Response to "Influence of Diabetes on Antiplatelet Drug Efficacy"

Tornio, Aleksi; Palmer, Colin N. A.; Doney, Alex S. F.

Published in:
Clinical Pharmacology & Therapeutics

DOI:
10.1002/cpt.1002

Publication date:
2018

RESPONSE TO LETTER

Response to "Influence of Diabetes on Antiplatelet Drug Efficacy"

Aleksi Tornio[1], Colin N.A. Palmer[2] and Alex S.F. Doney[3]

To The Editor: Gong *et al*. in their Letter to the Editor make valuable comments in relation to our study, which, as they correctly point out, included a substantial number of individuals with diabetes. First, they draw attention to the well-documented increased platelet reactivity in patients with diabetes, and a recent study showing increased platelet $P2Y_{12}$ expression may be contributory. They also highlight a recent fairly small study indicating that in stroke patients the *CYP2C19* loss-of-function allele had a reduced impact on clopidogrel response in individuals with higher glycated albumin levels independent of diabetes status. Such observations imply reduced efficacy of clopidogrel in this patient population. Indeed, a further study indicates impaired $P2Y_{12}$ inhibition by clopidogrel in individuals with diabetes is largely mediated by its reduced metabolism.[1] Second, they allude to studies indicating that obese subjects and smokers also have a prothrombotic state and that in smokers this may also be associated with increased platelet $P2Y_{12}$. Smokers, however, may have an increased clopidogrel responsiveness[2] through induction of CYP2C19, although more recent work has indicated that the impact of smoking on clopidogrel responsiveness is abrogated when accounting for hemoglobin levels.[3]

Our study comprised a bioresource linked to electronic medical records. In essence, we conducted a Mendelian-randomized prospective observational study of the clinical impact of *CYP2C19* loss-of-function genotype in a population of individuals who had all redeemed prescriptions for clopidogrel following hospitalization for an arterial thrombo-occlusive event. As a consequence, we are not able to directly compare the overall efficacy of clopidogrel therapy with a comparator arm to investigate the impact of diabetes and related features. However, it is possible to exploit *CYP2C19* genotype as a genetic instrument to probe the extent to which these features modify antiplatelet response. Our overall study comprised 72% individuals with diabetes and 77% of the outcome events occurred in this group. While we found that diabetes, obesity, smoking, and recent elevated glycated hemoglobin were, as expected, significantly associated with increased risk, we did not find any evidence of an interaction with the *CYP2C19* genotype. While we probably do not have adequate power in our current study to formally avoid a type II error, a meta-analysis of clinical trials also found no substantial effect of either diabetes or obesity on clopidogrel efficacy.[4] Our bioresource is currently expanding with the Scottish-wide GoSHARE study (www.goshare.org.uk). As a consequence, we anticipate the ability to explore these interesting and highly clinical relevant aspects in the future.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

FUNDING

The GoDARTS Bioresource has been funded by a wide range of sources of many years. The present study was unfunded.

1. Angiolillo, D.J. *et al*. Impaired responsiveness to the platelet P2Y12 receptor antagonist clopidogrel in patients with type 2 diabetes and coronary artery disease. *J. Am. Coll. Cardiol.* **64**, 1005–1014 (2014).
2. Zhao, Z.-G. *et al*. The impact of smoking on clinical efficacy and pharmacodynamic effects of clopidogrel: a systematic review and meta-analysis. *Heart* **100**, 192–199 (2014).
3. Kim, Y.G. *et al*. Cigarette smoking does not enhance clopidogrel responsiveness after adjusting VerifyNow P2Y12 reaction unit for the influence of hemoglobin level. *JACC Cardiovasc. Interv.* **9**, 1680–1690 (2016).
4. Zaccardi, F., Pitocco, D., Willeit, P. & Laukkanen, J.A. Efficacy and safety of P2Y12 inhibitors according to diabetes, age, gender, body mass index and body weight: systematic review and meta-analyses of randomized clinical trials. *Atherosclerosis* **240**, 439–445 (2015).

[1]Department of Clinical Pharmacology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [2]Pat MacPherson Centre for Pharmacogenetics and Pharmacogenomics, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK; [3]Medicines Monitoring Unit, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. Correspondence: A. Doney (a.doney@dundee.ac.uk)

Received 15 December 2017; accepted 17 December 2017; Advance online publication 30 December 1899. doi:10.1002/cpt.1002