OPINION ARTICLE

Dual Antiplatelet Therapy After Acute Coronary Syndrome: A Constantly Evolving Strategy

La terapia antiplaquetaria dual luego de un síndrome coronario agudo, una estrategia en proceso de cambio perpetuo

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In cardiovascular medicine, every attempt to change an established strategy generates resistance, with arguments that can range from criticizing the methods to denying the new evidence. When the evidence becomes larger in terms of studies and number of patients, its applicability to a particular patient is questioned. Such is the case of duration of dual antiplatelet therapy (DAPT) after an acute coronary syndrome (ACS) requiring percutaneous coronary intervention with stent implant. There is increasing evidence for reducing DAPT duration and continuing treatment with antiplatelet monotherapy with P2Y12 inhibitors, or using de-escalation strategies, defined as switching from a full dose of a potent drug, to a less potent drug, or a reduced dose of a potent drug.

When treating a patient with ACS with antiplatelet therapy, our goal is to reduce ischemic events (efficacy) without increasing bleeding events (safety). In the last years, reducing bleeding events has become particularly important, prioritizing patients' safety. It has been clearly demonstrated that the longer the duration of DAPT, the greater the probability of bleeding, and that the use of more potent P2Y12 inhibitors as ticagrelor or prasugrel reduces ischemic events but inevitably increases major bleeding; time plus potency, a dangerous association.

But, ¿where does the evidence for using DAPT for one year come from? Undoubtedly, the CURE study (1) was the pioneer trial. Patients were treated for one year, and this duration was adopted by the guidelines on ACS. Subsequent studies as the TRITON trial (2) and PLATO trial (3) also followed-up patients for this time interval or greater. We are talking about a study published 22 years ago, with different stent technologies and a significantly higher rate of stent thrombosis, besides secondary prevention strategies that were very different from those used nowadays (less use of statins, etc.). In addition, because of their randomized nature, these studies included patients with lower risk of bleeding than those encountered in our daily practice.

But furthermore, to increase our conviction, as we observed that our patients who discontinued DAPT before one year had more ischemic events, we were convinced that 12 months was the mandatory time for DAPT, and nobody argued against this idea. But those patients discontinued the P2Y12 inhibitor and continued with aspirin. So, one-year DAPT was more effective than aspirin alone. Wrong drug?

Currently, when we analyze events after an ACS, we observe that ischemic events decrease after 1 to 3 months, but bleeding events persist throughout the duration of DAPT. (4) So, why not reduce DAPT to a shorter period, but discontinuing aspirin and continuing monotherapy with the more potent drug, or reducing DAPT potency after this critical 1–3-month period? Nowadays, there is increasing evidence for these strategies.

Several studies have evaluated monotherapy with potent drugs, discontinuing aspirin. Monotherapy with ticagrelor after 1-3 months of DAPT has demonstrated a significant reduction in bleeding events without increasing ischemic events. For example, the TICO study, which included 3056 patients with ACS in South Korea, showed a significant reduction in bleeding events without increasing ischemic events, which in fact were 44% lower than with standard therapy with ticagrelor monotherapy after 3 months of DAPT, compared with ticagrelor plus aspirin for 12 months. (5) Other studies as the GLOBAL LEADERS trial (6) and the TWILIGHT trial (7) have also shown a significant reduction in bleeding events without increasing ischemic events with ticagrelor monotherapy after 1-3 months of DAPT, compared with standard therapy. The TWILIGHT study also analyzed subgroups with ACS, diabetes and complex percutaneous coronary interventions (PCI), and bleeding was reduced in all subgroups without increasing ischemic events. While one may argue that the number of patients or the low event rate in patients undergoing PCI for ACS in the TWILIGHT study may raise doubt about the safety of this strategy, there are several meta-analyses of

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ing 4169 patients with ACS that demonstrated that clopidogrel monotherapy after 1-2 months of DAPT reduced the incidence of bleeding by 54% but was associated with a 50% increase in the composite end point of cardiovascular death, myocardial infarction, stroke, and stent thrombosis, and a 2-fold increase in the rate of myocardial infarction compared with standard DAPT. (9) Thus, with the current evidence clopidogrel would not be the drug of choice for monotherapy after abbreviated DAPT. The standard strategy of DAPT for 12 months is the one which produces less bleeding, so with the current evidence this would be the indication, and it can be abbreviated if the risk of bleeding is high.

De-escalation strategies to less potent drugs or lower doses within DAPT may be unguided or guided by genetic or platelet function testing (the latter is not likely to be massively applicable to our practice).

Unguided de-escalation therapy with DAPT is an interesting idea, switching from ticagrelor or prasugrel to clopidogrel, or reducing prasugrel dose to 5 mg/day, starting one month after PCI due to ACS when the ischemic risk decreases but the bleeding risk remains high. Studies such as the TOPIC trial with 646 ACS patients showed 52% reduction in the composite end point of cardiovascular death, urgent revascularization, stroke and bleeding defined as BARC (Bleeding Academic Research Consortium) classification 2-5 with de-escalation strategy switching DAPT from aspirin plus a potent drug, to aspirin plus clopidogrel 1 month after ACS compared to standard therapy. (10) The TALOS-AMI study (n = 2697) reported a significant 45% reduction in the primary end point (CV death, myocardial infarction, stroke, and bleeding type 2-5 according to the BARC criteria) by de-escalation DAPT strategy, switching from aspirin-ticagrelor to aspirin-clopidogrel after 1 month compared to 12 months of DAPT with ticagrelor in patients with acute myocardial infarction. (11) In both studies the reduction in the primary end point was due to less BARC type 2-5 bleeding .

Reducing the dose of prasugrel to 5 mg/day in DAPT, after 1 month with the usual dose of 10mg/day in 3429 patients undergoing PCI due to ACS, (HOST-REDUCE-POLYTHEC-ACS study) was associated with a 30% significant reduction in the composite of all-cause death, myocardial infarction, stent thrombosis, repeat revascularization, stroke, and bleeding events of grade 2-5 according to BARC criteria. (12) To date, there are no studies comparing different de-escalation strategies, and the only evidence comes from network meta-analyses based on indirect comparison, with the inherent associated limitations. (13)

Many arguments have been raised against these studies, such as the extrapolation to other populations of an effect demonstrated in Asian patients, the inclusion of patients with non-complex PCIs, small number to detect differences in ischemic events, etc.; but the truth is that there is increasing evidence to reduce the potency of DAPT or to use monotherapy with potent drugs after those first months, when the prevalence of ischemic events is significantly reduced. It has also been argued that the use of intracoronary imaging as intravascular ultrasound (IVUS) could help to reduce stent thrombosis and impact outcomes, but this is not very prevalent in the aforementioned studies. Stent technology is not different from the one we use in our centers, so these should not be arguments against the implementation of evidence in our patients.

So, with the current evidence, and unlike what we did before, we should evaluate which particular patient is a candidate for one-year DAPT with potent drugs and conclude that only patients at high ischemic risk without high bleeding risk are likely to be candidates for this strategy. In all other patients we should prioritize safety, using de-escalation therapy with less potent drugs or ticagrelor monotherapy after the third month of a PCI due to ACS, in case DAPT with ticagrelor has been started.

In cardiology, before changing treatment management, we require that the new evidence comes from many large studies involving many patients to convince us to abandon an established treatment which was based on much less evidence, or, as in this case, had been adopted because it was the established follow-up of the randomized studies of that time. This resistance to change may be caused by the prudence of waiting for more evidence (how much more?). Considering the current evidence, we should know that, by waiting for more evidence, we are causing more bleeding in our patients, affecting their safety. Maybe it is time to leave our comfort zone.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

Ethical considerations

Not applicable.

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