Pharmacogenetic of Clopidogrel and Platelet Function Testing: The Clinical Impact

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Cytochrome 450 (CYP 450) 2C19 is a well known polymorphic metabolising enzyme which is responsible for converting clopidogrel to its active form [1]. Measuring the resulting activity based on Platelet Reactivity Units (PRU) or inhibition rates of the platelet is well correlated with the genetic polymorphism in several studies worldwide [1-3]. However, the debate is whether the polymorphism or PRU may result in any significant clinical endpoint.

Generally there are two main confounders, the expected time of the clinical endpoints, and the time of measuring the PRU/inhibition rate following clopidogrel initiation. For the first issue, most of the studies measured the clinical endpoints within 1-24 months, and hence long term endpoints can't be conclusive [4-6]. For the other issue, clopidogrel PRU is difficult to be assumed stable especially for the first month following initiation [7]. Thus, if the study measured it after 5 days and considered long term clinical endpoints, it is unlikely to spot a real effect, if exist [8-12]. Accordingly, it is difficult to predict the clinical response for individual patients in in short-term studies and just after clopidogrel initiation.

We presented two different studies: in-patient and out-patient cohorts, both showed clear polymorphic population, but no clinical associations were seen in both [7,13,14]. The PRUs were significantly different in our out-patient cohort compared to the in-patient cohort. This is likely due to the unstable patterns of clopidogrel metabolism during initiation and hence variable PRUs in the first month. After the PRUs reached the steady-state, a clear significant difference based on pharmacogenetic can be detected. The adequacy of PRUs may be assessed early during in-patient course but likely to differ significantly during the first days after initiation. Thus, if clopidogrel is on board, it may be judicious to assess the PRU just before the cardiac procedure and perhaps after one month of initiation to ensure a reasonable PRU for in-hospital stay and out-patient follow up.

No concrete PRU levels were well established. Besides, PRU have been proposed to range from 60-240 in several studies with heterogeneous cohorts. These studies contain multiple confounders, including: gender, age, diseases, medications, and procedures. For instance, while smokers showed more sensitivity toward PRU, females might show higher PRUs than males [15]. Therefore, It is suggested that a PRU cut-off value be assessed for each hospital based on their clinical data, as there is no clear consensus on the optimal PRUs.

Although the clinical benefits are very controversial, the possible clinical endpoints are devastating. It is clinically questionable to leave patients on clopidogrel with very minimal inhibitions when effective alternatives are available. All the proposed clinical decisions have been included in some of the guidelines under investigations or at most with very week level of evidence, including Up-to-Date [16,17]. At the same time, some guidelines have given the preference to Prasugrel or Ticagrelol in favour of clopidogrel in many clinical scenarios. Once a clinical endpoint occurred while on clopidogrel, most of the guidelines advocate screening for clopidogrel resistance and changing to other alternatives.

Finally, we suggest for clinicians to bear in mind clopidogrel resistance and to run PRU if feasible and easily accessible. If the patient shows very low PRU/inhibition rates lower than all the published data, it may be judicious to change to other alternatives. If alternatives are not available, close monitoring with patient education are warranted.

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