ISAR-REACT 5 trial: ticagrelor lost in translation

ISAR-REACT 5: el ticagrelor perdió en la comparación

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The ISAR REACT trial is a multicenter, randomized, open-label trial that compared the efficacy and safety of the last generation antiplatelet drugs, prasugrel and ticagrelor¹. This is the first completed study that made an head to head comparison between the drugs. The trial enrolled 4,018 patients with acute coronary syndrome and planned invasive strategy. The sample size was calculated assuming the results of the PLATO trial, and according to this study a superiority of ticagrelor was hypothesized^{2,3}. The primary end point was the composite of death, myocardial infarction, or stroke at 1 year. A major secondary end point (the safety end point) was bleeding. The primary end point rate was 9.3% in the ticagrelor group and 6.9% in the prasugrel group (hazard ratio, 1.36; 95% confidence interval [CI]: 1.09-1.70; $p=0.006$). The respective incidences of the individual components of the primary end point in the ticagrelor group and the prasugrel group were: death, 4.5% and 3.7%; myocardial infarction, 4.8% and 3.0%; and stroke, 1.1% and 1.0%. Definite or probable stent thrombosis occurred in 1.3% of patients assigned to ticagrelor and 1.0% of patients assigned to prasugrel, and definite stent thrombosis occurred in 1.1% and 0.6%, respectively. Major bleeding (as defined by the Bleeding Academic Research Consortium scale) was observed in 5.4% of patients in the ticagrelor group and in 4.8% of patients in the prasugrel group (hazard ratio, 1.12; 95% CI, 0.83 to 1.51; $P=0.46$).

Thus, prasugrel is clearly superior to ticagrelor in this comparison, with a clear reduction of myocardial infarction during follow-up which importantly, are not only “troponin leaks” but also new spontaneous myocardial infarction.

The results of the ISAR-REACT 5 are unexpected assuming the good quality of the PLATO trial. But if we focus our attention to the results of the PLATO and other studies such as the PHILO trial⁴ and registries studies^{5,6}, the results of the ISAR-REACT 5 should be considered as largely expected.

First, the PLATO was sponsored by the drug company, and the advantages of ticagrelor over clopidogrel were inconsistent, exhibiting unique “geographical” differences. No superiority of ticagrelor could be demonstrated in the US patient cohort (1,413 patients). The PLATO-US sites were monitored by the independent third party CRO, and revealed outcomes which were completely opposite to the sponsor-monitored results in non-USA countries arising the suspect of inappropriate intervention of the company in the management of data.

Second, the PHILO trial, that enrolled 801 patients from Japan, Korea and Taiwan with a study design that mirrored the PLATO could not demonstrate any superiority of ticagrelor over clopidogrel in both efficacy (9% in ticagrelor group and 6.3% in the clopidogrel group) and safety endpoints, with a significant increase of the composite of minor and major bleeding in the ticagrelor group (23.8% and 14.7%, respectively)⁴. It is notable that this study was funded by the drug company, but differently from PLATO, the events were adjudicated by a third party (Uppsala Clinical Research Centre, Sweden). Again, PHILO trial was completed in July 2012, but the paper was submitted 3 years later, delaying the public access to the trial results, suggesting a deliberate marketing trick to protect ticagrelor expansion in the Asian market.

Finally, 2 large registries comparing ticagrelor with prasugrel, clearly show the superiority of prasugrel^{5,6}.

Differently from the other randomized studies comparing ticagrelor or prasugrel with clopidogrel, the ISAR-REACT 5 trial was investigator-initiated, which underscore the absence of industry funding or participation to the organization, design or conduct of the trial making the study results a reliable evidence.

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