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CORRESPONDENCE

Research Correspondence

Evaluation of Platelet Inhibition by Tirofiban in Patients Stratified According to Aspirin and Clopidogrel Responsiveness

The 3T/2R (Tailoring Treatment with Tirofiban in patients showing Resistance to aspirin and/or Resistance to clopidogrel)

To the Editor: Large interindividual variability in the response to aspirin and clopidogrel (oral antiplatelet agents [OAA]) is known to exist, and previous studies showed that poor response to OAA is associated with higher risk of ischemic complications after percutaneous coronary intervention (PCI) (1–3). Whether poor responders to OAA display similar inadequate platelet inhibition (PI) also after glycoprotein (GP) IIb/IIIa inhibitor administration remains undefined.

This is a pre-specified mechanistic substudy of the 3T/2R (Tailoring Treatment with Tirofiban in patients showing Resistance to aspirin and/or Resistance to clopidogrel) trial (4). Accordingly, inclusion and exclusion criteria, study design, screening procedure, definitions, primary end point, and sample size have been previously reported (4,5). Briefly, we evaluated tirofiban responsiveness in a random selection of full versus poor responders to OAA (31 vs. 31 patients) and clopidogrel responsiveness in full versus poor responders to aspirin (15 vs. 15 patients). In all patients, before clopidogrel intake, blood was sampled to evaluate baseline platelet reactivity (PR) with light transmission aggregometry (20 μM of adenosine diphosphate). To assess clopidogrel and tirofiban responsiveness (using VerifyNow P2Y12 and IIb/IIIa assays [Accumetrics Inc., San Diego, California], respectively [4,5]), blood samples were collected 1, 2, 6, 18, and 24 h after the start of the therapy. Continuous data are shown as mean ± SD. Comparisons between 2 or more groups were performed by Student *t* test and analysis of variance. Probability was significant at a level of $p < 0.05$. Analysis was performed using STATISTICA version 8 (Statsoft Inc, Tulsa, Oklahoma).

Patient populations were well matched for age, cardiovascular risk factors, clinical presentation, and vessel disease. Baseline PR was significantly higher in poor responders to OAA (58 ± 8 P2Y12 reactivity units [PRU] vs. 48 ± 12 PRU, $p < 0.01$), as assessed by light transmission aggregometry. This finding was also confirmed by analyzing only poor responders to aspirin or those to clopidogrel. One hour (T_1) after tirofiban infusion, no differences were noted in PI between full versus poor responders to OAA (Fig. 1A). Twenty-nine (93%) full responders to OAA and 28 (90%) poor responders to OAA showed full response to tirofiban (PI >90%) at T_1 ($p = 0.9$). Moreover, PI by tirofiban did not differ at any time point (Fig. 1B). Two hours after a 600-mg loading dose of clopidogrel, aspirin poor responder patients showed a very low PI (20 ± 23% vs. 56 ± 23%, $p < 0.01$) with higher residual on-treatment PR (200 ± 62 PRU vs. 115 ± 64 PRU, $p < 0.01$), as compared with aspirin full responder patients (Figs. 1C and 1D). According to the used definition, 14 (93%) aspirin poor responders were also clopidogrel poor responders, as compared with 3 (20%) aspirin full responders ($p = 0.03$). At 1-month follow-up, no major ischemic and bleeding complications occurred.

This study shows that poor responders to aspirin and/or clopidogrel have levels of PI by tirofiban, which are comparable to those achieved in full aspirin and clopidogrel responders. Tirofiban response, evaluated both as a continuous variable and as full response, did not differ between poor versus full responders to aspirin/clopidogrel at any time point. Our study carries important clinical implications because previous reports consistently showed that patients undergoing PCI with high on-treatment (aspirin and/or clopidogrel) PR are at heightened risk of peri-procedural myocardial infarction (MI) (1,2). We provide, for the first time, the mechanistic evidence supporting the use of a GP IIb/IIIa inhibitor to overcome, during PCI, high on-treatment PR and to reduce the rate of peri-procedural MI in this subset of patients (5). Although not entirely conclusive, peri-procedural MI has been consistently associated with worse clinical outcome. This notion is of paramount importance in stable and low-risk patients (as those recruited in the 3T/2R study [5]) in whom coronary revascularization does not significantly decrease mortality or overall MI rate (6).

Poor response to aspirin and to clopidogrel have been shown to be frequently associated (2). In our study, aspirin poor responders showed a lower PI by clopidogrel and were more frequently clopidogrel poor responders. Interestingly, responsiveness to clopidogrel also increases throughout time in poor responder patients. Nevertheless, response to clopidogrel still remained suboptimal compared with that of full responders. Thus, a strategy of GP IIb/IIIa inhibitor administration remains attractive to reduce the peri-procedural ischemic burden of high on-treatment PR, especially in clinical settings where delaying the procedure to allow more complete PI is not acceptable (3).

Our study was designed as a proof of concept mechanistic investigation; its sample size is relatively small and therefore does not allow for definitive conclusions. Moreover, we enrolled highly selected patients who were at low risk. Thus, our findings cannot be automatically extrapolated to higher-risk patients.

We concluded that poor responders to aspirin and/or clopidogrel undergoing PCI show a PI by tirofiban that is comparable to that observed in full responders, explaining the previously reported benefit in reducing peri-procedural MI as compared with standard care (5).

***Gianluca Campo, MD**

*Cardiovascular Institute
Azienda Ospedaliera Universitaria S. Anna
Dipartimento di Medicina Clinica Sperimentale
Corso Giovecca 203
Ferrara 44100
Italy
E-mail: cmpglc@unife.it

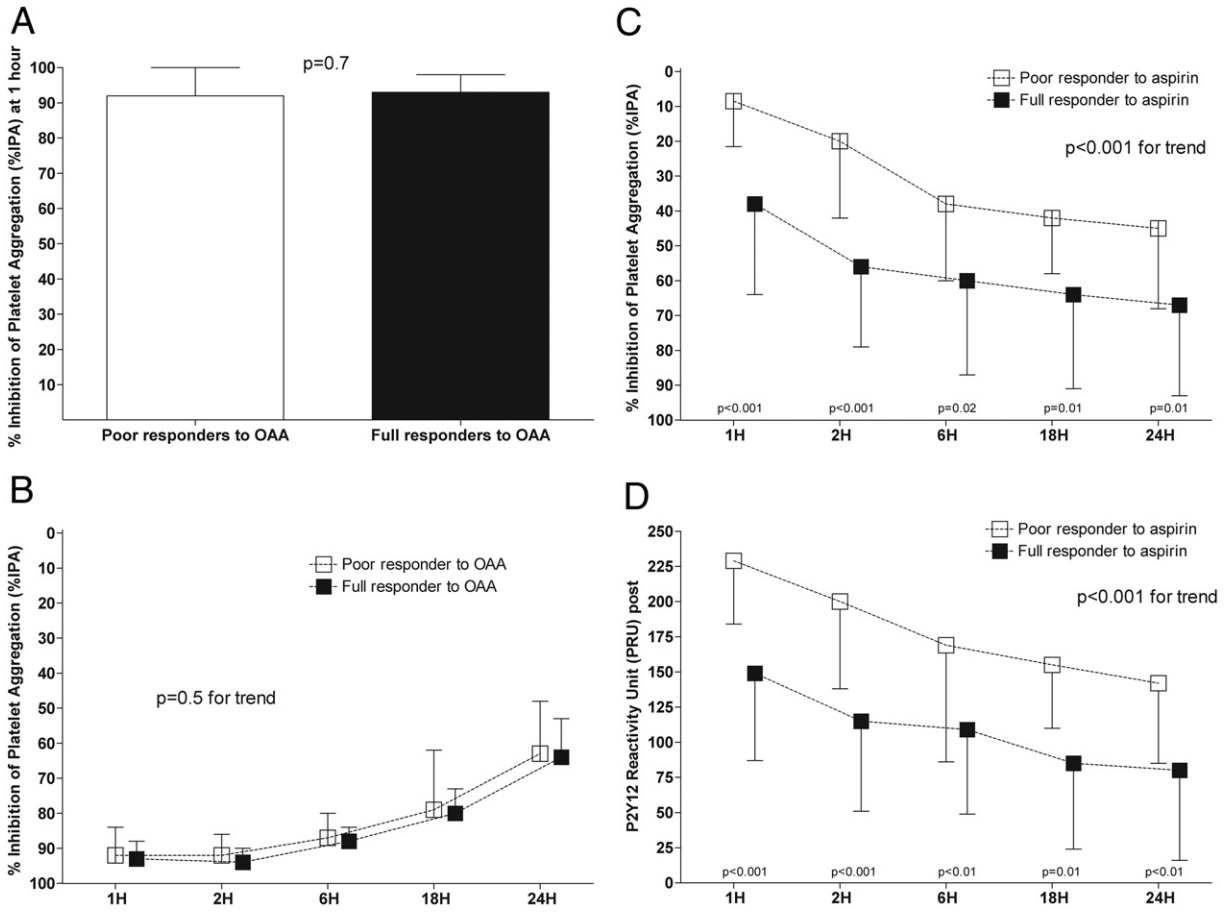

Figure 1 Tirofiban and Clopidogrel Responsiveness (Assessed by VerifyNow System)

(A and B) Tirofiban response in full versus poor responders to oral antiplatelet agents (OAA). **(C and D)** Clopidogrel response in patients full versus poor responders to aspirin.

Marco Valgimigli, MD, PhD
Alice Frangione, MD
Serena Luccarelli, MD
Elisa Cangiano, MD
Caterina Cavazza, MD
Luca Fileti, MD
Roberto Ferrari, MD, PhD
On behalf of the 3T/2R Investigators

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