inter-individual variability in antiplatelet efficacy. Cumulative evidence indicates that up to one-third of treated patients have insufficient laboratory inhibition of platelet ($P2Y_{12}$) receptors for adenosine diphosphate [3,4]. High on-treatment platelet reactivity (HTPR) is significantly associated with an increased risk of ischemic events at short- and long-term follow-up [5,6].

The new $P2Y_{12}$ antagonists prasugrel and ticagrelor have overcome pharmacokinetic limitations of clopidogrel and, with a significant reduction of ischemic major cardiovascular events (cardiovascular death, myocardial infarction, stroke), also exceeded its clinical benefit [7,8]. Both prasugrel and ticagrelor are recommended as first-line drugs for antiplatelet therapy in ACS treated by intracoronary stent implantation [1,2]. Wider utilization of these highly effective antiplatelet drugs is limited by the presence of risk factors for bleeding. Prasugrel should also be avoided in patients with a history of transient ischemic attack or stroke.

The implementation of prasugrel and ticagrelor has shown continuous and steady progress [9,10]. With the increasing number of patients treated, further limitations of these new agents may gradually appear. However, the availability of three $P2Y_{12}$ antagonists, each with strengths and limitations, creates the possibility for individualizing antiplatelet therapy. The present study aimed to compare the characteristics related to selection of a $P2Y_{12}$ antagonist, investigate the initiation of therapy with the new agents, and identify predictors of high on-treatment platelet reactivity in patients with an acute coronary syndrome treated with stent percutaneous coronary intervention (PCI).

* Corresponding author at: Cardiocentre, University Hospital Kralovske Vinohrady, Šrobárova 50, Prague 100 34, Czech Republic. Tel.: +420 267 163 760; fax: +420 267 163 763.
E-mail address: zuzana.motovska@fnkv.cz (Z. Motovska).

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Methods

Registry

The prospective single-center PCI-VASP registry was analyzed. This ongoing LAPCOR (Laboratory AntiPlatelet efficacy and Clinical Outcome Registry; ClinicalTrials.gov Identifier: NCT02264912) registry was initiated in 2008 at a tertiary care cardiac center [11], and consecutive patients who underwent intracoronary stent implantation were included regardless of whether PCI was performed on an urgent or elective basis. The registry protocol was approved by the Ethics Committee of the University Hospital Kralovske Vinohrady in Prague (Czech Republic). Patients were included in the registry after signing an informed consent for participation. No exclusion criteria were applied for registry participation.

Data Collection

Standardized data were collected including demographics, anthropometric parameters, lifestyle habits, cardiovascular risk factors, major comorbidities, outpatient and inpatient medications, laboratory measures, and echocardiographic assessment of left ventricular ejection fraction. Positive family history was defined as the presence of myocardial infarction (MI) or coronary revascularization in a first-degree relative at any age. Administration of antiplatelet and anticoagulant medications, including specific agents and dosages, was recorded in relation to the start of coronary angiography as either pre-procedural (before coronary angiogram) or peri-procedural (after coronary angiography and before PCI). Procedure-related variables were also recorded (type and lesion location, number of intervened vessels, type and number of delivered stents, visual assessment of pre- and post-PCI severity of coronary stenosis, Thrombolysis in Myocardial Infarction flow grade).

Laboratory Assessment

Efficacy of $P2Y_{12}$ receptor antagonists was measured by quantitative flow cytometric analysis of vasodilator-stimulated phosphoprotein (VASP) phosphorylation [12] according to the manufacturer's protocol (Platelet VASP; Diagnostica Stago, Biocytex) using a FACScan flow cytometer (Becton Dickinson). Flow cytometry analysis was performed in a laboratory accredited by the Joint Commission International, and examiners analyzing VASP phosphorylation state were blinded to treatment-related data.

Whole blood for the assessment was taken 24 ± 4 hours after a loading dose of clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg). Results were expressed by platelet reactivity index (PRI, %), defined as: $[MFI_{(PGEI)} - MFI_{(PGEI\ +\ ADP)}/MFI_{(PGEI)}] \times 100$, where MFI is mean fluorescence intensity and PGE1 is prostaglandin E1. A lower PRI indicates a greater antiplatelet effect. High on-treatment platelet reactivity was defined as PRI ≥ 50%.

Study Subjects

For the present analysis, the study population consisted of patients with invasively managed ACS and stent PCI from 2011–2013. ACS was defined as ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina according to the current guidelines [1,2,13]. Patients who received two $P2Y_{12}$ receptor antagonists (mostly clopidogrel and ticagrelor) were excluded.

Data Analyses

Continuous data are presented as means and standard deviations, or as medians and 25th–75th percentile ranges. Between-group comparisons were carried out using analysis of variance and Kruskal-Wallis test and characterized by mean or median differences with 95% confidence intervals (95% CI). For significant results, Sidak's multiple comparisons procedure was used to determine which pairs of groups differ. Logistic regression was used to identify predictors of high on-treatment platelet reactivity. Variables included in the model were sex; BMI; history of hypertension, diabetes, hyperlipidemia, MI, coronary artery bypass graft (CABG), peripheral artery disease, stroke, family history of coronary artery disease, cigarette smoking, or chronic kidney disease (CKD); therapy with a statin, angiotensin-converting enzyme inhibitor, or beta blocker; single vs. multivessel disease; number of implanted stents; and serum levels of urea, creatinine, estimated glomerular filtration rate, hemoglobin, platelet count, and mean platelet volume. For categorical data, the differences in proportions among groups were analyzed using Fisher's exact test. All statistical tests were evaluated as two-sided with a significance level of 0.05. Statistical analysis was performed with Stata statistical software, release 9.2 (Stata Corp LP).

Results

Patient-to-Drug Selection

The study group consisted of 589 patients who received a loading dose of clopidogrel (N = 407, mean age 67 ± 12.9 years, 63.6% males), prasugrel (N = 106, mean age 61.8 ± 11.7 years, 71.4% males), or ticagrelor (N = 76, mean age 65.8 ± 13.3 years, 67.1% males). Subjects' baseline characteristics are shown in Table 1. Patients selected for therapy with prasugrel were younger than those who received clopidogrel or ticagrelor, and the proportion of those ≥75 years old (N = 13/106) was lowest in this treatment group. The overall number of registry participants weighing <60 kg was low (N = 34, i.e. 5.8%), of whom four received prasugrel and four ticagrelor. However, none of these individuals had a BMI below 18.5; all were healthy to overweight. Among these patients with low body weight, two administered a loading dose of prasugrel and one given ticagrelor were also older: both such subjects receiving a peri-PCI loading dose of prasugrel were discharged on clopidogrel. New agents were preferentially selected for patients with STEMI: 78.9% of prasugrel-treated and 79.5% of ticagrelor-treated patients, respectively. However, the type of ACS (STEMI or NSTE-ACS) did not influence preference for one of the new drugs (p = 1.0).

The proportion of patients with a history of CKD was highest in the ticagrelor group (22.4%) in comparison to the clopidogrel (10.1%) and prasugrel groups (10.5%; p for intergroup analysis = 0.015). An initial loading dose of prasugrel was administered to 2.9% of patients with a prior history of stroke, since the information was absent at the time of PCI.

According to the laboratory assessment at admission to the Coronary Care Unit, patients selected for treatment with prasugrel had significantly higher hemoglobin levels than those given clopidogrel or ticagrelor (Table 2). Renal function parameters, blood urea nitrogen, and serum creatinine concentrations were significantly lower in individuals given prasugrel in comparison to those given clopidogrel or ticagrelor.

Angiographic characteristics of the study population are presented in Table 3. Among individuals with an indication for PCI of the left anterior descending coronary artery, prasugrel was chosen for 42 patients and ticagrelor for 29 patients; 39.6% of prasugrel-treated patients and 38.2% of ticagrelor-treated patients underwent stent placement in this vessel. Prasugrel and ticagrelor were each the drug of choice for one patient who underwent left main-PCI with stent implantation.

Treatment Initiation

Data relating to the initiation of antiplatelet medication are detailed in Table 4. Patients were started on aspirin predominantly before coronary angiography. Among those in whom clopidogrel was initiated before coronary angiography (N = 185), 58% had a STEMI. With the exception of one hemodynamically unstable patient after resuscitation,