

Letters to the Editor

Risk of ticagrelor versus clopidogrel discontinuation



Riesgo de interrupción del ticagrelor frente al clopidogrel

To the Editor,

In their recent article, Almendro-Delia et al.¹ concluded that the association between nonadherence to ticagrelor vs clopidogrel and the risk of major adverse cardiac events (MACE) was not modulated by the choice of P2Y₁₂ receptor inhibitor. Nonetheless, 60 of the 1078 patients on ticagrelor (5.5%) stopped using this drug, while almost twice as many (114/1102 patients, 10.4%) stopped using clopidogrel. In the analysis of factors associated with premature cessation of dual antiplatelet therapy (DAPT), ticagrelor (vs clopidogrel) had an adjusted hazard ratio of 0.97 (95%CI, 0.93–1.01) and a *P* value of .080, suggesting that the association between nonadherence to DAPT and MACE can in fact be modulated by choice of inhibitor. That said, previous studies have shown an increased risk of bleeding with ticagrelor compared with clopidogrel,^{2–4} whereas the data presented by Almendro-Delia et al.¹ seem to suggest that patients on clopidogrel have a lower risk of DAPT cessation than those on ticagrelor. These findings warrant further discussion and clarification.

FUNDING

No funding.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used for this work.

CONFLICTS OF INTEREST

None.

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Response

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Respuesta

To the Editor,

In reference to the article published in *Revista Española de Cardiología*,¹ it is accurate to note that the overall unadjusted treatment interruption rate was higher with clopidogrel than with ticagrelor due to greater physician-guided discontinuation (*P* = .003, Table 4 of the supplementary material)¹, and was not associated with a higher risk of major adverse cardiovascular events (MACE) (*P* = .079). In contrast, the rate of disruptions was proportionally higher with ticagrelor (*P* = .003, Table 4 of the

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supplementary material)¹, especially in the 90 days following the index acute coronary syndrome (*P* < .001, Table 4 of the supplementary material). Taking this into consideration, disruption was indeed associated with a higher risk of MACE (*P* = .001), particularly when it occurred within the first 90 days of treatment (adjusted hazard ratio, 3.83; *P* < .001, Figure 7 of the supplementary material), unlike what was seen with physician-guided discontinuation. Therefore, after adjustment for potential differential nonadherence based on the P2Y₁₂ receptor inhibitor used, the time to interruption (earlier with ticagrelor than clopidogrel: 22 vs 53 days; *P* = .035, Table 5 of the supplementary material)¹, and the interaction between these 2 variables on an additive scale, the association between mode/timing of treatment interruption and MACE risk according to the type of P2Y₁₂ receptor inhibitor did not reach statistical significance (Table 5 of the

supplementary material)¹ in contrast to the results in all previous studies.

Concerning the bleeding rates, the studies cited by Martínez-Sellés used intention-to-treat (ITT) analyses, whereas this investigation was based on the on-treatment^{1,2} principle. Current evidence indicates that in observational studies, ITT analysis leads to biased effect estimates when there are differential time-dependent adherence rates.^{3,4} Notably, a recent study reported for the first time that ITT simulation consistently generated biased estimates of higher bleeding risk with ticagrelor than with clopidogrel in a real-world setting.²

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DECLARATION REGARDING THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence was not used in the preparation of this article.

AUTHORS' CONTRIBUTIONS

All authors have contributed to the conception/design, writing, critical revision, and final approval of the manuscript. The authors assume responsibility for all aspects of the article and will investigate and resolve any issues related to the accuracy and veracity of any part of the study. M. Almendro-Delia and Juan C. García-Rubir were responsible for acquisition, analysis, and interpretation of the data.

CONFLICTS OF INTEREST

M. Almendro-Delia has received speaker fees from Eli Lilly and Company, Daiichi Sankyo, and AstraZeneca, as well as remuneration for consulting work for Daiichi Sankyo and AstraZeneca. The remaining authors declare no conflicts of interest.

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