genotype) polymorphism association with variable clopidogrel response has been validated in both healthy and acute coronary syndrome individuals (3). The association of platelet glycoproteins IIIa and $P2Y_{12}$ receptor polymorphisms with clopidogrel variable response has not been confirmed in previous studies (4), and it should also be examined in the study by Ang et al. (1).

Finally, other mechanisms, such as cellular factors (accelerated platelet turnover, reduced CYP3A metabolic activity, increased ADP exposure, up-regulation of P2Y pathways), or clinical factors (noncompliance, underdosing, poor absorption) may cause suboptimal clopidogrel response.

This interesting study by Ang et al. (1) sheds some light on mechanisms underlying reduced response of platelets to the antiaggregatory effect of clopidogrel. Although the limited number of patients with lower inhibition of platelet reactivity by clopidogrel makes the findings exploratory, further studies with a larger cohort of patients are needed to elucidate the multiple mechanisms involving clopidogrel response.

Gerasimos Siasos, MD, PhD
***Dimitris Tousoulis, MD, PhD, FACC**
Christodoulos Stefanadis, MD, PhD, FACC

*1st Cardiology Unit
Hippokration Hospital
Athens University Medical School
69 South Karagiorga Street
Glifada, Athens 16675
Greece
E-mail: drtousoulis@hotmail.com

doi:10.1016/j.jacc.2008.09.062

REFERENCES

1. Ang L, Palakodeti V, Khalid A, et al. Elevated plasma fibrinogen and diabetes mellitus are associated with lower inhibition of platelet reactivity with clopidogrel. J Am Coll Cardiol 2008;52:1052–9.
2. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Contribution of gene sequence variations of the hepatic cytochrome P450 3A4 enzyme to variability in individual responsiveness to clopidogrel. Arterioscler Thromb Vasc Biol 2006;26:1895–900.
3. Frere C, Cuisset T, Moragne PE, et al. Effect of cytochrome P450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. Am J Cardiol 2008;101:1088–93.
4. Lev EI, Patel RT, Guthikonda S, et al. Genetic polymorphisms of the platelet receptors P2Y(12), P2Y(1) and GP IIIa and response to aspirin and clopidogrel. Thromb Res 2007;119:355–60.

Reply

We appreciate the comments by Dr. Siasos and colleagues in response to our recent study published in the *Journal* (1). We agree that many factors are associated with variable platelet reactivity response to clopidogrel, including drug absorption, generation of active drug metabolites, cytochrome P450 isoenzyme variants, drug–drug interactions, and P2Y12 receptor polymorphisms. In particular, significant efforts have been directed at clarifying the role of hepatic cytochrome P450 isoenzymes, including CYP3A4, CYP3A5, and CYP2C19 polymorphisms. Although there are conflicting data, a significant role of CYP3A4*1B or CYP3A5*3 polymorphisms in accounting for lower platelet inhibition (PI) with clopidogrel seems unlikely (2). However, CYP2C19 genotyping allows identification of >90% of poor clopidogrel metabolizers (3), and carriers of the CYP2C19*2 mutant allele seem to have an attenuated PI response when presenting with an acute coronary syndrome (ACS) or undergoing an elective percutaneous coronary intervention (2,4).

The goal of our study was to determine the role of clinical and biochemical factors known to affect platelet reactivity on the PI attained with clopidogrel in patients with cardiovascular disease (1). Elevated serum fibrinogen, diabetes mellitus, and higher body mass index were associated with a lower PI. A significant interaction was also observed between diabetes and elevated fibrinogen, accounting for at least one mechanism for the poor response of diabetics to clopidogrel. As acknowledged in the Study Limitations section of our article (1), we did not assess patients for genetic polymorphisms. In patients with ACS treated with clopidogrel, Frere et al. (2) found a significant association between being a carrier of the CYP2C19*2 mutant allele and higher platelet reactivity. Nevertheless, higher body mass index remained independently associated with higher post-treatment platelet reactivity. Malek et al. (5) have shown that ACS patients with polymorphisms for both the P2Y12 platelet receptor and CYP2C19 are at an increased risk of excess platelet activity after clopidogrel treatment, and have a higher risk of ischemic cardiovascular events. However, no known data suggest that the role of the clinical and biochemical markers that we have identified would be altered in the presence or absence of a P2Y12 receptor or CYP2C19 polymorphism. Future studies should expand on our findings by determining P2Y12 and glycoprotein IIIa platelet cell-surface receptor, and CYP450 isoenzyme genotypes, and evaluating their interactions with the clinical and biochemical markers of poor platelet inhibition with clopidogrel.

Lawrence Ang, BS
***Ehtisham Mahmud, MD, FACC**

*Cardiovascular Catheterization Laboratories
University of California, San Diego School of Medicine
UCSD Medical Center
200 West Arbor Drive, MC 8784
San Diego, California 92103-8784
E-mail: emahmud@ucsd.edu

doi:10.1016/j.jacc.2008.11.041

REFERENCES

1. Ang L, Palakodeti V, Khalid A, et al. Elevated plasma fibrinogen and diabetes mellitus are associated with lower inhibition of platelet reactivity with clopidogrel. J Am Coll Cardiol 2008;52:1052–9.
2. Frere C, Cuisset T, Moragne PE, et al. Effect of cytochrome P450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. Am J Cardiol 2008;101:1088–93.
3. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med 2005;352:2211–21.
4. Trenk D, Hocholzer W, Fromm MF, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol 2008;51:1925–34.
5. Malek LA, Kisiel B, Spiewak M, et al. Coexisting polymorphisms of P2Y12 and CYP2C19 genes as a risk factor for persistent platelet activation with clopidogrel. Circ J 2008;72:1165–9.