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Editorial comment

Nonadherence to dual antiplatelet therapy: old problems without new solutions

Falta de adherencia al tratamiento antiagregante plaquetario doble: viejos problemas sin nuevas soluciones

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Dual antiplatelet therapy (DAPT) consisting of aspirin plus a $P2Y_{12}$ receptor inhibitor is a class I guideline-recommended approach for patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI).[1] Although DAPT regimens are relatively short (up to 12 months), nonadherence to DAPT is fairly common and has important prognostic implications. The patterns of nonadherence to dual antiplatelet regimen in stented patients (PARIS) registry reported in 2013 set the groundwork for a better understanding of the consequences of nonadherence to DAPT after PCI, mostly with the $P2Y_{12}$ inhibitor clopidogrel.[2] At 2 years, DAPT disruption was associated with a higher risk of major adverse cardiovascular events (MACE) compared with patients who remained adherent, with the risk being time-dependent and highest among patients showing nonadherence within the first week. Although the PARIS data remain relevant, the introduction of newer generation oral $P2Y_{12}$ inhibitors (ie, prasugrel and ticagrelor) and changes in clinical practice pertaining to DAPT regimens raise the need to validate core concepts derived from this landmark registry.

In a recent article published in *Revista Española de Cardiología*, investigators of the CREA-ARIAM registry provide insights into nonadherence patterns to DAPT involving ticagrelor vs clopidogrel and its association with clinical outcomes in participants with ACS.[3] In brief, this is a prespecified subanalysis of the CREA-ARIAM (Antiplatelet therapy in acute coronary syndrome (ACS) Safety and effectiveness of switching between antiplatelet agents) registry, which is an investigator-initiated extension of the main ARIAM-Andalucía (Analysis of delay in acute myocardial infarction in Andalucía) registry.[4]

The study included participants with ACS who were admitted to cardiac care units and designated to receive at least 12 months of DAPT with clopidogrel or ticagrelor. Major exclusion criteria were prior intracranial hemorrhage or recent major bleeding and patients discharged on prasugrel or oral anticoagulation. The primary endpoint was time to first occurrence of MACE (a composite of all-cause mortality, myocardial infarction, stroke, unplanned target-lesion revascularization, or definite stent thrombosis) at 1 year.[5] Bleeding events were defined according to the Bleeding Academic Research Consortium.[6] Exposure to DAPT and related events were assessed prospectively and systematically after discharge by means of hospital and telephone visits at 1-, 6- and 12-months, using a dedicated questionnaire for DAPT adherence assessment together with calculation of the medication possession ratio. Cessation was defined as any unplanned DAPT discontinuation before 12 months, including temporary ($<$ 14 days) or permanent discontinuation ($>$ 3 days), with or without aspirin cessation. Drug cessation in relation to hospital discharge was classified as early ($<$ 90 days) and late ($>$ 90 days). At 1 year, 1 in 12 post-ACS participants self-reported any type of DAPT cessation. Compared with physician-recommended discontinuation, disruption resulted in a significantly higher risk of MACE. After adjustment for DAPT duration, there was no difference in MACE between ticagrelor-treated and clopidogrel-treated participants.

The investigators should be commended for this investigation, which provides real-world evidence on nonadherence to ticagrelor vs clopidogrel in ACS patients. The strengths of the study include its relatively large sample size (n = 2180), dedicated adherence assessment methods, and surveillance through the medication possession ratio. At 1 year, the incidence of self-reported DAPT cessation was 8.3%. Of these, 6.0% were physician-guided discontinuations, and 2.4% were disruptions.

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Of all self-reported DAPT cessations, most participants permanently discontinued DAPT after the first 6 months (88.5%), mostly involving only the $P2Y_{12}$ inhibitor. In contrast, a minority (11.5%) reported temporary interruptions with a median duration of less than 1 week. Although the differences in definitions hamper any cross-study comparisons, the results of the CREA-ARIAM registry are similar to those reported in prior investigations.[2,7] In the PARIS registry, at 1 year, 11.5% of the participants reported discontinuation (ie, recommended physician-directed withdrawal for patients thought to no longer need DAPT), 9.8% an interruption (ie, temporary cessation due to surgical necessity with reinstitution of DAPT within 14 days), and 4.6% a disruption (ie, cessation due to bleeding or nonadherence). The profile of nonadherence was similar between the CREA-ARIAM and PARIS, with most of the participants permanently discontinuing or temporally interrupting DAPT beyond 6 months under physician guidance. In those reporting temporary interruptions, these were shorter than 1 week.

The factors associated with DAPT cessation were strongly related to high bleeding risk characteristics or the selected therapeutic strategy (bare metal stent, coronary artery bypass grafting, and medical treatment).[8] The risk of DAPT discontinuation was highest in participants with myocardial infarction with nonobstructive coronary arteries, probably indicating the unclear role of DAPT in this cohort.[9] Conversely, characteristics of PCI complexity (multivessel PCI, stent overlap, and >1 stent) were associated with a reduced likelihood of DAPT cessation. These findings suggest that the key decision-making factors leading to DAPT cessation were mostly related to bleeding and ischemic risk. In contrast with some evidence, dyspnea was not associated with DAPT cessation.[10] Indeed, the fact that only $<1\%$ of the participants reported ticagrelor-related dyspnea leading to drug discontinuation raises concerns on the ascertainment of this common adverse effect associated with a $\sim$5% drug discontinuation rate.[11]

The authors identified different patterns of DAPT cessation. In the overall cohort, there was a significantly higher incidence of late cessation in clopidogrel-treated participants, mainly driven by physician-guided permanent discontinuations. However, in participants with self-reported disruption, there was a higher incidence of early cessation, which was more frequent in ticagrelor-treated participants and was mainly driven by nonadherence (ie, the perception of no additional benefit of prolonging treatment, dosing-related issues, or lack of accessibility/affordability). These patterns represent common situations in daily practice discussed in current guidelines: *a)* physician-guided discontinuation of DAPT secondary to adverse events (mainly bleeding) or due to high bleeding risk and/or low ischemic risk in patients who already completed a reasonable DAPT duration (eg, >180 days)[12]; *b)* unguided de-escalation of potent $P2Y_{12}$ inhibitors because of high bleeding risk (bleeding or new need for oral anticoagulation) and/or low ischemic risk[12]; *c)* DAPT temporary interruption in patients who need surgery/invasive procedures (>180 days from the index procedure)[13]; and *d)* DAPT disruption because of nonadherence. Hence, these patterns represent the actions of treating physicians (ie, shortening duration, de-escalation, or interruption for surgery/procedures) to adapt to the changes in the patient risk profile and adverse events during the first year after PCI.

At 1 year, most events were clustered within the first 90 days. DAPT cessation was associated with a higher risk of MACE, driven by worse outcomes in patients who self-reported disruption but without significant differences in those reporting physician-guided discontinuation. Indeed, the results of CREA-ARIAM are aligned with the results of PARIS, strongly suggesting that disruptions occurring at an early stage are associated with worse clinical outcomes compared with patients who are adherent to DAPT.[2] Conversely, an older and smaller registry conducted in another region of Spain reported that DAPT disruption was not associated with worse clinical outcomes.[7] In light of the available evidence, we consider early DAPT disruption, particularly during the first week after PCI, a major risk factor for MACE, including stent thrombosis. Although observational data could not support causation, these findings are biologically plausible, as the highest risk coincides with the high residual prothrombotic/inflammatory risk after an ACS and when the stent surface is still not endothelialized and is prothrombotic.[1]

Of particular note, compared with clopidogrel, ticagrelor was not associated with a higher risk of self-reported premature discontinuation (adjusted-hazard ratio [HR], 0.97; 95% confidence interval 95%CI, 0.93-1.01; $P=.08$). The adjusted risk of MACE after DAPT cessation was significantly higher in participants treated with ticagrelor than in those treated with clopidogrel regardless of the cessation mode (ticagrelor: adjusted-HR, 1.59; 95%CI, 1.17–2.17; $P=.003$ and clopidogrel: adjusted-HR, 1.26; 95%CI, 1.03–1.55; $P=.023$; $P_{\text{interaction}}<.001$). Interestingly, when this finding was analyzed considering the timing and pattern of cessation, the interaction was only significant in participants self-reporting early disruptions (ticagrelor: adjusted-HR, 4.77; 95%CI, 3.42–6.67; $P<.001$ and clopidogrel: adjusted-HR, 1.69; 95%CI, 1.18–1.42; $P=.004$; $P_{\text{interaction}}<.001$), without significant interactions in any of the other comparisons, including early or late physician-guided discontinuation and late disruption. These results of the CREA-ARIAM registry are not consistent with prior evidence from randomized controlled trials (RCTs) showing higher rates of premature discontinuation of ticagrelor compared with the comparator drug.[11] In a meta-analysis of 4 placebo-controlled RCTs comparing ticagrelor vs clopidogrel or aspirin (n = 66 870) for secondary prevention of atherosclerotic cardiovascular disease, at 18 months, premature ticagrelor discontinuation occurred in 25% of participants (relative risk of ticagrelor discontinuation compared with control was 1.25; 95%CI, 1.11–1.39) and was related to adverse events, with the most frequent being bleeding and dyspnea.[11] Notably, compared with clopidogrel or aspirin, the relative risk of dyspnea-related discontinuation during follow-up was 6.4-fold higher, and the relative risk of bleeding was 3.2-fold higher. Observational studies have reported mixed results, but the overall data favor the hypothesis that ticagrelor-based DAPT is associated with lower adherence rates than clopidogrel-based DAPT.[14–16] A large-scale retrospective study with propensity score matching of participants with ACS (n = 62 580) conducted in the United States and South Korea reported a consistently lower medical possession ratio in participants on ticagrelor-based DAPT compared with clopidogrel-based DAPT, without differences in net adverse clinical events (ie, composite of ischemic and bleeding events) at 1 year.[15] In another large-scale cohort study in patients with ACS undergoing PCI (n = 14 450) conducted in Denmark, ticagrelor-based DAPT was associated with a 5% lower adherence rate compared with clopidogrel-based DAPT and 14% of the participants on ticagrelor were switched to another $P2Y_{12}$ inhibitor, mainly clopidogrel.[16] Conversely, in a large-scale cohort study including participants with ACS (n = 11 185) conducted in Canada, those on ticagrelor-based DAPT had

higher rates of medication refill adherence compared with clopidogrel-based (81.6% vs 73.9%; $P < .001$), but ticagrelor was associated with a higher rate of switches than clopidogrel (14.0% vs 2.3%; $P < .001$).[14] Moreover, higher adherence ($\geq$ 80%) was associated with better clinical outcomes compared with low adherence ($<$ 80%) without interaction with the type of $P2Y_{12}$ inhibitor. Altogether, the high-quality data from RCTs strongly suggest that ticagrelor is associated with lower adherence than clopidogrel. Nevertheless, it is unclear whether this lower rate of adherence has a direct impact on outcomes as the RCTs do not provide specific adherence analyses, and observational studies provide mixed results.

The results reported by the CREA-ARIAM registry should be considered in light of some limitations. First, the study may suffer from potential selection biases due to its observational design. Because of the selection criteria, only 77% of the total sample was eventually analyzed. Notably, the choice of DAPT was at the discretion of the treating physician, and the adherence assessment was self-reported, leading to a potential recall bias. Second, the study was conducted between 2015 and 2019 within a specific health care system. Thus, the results may not be generalizable. Third, the exclusion of participants on prasugrel-based DAPT is a significant limitation as it precludes comparison of 2 potent $P2Y_{12}$ inhibitors, which are recommended over clopidogrel in patients with ACS. Fourth, the lack of adherence to the Non-adherence Academic Research Consortium (NARC) consensus definitions hampers the standardization and cross-study comparison of the results.[17] Fifth, it is unclear to what extent the active evaluation of adherence could create under- (ie, promoting patient adherence) and overdiagnosis (ie, detecting patient at risk and promoting $P2Y_{12}$ switches) of nonadherence events. Ultimately, it is unclear how these results fit into the newer DAPT regimens (ie, shorter duration, de-escalation, and aspirin-free strategies), as technically, these strategies would be considered nonadherence, but are currently recommended by guidelines. In this regard, implementing the NARC nonadherence definitions (ie, sustained discontinuation of the study regimen for a period longer than the pharmacological life) could help overcome this limitation.

Health care systems should increase their efforts to identify patients at risk of DAPT nonadherence and react promptly. Smartphone apps and dedicated clinics may enhance medication adherence, but their implementation in clinical practice is marginal.[17] Identifying patients at risk for nonadherence in daily practice is challenging as there is a lack of dedicated tools. Therefore, the implementation of artificial intelligence algorithms in electronic health records that can identify patients at risk of DAPT nonadherence and notify the treating physician and patient could be of interest. Clinicians should thoroughly assess biological (eg, high bleeding risk, ischemic risk, and need for surgery/invasive procedure) and social factors (eg, affordability, accessibility, disease insight, and environmental support) to select safe and effective DAPT regimens personalized to each patient's characteristics. Some practical considerations to mention are the following: *a)* short-DAPT regimens in patients with high bleeding risk, low ischemic risk, or requiring surgery/invasive procedure could avoid premature DAPT cessation or interruption; *b)* genotyping for cytochrome P450 2C19 alleles could provide important information to support clopidogrel-based DAPT or guided de-escalation, particularly in patients with high bleeding risk and/or ACS patients; *c)* evaluating the risk of dyspnea (eg, concomitant respiratory diseases) and promoting patient education could avoid switching from ticagrelor to prasugrel or clopidogrel; and *d)* identifying patients at high risk of nonadherence and adopting strategies that do not require critical DAPT adherence (eg, coronary artery bypass grafting or medical management) could avoid adverse events secondary to early DAPT disruption.

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CONFLICTS OF INTEREST

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