International Journal of Cardiology 202 (2016) 331–335

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Comparative effect on platelet function of a fixed-dose aspirin and clopidogrel combination versus separate formulations in patients with coronary artery disease: A phase IV, multicenter, prospective, 4-week non-inferiority trial☆

Pyung Chun Oh [a], Taehoon Ahn [a,*], Dong Woon Kim [b], Bum-Kee Hong [c], Dong-Soo Kim [d], Jun Kwan [e], Cheol Ung Choi [f], Yong-Mo Yang [g], Jang Ho Bae [h], Kyung Tae Jung [i], Woong Gil Choi [j], Dong Woon Jeon [k], Deok Kyu Cho [l], Wook Bum Pyun [m], Kwang Soo Cha [n], Tae-Joon Cha [o], Kook Jin Chun [p], Young Dae Kim [q], Byung Soo Kim [r], Doo-Il Kim [s], Tae Ik Kim [t]

[a] Division of Cardiology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea
[b] Division of Cardiology, Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, Republic of Korea
[c] Division of Cardiology, Department of Internal Medicine, Gangnam Severance Hospital, Seoul, Republic of Korea
[d] Division of Cardiology, Department of Internal Medicine, Inje University, Busan Paik Hospital, Busan, Republic of Korea
[e] Division of Cardiology, Department of Internal Medicine, Inha University Hospital, Incheon, Republic of Korea
[f] Division of Cardiology, Department of Internal Medicine, Korea University Guro Hospital, Incheon, Republic of Korea
[g] Division of Cardiology, Department of Internal Medicine, Cheongju St. Mary's Hospital, Cheongju, Republic of Korea
[h] Division of Cardiology, Department of Internal Medicine, Konyang University Hospital, Daejeon, Incheon, Republic of Korea
[i] Division of Cardiology, Department of Internal Medicine, Eulji University Hospital, Daejeon, Republic of Korea
[j] Division of Cardiology, Department of Internal Medicine, Konkuk University Chungju Hospital, Chungju, Republic of Korea
[k] Division of Cardiology, Department of Internal Medicine, National Health Insurance Corporation Ilsan Hospital, Goyang, Republic of Korea
[l] Division of Cardiology, Department of Internal Medicine, Myongji Hospital, Goyang, Republic of Korea
[m] Division of Cardiology, Department of Internal Medicine, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea
[n] Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea
[o] Division of Cardiology, Department of Internal Medicine, Kosin University Gospel Hospital, Busan, Republic of Korea
[p] Division of Cardiology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea
[q] Division of Cardiology, Department of Internal Medicine, Dong-A University Medical Center, Busan, Republic of Korea
[r] Division of Cardiology, Department of Internal Medicine, DaeDong Hospital, Busan, Republic of Korea
[s] Division of Cardiology, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Busan, Republic of Korea
[t] Division of Cardiology, Department of Internal Medicine, Maryknoll Medical Center, Busan, Republic of Korea

ARTICLE INFO

Article history:
Received 1 March 2015
Received in revised form 7 September 2015
Accepted 19 September 2015
Available online 21 September 2015

Keywords:
Platelet function
Fixed-dose combination
Aspirin
Clopidogrel

ABSTRACT

Background/objectives: The effect of aspirin and clopidogrel in a fixed-dose combination (FDC) on platelet function was compared with separate formulations in patients that had undergone percutaneous coronary intervention (PCI) with drug-eluting stent (DES).
Methods: This was a phase IV, prospective, multicenter, single-arm, non-inferiority study. Patients that had taken aspirin 100 mg and clopidogrel 75 mg once daily as separate formulations for >6 months after PCI with DES were enrolled, and then switched to an aspirin/clopidogrel FDC once-daily for 4 weeks. Platelet reactivity was determined using the VerifyNow® P2Y12 assay at baseline (immediately prior to switching) and 4 weeks later.
Results: A total of 648 patients (the full-analysis population; age, 63.6 ± 9.0 years; male, 76.5%) finished the study, and 565 (the per-protocol population) completed without protocol violations. In the per-protocol population, the % inhibitions of P2Y12 and ARU were not significantly different between baseline and after 4 weeks of FDC treatment (29.2 ± 20.0% to 29.0 ± 19.9%, P = 0.708; 445.1 ± 69.2 to 446.2 ± 63.0, P = 0.799, respectively) and the difference in P2Y12 inhibition observed did not exceed the predetermined limit of non-inferiority (95% CI, −0.9 to 1.3). In the full-analysis population, the % inhibitions of P2Y12, PRU, and ARU were not significantly changed after 4 weeks of FDC treatment.

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Division of Cardiology, Department of Internal Medicine, Gachon University Gil Medical Center, 1198 Kuwol-dong, Namdong-gu, Incheon 405-760, Republic of Korea.
E-mail address: encore@gilhospital.com (T. Ahn).

http://dx.doi.org/10.1016/j.ijcard.2015.09.024

Conclusions: This study demonstrates that the efficacy of platelet inhibition by an aspirin/clopidogrel FDC was not inferior to that of separate aspirin and clopidogrel formulations in patients that had undergone PCI with DES.

1. Introduction

Dual antiplatelet therapy with aspirin and clopidogrel reduces the incidences of adverse cardiac events in patients with acute coronary syndrome and in those that had undergone percutaneous coronary intervention (PCI) [1,2]. Furthermore, premature discontinuation of dual antiplatelet therapy after coronary stenting increases the risk of stent thrombosis [3]. Thus, current guidelines recommend that patients should be treated with dual antiplatelet agents up to 12 months after drug-eluting stent (DES) implantation [4,5]. However, a recent study showed that nearly 30% of patients with coronary artery disease do not consistently use aspirin and that only 21% take all prescribed medications [6].

Several fixed-dose combination (FDC) formulations have been developed for the control of multiple cardiovascular risk factors, such as, hypertension, dyslipidemia, and diabetes. These approaches simplify drug regimens and improve patient compliance [7]. In Korea, a recently developed aspirin/clopidogrel FDC is being widely prescribed for patients with coronary artery disease. However, the effect of this FDC on platelet function has not been specifically compared with that of separate formulations. Accordingly, in the current study, we compared the effect of an aspirin/clopidogrel FDC (Clopirin®; Jeil Pharmaceutical Co., Ltd., Seoul, Republic of Korea) with that of separate aspirin and clopidogrel formulations on platelet function in patients that had undergone PCI with DES.

2. Methods

This phase IV, prospective, single-arm, non-inferiority study was conducted at 23 hospitals in Korea between August 2012 and July 2013. The study protocol and the informed consent form used were approved by the institutional review boards of all involved hospitals. Informed written consent was obtained from all eligible patients, and the study was performed in accordance with the Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki [8].

2.1. Subjects

Korean patients aged 20 to 85 years who had taken aspirin 100 mg and clopidogrel 75 mg once daily as separate formulations for >6 months after PCI with DES were considered eligible. Patients requiring coronary angiography or any revascularization procedure for exacerbation of coronary artery disease were excluded. The exclusion criteria applied were as follows: allergy to any medication, use of an anticoagulant or any antiplatelet agent except aspirin or clopidogrel, severe liver dysfunction, bleeding tendency, pregnancy or breastfeeding, and women not using an effective method of contraception. The use of glycoprotein IIb/IIIa inhibitor, thrombolytics, anticoagulants, other antiplatelet agents (e.g., cilostazol, ticagrelor, or prasugrel), or substances that possibly interacted with the study drug was not permitted during the study, except for temporary use of non-steroidal anti-inflammatory drugs for <7 days.

2.2. Investigational drug

The investigational drug was a FDC containing aspirin 100 mg and clopidogrel 75 mg (Clopirin®; Jeil Pharmaceutical Co., Ltd., Seoul, Republic of Korea), composed of an enteric-coated aspirin pellet and direct compression granules of clopidogrel.

2.3. Study procedures

Subjects administered separate formulations of aspirin 100 mg and clopidogrel 75 mg were switched to a capsule of the investigational drug once-daily for 4 week ± 5 days. To evaluate anti-platelet effects, we used the VerifyNow® P2Y12 test (Accumetrics, Inc. San Diego, CA, USA) at baseline (immediately before switching to the FDC) and after 4 weeks of FDC administration. Compliance with the investigational drug was assessed at last visits.

2.4. Platelet function assay

Platelet function was measured using the VerifyNow® P2Y12 test, according to the manufacturer's instructions. This test is a rapid whole-blood point-of-care assay that uses increases in light transmittance to measure platelet aggregation induced by arachidonic acid or adenosine diphosphate. Results are reported as aspirin reaction units (ARU) or P2Y12 reaction units (PRU), respectively. In addition, baseline value for platelet function independently of P2Y12 is measured through thrombin receptor activating agonist and a percentage inhibition index (% inhibition) can be calculated as [(1-PRU/baseline) × 100].

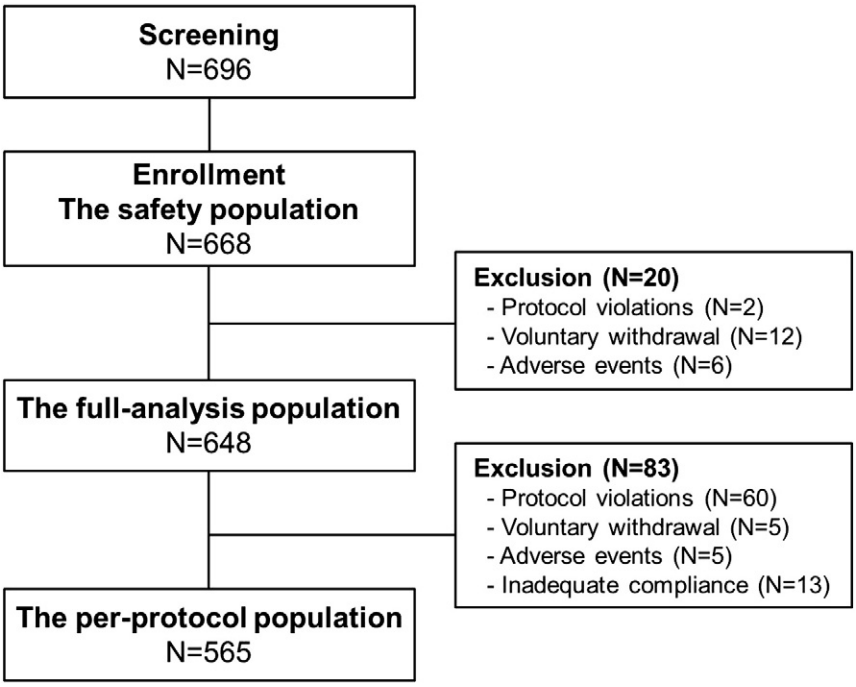

Fig. 1. Study flow chart.