Toward a therapeutic window for antiplatelet therapy in the elderly

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This editorial refers to ‘High on-thienopyridine platelet reactivity in elderly coronary patients: the SENIOR-PLATELET study’6,7, by J. Silvain et al., on page 1241

Pathophysiologic changes reported in the elderly include increased platelet activation and reactivity, elevated levels of coagulation factors and plasminogen activator inhibitor type-1, and decreased bleeding time—all consistent with an increased risk for thrombosis.1 However, elderly patients with coronary artery disease (CAD) also encounter an increased risk of bleeding during antiplatelet therapy. Thus, we face a challenging treatment dilemma in these patients that is further complicated by frequent co-morbid diseases and polypharmacy. Guideline recommendations for antiplatelet therapy in the elderly are fuzzy due to a lack of dedicated pharmacodynamic and clinical outcome studies in this population.

Since the first description of clopidogrel response variability and resistance, much has been learned about numerous factors influencing the metabolism of clopidogrel that directly translate into the pharmacodynamic response (Figure 1).2,3 Non-responsiveness to the world’s second most widely used antiplatelet agent, now de facto, has fuelled the development of and widespread interest in new and more pharmacodynamically predictable P2Y12 receptor blockers and laid the cornerstone for personalized antiplatelet therapy.3

The work of Silvain et al. conducted in a heterogeneous percutaneous coronary intervention (PCI)-treated population supports yet another factor independently influencing platelet reactivity during clopidogrel therapy—age.4 Platelet reactivity was measured by conventional aggregometry and VerifyNow (total, n = 1027; ≥75 years old, n = 148) treated with dual antiplatelet therapy for ≥14 days. The time intervals between platelet function measurements and PCI or last-dose thienopyridine administration were not pre-specified and will influence the platelet reactivity reported.2,3 These important limitations should be taken into consideration when interpreting the authors’ findings. They report that the elderly had significantly higher platelet reactivity during 75 mg clopidogrel therapy by VerifyNow; a borderline finding by conventional maximal aggregation (P = 0.05). In addition, the prevalence of high on-treatment platelet reactivity (HPR) by two VerifyNow P2Y12 cut-off points was higher in the elderly during the latter therapy. There were no differences in on-treatment platelet reactivity and the prevalence of HPR between groups during treatment with 150 mg clopidogrel or 10 mg prasugrel. The discrepancy between the frequency of HPR reported in the current study and others during prasugrel therapy may be related to the treatment group—all ST-elevation myocardial infarction (STEMI) patients (see below). The current study supports previous observations of the limited effectiveness of high-dose clopidogrel in overcoming HPR and the continued presence of HPR in acute coronary syndrome (ACS) patients treated with prasugrel.6,7 The authors suggested that age integrates several factors affecting clopidogrel metabolism, resulting in a higher prevalence of HPR. In their multivariate analysis, age was an independent predictor of HPR.

The report of Silvain et al. is not the first evidence that platelet physiology is influenced by age during clopidogrel therapy. In a genome-wide association study in healthy subjects, increasing age was a significant factor for clopidogrel response (3.8% of variance, P = 0.001).8 In recent large translational studies, old age (defined as ≥65 or 75 years) was associated with HPR to ADP and also adverse ischaemic outcomes.6,9 However, the latter studies were not specifically designed to address the influence of age on platelet reactivity.

Pre-clopidogrel platelet reactivity has been previously associated with post-treatment reactivity.2 The authors suggested that higher ‘base’ values by VerifyNow contribute to the higher post-treatment platelet reactivity in the elderly. However, no actual pre-treatment (baseline) platelet function measurements were made; a limitation acknowledged by the authors. Since P2Y12 modulates the response to all agonists including TRAP that degranulate the platelet, including TRAP, ‘base’ is not the equivalent of a pre-treatment assessment of platelet function. Therefore, the response to clopidogrel was not truly measured...
in the current study. The conclusion that elderly patients present an impaired ‘response’ to clopidogrel, although implied by the data, is not entirely correct.

What can we do now to choose antiplatelet therapy in the elderly? In large-scale ACS trials, the elderly have high ischaemic event rates even during treatment with more potent P2Y12 receptor blockers. In the TRITON trial, patients ≥75 years old (13% of the total population) had a 17.3% vs. 18.3% primary end-point compared with 8.1% vs. 10.6% in those <65 years old during prasugrel vs. clopidogrel therapy, respectively. In Silvain’s study, prasugrel (10 mg) was only administered to STEMI patients or diabetic patients presenting with non-STEMI. The 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients with Unstable Angina/Non-STEMI states that prasugrel therapy may be considered in patients ≥75 years old who have ‘high risk’ situations: diabetes or prior myocardial infarction.11 Why are STEMI, diabetes, and prior infarction ‘high risk’ situations? They are linked by the common pathophysiology of HPR. Now we have further evidence that age is another ‘high risk’ component in part due to a high prevalence of HPR. In this situation, it would be expected that the most pharmacodynamically effective agent would be associated with the greatest reduction in primary efficacy endpoint occurrence. However, this hypothesis is not supported by the data from either ≥75 years old (15% of the total population) had a 16.8% vs. 18.3% primary endpoint compared with 8.6% vs. 10.4% in those <75 years old during ticagrelor vs. clopidogrel therapy, respectively.12

In addition to the occurrence of a greater number of ischaemic events, the elderly also have more frequent serious bleeding. Personalized antiplatelet therapy may have a significant clinical impact in the elderly given their overall high prevalence of treatment failure (ischaemia + bleeding). An interesting observation in Silvain’s study was the low prevalence of low P2Y12 reaction units (<30) in elderly patients treated with thienopyridines. We desperately need a better understanding of how on-treatment platelet reactivity is related to both events. Platelet function studies of adequate number have never been conducted in large-scale ACS trials to provide this answer. At this time, dedicated pharmacodynamic and clinical endpoint trials in the elderly specifically to address the issue of antiplatelet therapy are warranted. The ongoing TaRgeted platelet Inhibition to cLarify the Optimal strategy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial will enrol a large pre-specified number of elderly patients and, for the first time, the efficacy of the 5 mg prasugrel dose will be evaluated and a large longitudinal platelet function substudy (n > 2500) will be imbedded to help us better understand the platelet-related mechanisms underlying efficacy and safety.13

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