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CORRESPONDENCE

Research Correspondence

Bioequivalence in the Real World Is a Complex Challenge

The Case of Clopidogrel

To the Editor: High platelet reactivity (HPR) on clopidogrel has been found to be associated with a significantly higher incidence of ischemic recurrence in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention with stent implantation (1–3). We have documented that HPR in the acute phase of ACS is associated with a risk of cardiovascular death and major adverse cardiac events at a 2-year follow-up (4), allowing us to identify high-risk patients for whom more aggressive antiplatelet therapy might be beneficial.

Based on these findings, our department has adopted the strategy to routinely measure the entity of platelet inhibition in the acute phase of patients admitted for ACS by light transmission aggregometry (LTA).

Platelet reactivity assessment is made by LTA (APACT 4, Helena Laboratories, Milan, Italy) using 10 μmol/l adenosine diphosphate (ADP), 1 mmol/l arachidonic acid (AA), and 2 μg/ml collagen as agonists. Blood samples anticoagulated with 0.109 mol/l sodium citrate (ratio 9:1) were obtained within 48 h from clopidogrel loading. HPR by ADP is defined as the presence of 10 μmol/l ADP LTA $\geq$70% (5).

Since October 2011, our pharmacy delivers clopidogrel base instead of clopidogrel hydrogen sulfate to the departments of our University Hospital (AOU Careggi, Florence, Italy). Clopidogrel base is a generic preparation not identical to the initial clopidogrel hydrogen sulfate.

We compared laboratory data for the period October 2011 through March 2012 (on clopidogrel base [A]) with data obtained for the same period of the previous year (i.e., October 2010 through March 2011) (on clopidogrel hydrogen sulfate [B]).

We included 1,579 patients (1,111 men and 468 women, 71.7 $\pm$ 11.7 years of age) with ACS (765 ST-segment elevation myocardial infarction [STEMI]/814 non–ST-segment elevation myocardial infarction [NSTEMI]).

No significant differences were found in age (A: 72 $\pm$ 12 years vs. B: 71 $\pm$ 12 years, p = 0.108), sex (male/female: A, 521/220 vs. B, 590 of 248; p = 0.999) and prevalence of classic cardiovascular risk factors between the 2 groups of patients (diabetes: A, 21.9% vs. B, 22.9%; p = 0.673; hypertension: A, 68.8% vs. B, 68%; p = 0.745; smoking: A, 50.3% vs. B, 49.5%; p = 0.762; dyslipidemia: A, 39.1% vs. B, 39.3%; p = 0.959). In addition, a similar percentage of patients was admitted for STEMI (A, 363/741 vs. B, 402/436; p = 0.724).

From our laboratory dataset, we have observed a significantly higher percentage of patients with HPR by ADP during the administration of clopidogrel base with respect to clopidogrel hydrogen sulfate (314 of 741, 42.4% vs. 213 of 838, 25.4%; p < 0.0001) (Fig. 1). LTA by AA did not significantly differ between the 2 periods (A, 18 $\pm$ 7% vs. B, 17 $\pm$ 9%; p = 0.715). LTA by collagen was significantly higher during the administration of clopidogrel base (A, 36.7 $\pm$ 15.2% vs. B, 33.5 $\pm$ 16.6%; p < 0.001.

After adjustment for age, sex, classic cardiovascular risk factors, and STEMI/NSTEMI, the prevalence of HPR by ADP remained significantly higher in the clopidogrel base group compared with the clopidogrel hydrogen sulfate group (Fig. 1).

Apart from differences in chemical structure of clopidogrel, there was no variation in the methodology, type of instruments, reagents, or laboratory staff.

We are aware that several determinants might play a role in generating these results, independently of the inhibitory effect of the drug (6). In our group of patients, no significant differences were found in the prevalence of the cardiovascular risk factors in relation to the different molecules of clopidogrel administered. Furthermore, the clinical presentation of ACS (i.e., STEMI vs. NSTEMI patients) was similar in the different periods examined. In addition, the procedures of the catheterization laboratories and the cardiologists were the same. Furthermore, no modification was made

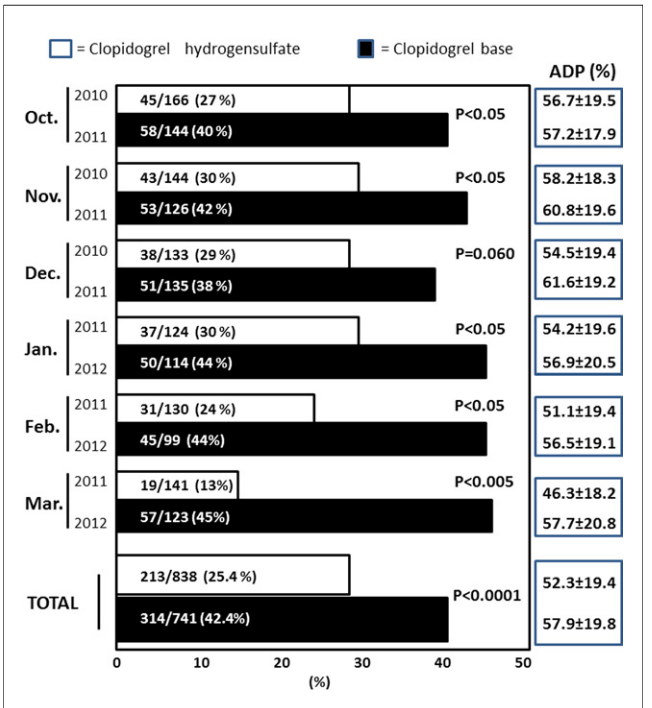

Figure 1 HPR by ADP According to the Type of Clopidogrel Administered

High platelet reactivity (HPR) by adenosine diphosphate (ADP) (defined as 10 μmol/l ADP-induced platelet aggregation $\geq$70%). Clopidogrel hydrogen sulfate **(open bars)**, clopidogrel base **(solid bars)**.

in the organization of the reperfusion strategy of ACS in our city, from the first aid to the emergency department and the catheterization laboratory. In other words, we were not able to recognize, apart from the change in the molecule of clopidogrel, a significant variation in the clinical characteristics of patients or in the interventional procedures, which accounts for the higher prevalence of HPR.

We emphasize that this finding only represents the descriptive analysis of laboratory data produced in our department in relation to the shift to the new preparation of clopidogrel and cannot be applied to the several other generic forms of clopidogrel now available.

A specific ad hoc study implying the randomization to the 2 different formulations of clopidogrel is needed to definitely prove the different effects on platelets. Present data emphasize the need for accurate post-marketing surveillance of generic forms of a drug such as clopidogrel for which the lack of effective platelet inhibition is associated with a documented increased ischemic risk.

***Rossella Marcucci, MD, PhD**
Rita Paniccia, BS
Anna Maria Gori, BS
Gian Franco Gensini, MD
Rosanna Abbate, MD

*Department of Medical and Surgical Critical Care
University of Florence
Department of Heart and Vessel
Careggi Hospital
Largo Brambilla 3
50134 Florence
Italy
E-mail: rossella.marcucci@unifi.it

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Letters to the Editor

Lack of Stroke Subtype Information May Hinder Indirect Comparison Between the ROCKET-AF and Other Trials of New Oral Anticoagulants

Although we agree with Lip et al. (1) on the limitation of their study, we argue that lack of stroke subtype information may hinder scientific conclusion by including the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) in any indirect comparison of new oral anticoagulants (NOA).

Several studies on indirect comparison among NOA in atrial fibrillation (AF) patients reported slightly different results (1–3). However, none of these studies took into account the distribution of stroke subtypes as a confounder against indirect comparison methods. To address the lack of comparability on high-risk patients among trial populations, Schneeweiss et al. (3) conducted a subgroup analysis in patients with a $CHADS_2$ (congestive heart failure; hypertension: blood pressure consistently above 140/90 mm Hg [or treated hypertension on medication]; age ≥75 years; diabetes mellitus; prior stroke, transient ischemic attack [TIA], or thromboembolism) score ≥3 and got similar results as those reported by Lip et al. Nevertheless, this may not balance the contribution of etiology of stroke or TIA to the treatment effects in ROCKET-AF and other trials. In the study by Mantha et al. (2), all stroke or TIA events were even considered as embolic episodes.

That strokes occur in patients with AF does not necessarily point to an embolic etiology. In the normal population, roughly 20% of all TIA and ischemic strokes have a cardiac origin—most commonly AF. Recent antithrombotic trials in AF patients vary in the proportion of patients who had a previous TIA or stroke, with a range between 14% and 24% (4). Approximately 60% to 70% of first recurrent strokes have the same mechanism as the index stroke (5). As a result, noncardioembolic strokes are the majority of the recurrent strokes, and they might not benefit from NOA. In ROCKET-AF, 52% of the patients experienced a stroke or TIA before study entry. Unfortunately, no information of subtype was reported in such trial with a large proportion of patients with ischemic cerebral events (6). The treatment effects of NOA may be diluted in ROCKET-AF by this, which may prevent it from being compared with other trials of NOA.

***Hai-feng Li, MD, PhD**
Ren-liang Zhao, MG, PhD