Journal of Cardiology 62 (2013) 158–164

Contents lists available at SciVerse ScienceDirect

Journal of Cardiology

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

Original article

Platelet reactivity in the early and late phases of acute coronary syndromes according to cytochrome P450 2C19 phenotypes

Zenko Nagashima (MD)[a], Kengo Tsukahara (MD)[a,*], Satoshi Morita (PhD)[b], Tsutomu Endo (MD)[c], Teruyasu Sugano (MD)[d], Kiyoshi Hibi (MD)[a], Hideo Himeno (MD)[e], Kazuki Fukui (MD)[f], Satoshi Umemura (MD, FJCC)[d], Kazuo Kimura (MD, FJCC)[a]

[a] Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan
[b] Department of Biostatistics and Epidemiology, Yokohama City University School of Medicine and University Medical Center, Yokohama, Japan
[c] Division of Cardiology, Saiseikai Yokohama City Southern Hospital, Yokohama, Japan
[d] Department of Medical Science and Cardiorenal Medicine, Yokohama City University School of Medicine, Yokohama, Japan
[e] Division of Cardiology, Fujisawa City Hospital, Fujisawa, Japan
[f] Division of Cardiology, Kanagawa Cardiovascular and Respiratory Disease Center, Yokohama, Japan

ARTICLE INFO

Article history:
Received 28 April 2012
Received in revised form 17 March 2013
Accepted 18 March 2013
Available online 22 July 2013

Keywords:
Genetics
Platelet inhibitors
Coronary heart disease
Stent

ABSTRACT

Background: It remains unknown whether the time course of the antiplatelet effects of clopidogrel differs according to cytochrome P450 (CYP) 2C19 phenotype in Japanese patients with acute coronary syndromes (ACS).

Methods and results: Platelet reactivity was serially assessed by VerifyNow-P2Y12 assay (Accumetrics, San Diego, CA, USA). Results were expressed as P2Y12-reaction-units (PRU) in 177 patients with ACS who underwent stent implantation and received aspirin plus a 300-mg loading dose of clopidogrel followed by 75 mg/day. High on-clopidogrel treatment platelet reactivity (HTPR) was defined as PRU > 235. On the basis of the CYP2C19*2 and *3 alleles, 46 patients (26.0%) were classified as extensive metabolizers (EM), 103 (58.2%) as intermediate metabolizers (IM), and 28 (15.8%) as poor metabolizers (PM). At <7 days, the PRU level (232 ± 102 vs. 279 ± 70, 308 ± 67, $p < 0.001$) and the incidence of HTPR (49% vs. 74%, 86%, $p = 0.001$) was lower in EM than in IM and PM. At 14–28 days the effects of CYP2C19 polymorphisms on PRU levels increased in a stepwise fashion (168 ± 99 vs. 213 ± 77 vs. 278 ± 69, $p < 0.001$), and EM and IM had lower percentages of HTPR than PM (28%, 37% vs. 73%, $p < 0.001$). There was no significant difference in the cumulative frequency of 12-month adverse cardiovascular events among 3 phenotypes (16.5%, 14.1%, 9.2%; $p = 0.67$).

Conclusion: About three quarters of Japanese patients with ACS carried CYP2C19 variant alleles. The majority of IM and PM had increased platelet reactivity during the early phase of ACS. Although HTPR was frequently observed even 14–28 days after standard maintenance doses of clopidogrel in PM, the incidence of adverse outcomes did not differ, irrespective of CYP2C19 genotype.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has been a cornerstone of medical treatment for patients who have acute coronary syndromes (ACS) or undergo percutaneous coronary intervention (PCI) [1,2]. However, the response to clopidogrel varies widely among individuals [3], and high on-clopidogrel treatment platelet reactivity (HTPR) is associated with adverse cardiovascular events, including stent thrombosis after implantation [4,5]. Clopidogrel is a prodrug that must be metabolized by the cytochrome P (CYP) 450 enzyme system to generate active metabolites. Metabolic activation by CYP2C19 is crucial for generation of such metabolites. Several gene variants are associated with reduced or enhanced CYP2C19 activity, however, CYP2C19*2 and CYP2C19*3 are the major mutant alleles of CYP2C19 that account for >99% of loss-of-function (LOF) alleles in Asian populations [6,7]. Carriers of the CYP2C19*2 and/or CYP2C19*3 LOF alleles have a reduced pharmacodynamic response to clopidogrel and worse clinical outcomes as compared with noncarriers in Asian countries [8,9]. However, it is unknown whether the time course of the antiplatelet effects of clopidogrel differs according to CYP2C19 phenotype in Japanese patients with ACS. We serially assessed platelet reactivity in the early and late phases of ACS according to CYP2C19 phenotypes

* Corresponding author at: Division of Cardiology, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan. Tel.: +81 45 261 5656; fax: +81 45 261 9162.
E-mail address: k-tsuka@urahp.yokohama-cu.ac.jp (K. Tsukahara).

0914-5087/$ – see front matter © 2013 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jjcc.2013.03.006

in Japanese patients who underwent coronary stent implantation.

Methods

Study population

We conducted a prospective, multicenter study designed to assess platelet function serially according to CYP2C19 genotype in ACS patients who were scheduled to undergo coronary stent implantation treated with DAPT. A total of 300 consecutive patients were assessed for eligibility. Patients who met the inclusion criteria were registered to randomized study to assess the impacts of omeprazole and famotidine on the antiplatelet effects of clopidogrel ($n = 180$). Patients excluded from the randomized study were registered to cohort study ($n = 88$). Finally, 177 patients were analyzed in the present study in whom platelet reactivity was serially assessed by VerifyNow-P2Y12 (Accumetrics, San Diego, CA, USA) assay and CYP2C19 phenotype was determined (Fig. 1).

The inclusion criteria for patients with ST-segment elevation myocardial infarction (STEMI) were ischemic symptoms that lasted for 20 min or more, ST-segment elevation of ≥1 mm in ≥2 continuous precordial leads or in ≥2 limb leads, elevated levels of a cardiac biomarker of necrosis, and undergoing primary PCI within 12 h after onset of symptoms. ACS patients without persistent ST-segment elevation had to have ischemic symptoms lasting ≥10 min and occurring within 72 h before the study entry, and either ST-segment deviation of ≥1 mm or elevated levels of a cardiac biomarker of necrosis.

Exclusion criteria included major bleeding events within 7 days before enrollment, a serum hemoglobin level of <11 g/dl or >17 g/dl, a platelet count of <120,000/mm^3 or >500,000/mm^3, hematologic or malignant disease, a serum creatinine level of >2.0 mg/dl, severe liver dysfunction, or the use of oral anticoagulant agents, thienopyridine derivatives, cilostazol, glycoprotein IIb/IIIa inhibitors, or fibrinolytic agents within 7 days before enrollment. Patients were also excluded if they did not receive stent implantation within 14 days after symptom onset, if they underwent coronary artery bypass grafting (CABG), or if they received oral anticoagulant agents during the study period.

Antiplatelet therapy and PCI procedure

All patients were required to receive aspirin 100 mg/day indefinitely and a 300-mg loading dose of clopidogrel followed by 75 mg/day for at least 12 months. A 200-mg loading dose of aspirin was administered only in aspirin-naïve patients. Primary PCI was performed immediately after a loading dose of clopidogrel was administered. Planned PCI was performed at least 6 h after patients received the loading dose of clopidogrel. PCI was performed in a standard manner. The choice of vessels treated, devices used (including stent type), and adjunctive medication administered to support PCI was left to the discretion of the treating physicians. At the time of the study, glycoprotein IIb/IIIa inhibitors and intravenous anticoagulants other than unfractionated heparin were not approved for use in patients with ACS or stent implants (or both) in Japan. Intravascular ultrasound (IVUS) examination was performed at the end of PCI procedure in all study patients. Intracoronary isosorbide dinitrate (2 mg) was administered before IVUS examination to prevent coronary spasm. All coronary angiograms and IVUS findings were evaluated by a single cardiologist who was blinded to all other clinical data.

Platelet function tests and genotyping

Platelet function tests were serially performed with the use of the VerifyNow P2Y12/aspirin assays before clopidogrel loading (baseline), within 7 days after clopidogrel loading (early phase),

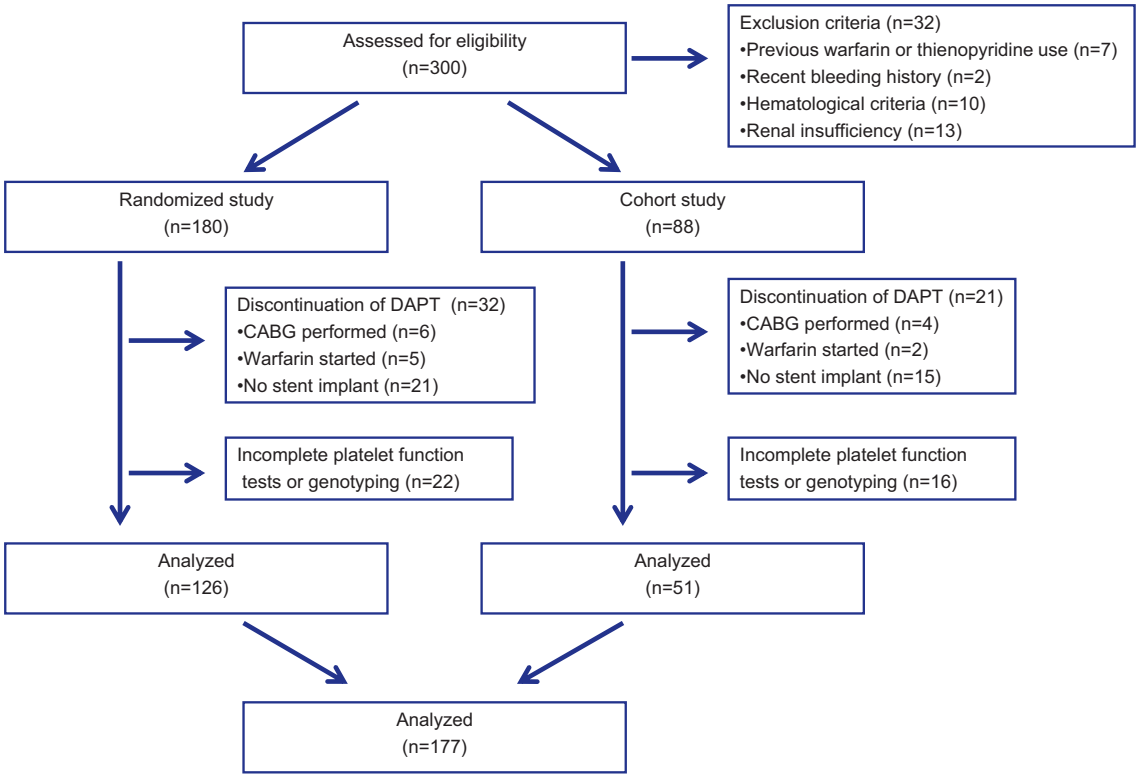

Fig. 1. Flow diagram. CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy.