Editorial

Ultrashort 1- to 3-month double antiplatelet therapy after drug-eluting stent implantation or the conquest of the South Pole

La pauta ultracorta de tratamiento antiagregante plaquetario doble de 1-3 meses tras el implante de *stent* liberador de fármacos o la conquista del polo sur

Imanol Otaegui Irurueta,[a,b] Bruno García del Blanco,[a,b,*] and Gerard Martí Aguasca[a,b]

[a] *Unidad de Hemodinámica, Servicio de Cardiología, Hospital Universitari Vall d'Hebron, Barcelona, Spain*
[b] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

The conquest of the South Pole was an undeniable challenge, full of passion and unimaginable feats. In the world of coronary intervention, the same could be said for the solution to acute occlusion after balloon angioplasty with the emergence of stents and the reduction in the rate of restenosis. A generation of cardiologists currently remains immersed in a scientific quest to reach our very own South Pole: reducing the duration of dual antiplatelet therapy (DAPT) and its associated bleeding events. The fight against thrombosis is a double-edged sword.

The newer generation of drug-eluting stents (DES) have achieved very high efficacy levels: the incidence of stent failure is remarkably low due to the improved navigation profile, but above all due to their biocompatibility with the intravascular environment where they are deployed, reducing the phenomena of arterial wall inflammation and platelet activation that were seen with the first DES. In addition, improved mechanical adaptation to the vascular wall, with a substantial reduction in the thickness of the metal filament, has resulted in less distortion of laminar flow. All these factors have contributed to the improved safety of new-generation DES in the form of a reduction in thrombotic events, raising the possibility shorter DAPT duration. This was set at 12 months with first-generation DES based on the observed incidence of late thrombosis in registries with long-term follow-up after DAPT cessation. The 2017 update of the European guidelines established, for patients treated with coronary stents for indications other than acute coronary syndrome (ACS), a class II A recommendation for a 3-month duration and a class II B recommendation for a 1-month duration in patients at high bleeding risk.[1,2] But how did they reach this point?

In 2017, the guidelines recommended 12 months of DAPT after DES implantation, based on observational studies reporting an association between coronary thrombosis and stopping DAPT and a lower incidence of death or infarction at 12 and 24 months if clopidogrel was continued beyond 6 months.[3]

The first trials evaluating shorter regimens, of 6 months, were the EXCELLENT[4] and PRODIGY[5] clinical trials, published in 2012.

Although these 2 trials confirmed noninferiority of the 6-month vs the 12 month regimen, they did not detect an advantage in terms of bleeding events at 12 months.

In 2012 and 2013, respectively, the results of the RESET[6] and OPTIMIZE[7] clinical trials were published. These evaluated even shorter regimens (3 months) with the zotarolimus-eluting stable polymer stent. The results of both studies, although favorable and with a very low incidence of stent thrombosis, were not widely accepted, probably due to their low statistical power.

Three further trials, published in 2014, ITALIC[8], SECURITY[9] and ISAR SAFE,[10] were needed to establish the class I indication for 6-months DAPT in stable patients. This fundamental change came about after the analysis of exclusively second-generation DES (as opposed to the mix of stents in the EXCELLENT[4] and PRODIGY[5] trials). The ITALIC[8] and SECURITY[9] trials showed noninferiority of the 6-month regimen in terms of net clinical events, although they did not reach the prespecified number of patients and there was patient crossover of between 15% and 33% to the longer-regimen arm. The ISAR-SAFE[10] trial was the most important of the 3: it included 4500 patients, was the only one that was double-blind, and of the patients included, 40% had had ACS and 90% had second-generation DES. This study demonstrated the noninferiority of the 6-month regimen for major cardiovascular events and, in addition, showed a significant reduction in major bleeding events, types 3 to 5 of the Bleeding Academic Research Consortium (BARC) classification. In addition, a prespecified subanalysis did not show that these findings were affected by ACS being the indication for revascularization. Just as in the South Pole, when the explorers established their base or starting point for expeditions along the Antarctic coast, this provided a starting point for reducing the duration of DAPT.

The SENIOR,[11] LEADERS FREE,[12] and ZEUS[13] trials, published between 2015 and 2017, evaluated ultrashort 1-month DAPT regimens after implantation of 1 of 3 different DES in patients with high bleeding risk, compared with their bare-metal counterparts. The ultrashort regimen with the DES was just as safe and more effective, with fewer restenoses, than the bare-metal stents. This path has also been explored by the recently-published Onyx ONE[14] trial, which directly compared 2 of these 3 DES. In that trial, patients with high bleeding risk were randomized to treatment with zotarolimus-eluting stents or biolimus A9-eluting stents and afterward received DAPT for 1 month. The clinical outcomes in the 2 groups were very similar during follow-up, with the same

incidences of major cardivacular events, stent thrombosis, and bleeding events.

However, these 4 studies compared different stent models in patients at high bleeding risk who received 1 month of DAPT; they did not compare different durations of DAPT in this population. Therefore, they do not allow us to infer the ideal DAPT duration for the population with high bleeding risk. In fact, the incidence of definite or probable stent thrombosis in these studies in any of the arms was 1% to 2%, somewhat higher than that normally observed with longer DAPT.

With all this evidence, the European Society of Cardiology published their recommendations in 2017. In the polar exploration analogy, this could correspond to Sir Ernest Shackleton's discovery of the Beardmore glacier, way back in 1908—the direct route to the polar plateau and the South Pole.

The recently-published meta-analysis by Verdoia et al.[15] in *Revista Española de Cardiología* incorporated the work of the 5 most relevant studies published after the guidelines, namely the SMART-CHOICE[16] and TWILIGHT[17] trials, which assessed a 3-month regimen, and the GLOBAL LEADERS[18] and STOPDAPT-2[19] trials, which assessed a 1-month regimen. The fifth study included was a clinical trial by the authors themselves, the REDUCE trial,[20] which compared 3- vs 12-month DAPT in patients who received DES for ACS.

The SMART-CHOICE[16] and TWILIGHT[17] trials, which assessed 3-month regimens, the first with clopidogrel and the second with ticagrelor, included 3000 and 7000 patients, respectively. They found similar results: the same incidence of ischemic events, with a significant, consistent reduction in major bleeding. The first study to comprehensively assess a 1-month DAPT regimen was the GLOBAL LEADERS trial,[18] published in 2018. It included 15 991 patients randomized to 1-month DAPT with aspirin and ticagrelor followed by ticagrelor alone, compared with 12 months of dual antiplatelet therapy. The results showed a similar incidence of both ischemic and hemorrhagic events in both arms; this was probably related to the population having a low bleeding risk and undergoing noncomplex procedures. Nonetheless, a post hoc analysis of the primary variable at 12 months showed a significant reduction in bleeding in the group with the ultrashort 1-month regimen, suggesting the possibility of a potential benefit.[19]

The STOPDAPT-2[19] trial, published in 2019, also assessed a 1-month DAPT regimen, in this case with aspirin and clopidogrel, followed by clopidogrel monotherapy. In a population of 3009 patients, with low prevalence of complex lesions and with practically all the angioplasties performed under intracoronary imaging guidance, results for the ultrashort regimen were favorable. The primary outcome variable was significantly better, due essentially to a significant reduction in bleeding events, with a particularly low incidence of stent thrombosis, which was similar in both study arms.

These contemporary studies included in the present meta-analysis involved patients treated with newer-generation DES. Considering that the unit of analysis was patients, the message is potentially very useful.

The authors define the main efficacy variable as all-cause death, and the main safety variable as the incidence of major bleeding, as well as the secondary variable of incidence of acute myocardial infarction and stent thrombosis, all of which are robust variables. Considering mortality as the single efficacy variable when all the separate studies compared composite variables could be considered overly simplistic. On the other hand, mortality is the hardest variable, not subject to interpretations or definitions. The analyzed population was very large, at 30 552 patients, and from a very short, recent period. The authors found similar mortality in both groups, with a significant reduction in bleeding events in patients on a short DAPT regimen (2% vs 3.1%; odds ratio = 0.62; 95%

confidence interval, 0.46-0.84; P = 0.002), confirming and reinforcing the findings of the individual studies. The secondary variables showed similar incidences in the 2 treatment arms and, specifically, there was a low overall incidence of stent thrombosis, at 0.4%. The proportion of patients whose indication for revascularization was ACS was 53.7%, which could be relatively representative of real-world clinical practice. The meta-regression analysis performed by the authors did not show the ACS indication as affecting any of the outcome variables analyzed in the study, which is also an important message.

Clear limitations of the meta-analysis, as recognized by the authors, are that it combines studies with different definitions of the primary composite variable and distinct antiplatelet regimens, and it cannot exclude design bias of the studies included, such as the crossover from a short to a longer regimen.

We believe that this study could help to assimilate these short or ultrashort regimens into clinical practice. Until the publication of the GLOBAL LEADERS[18] and STOPDAPT-2[19] trials, the incidence of definite or probable thrombosis had been high. An additional benefit of this meta-analysis is that it confirms the low incidence of thrombosis reported in the 2 studies included. Caution is required, however, since some of the data on thrombosis from other contemporary studies, such as the LEADERS FREE[12] and Onyx ONE[14] trials, do not corroborate this with their analysis of complex interventional procedures. In addition, it should be remembered that these 2 trials with an ultrashort regimen included patients of low or moderate complexity and used intracoronary imaging in a high percentage of cases.

Lastly, an attempt has been made to define the specific clinical situations in which short or ultrashort regimens should be used, taking into account bleeding risk, frailty, compliance with prescribed treatment, and the complexity of the procedure performed. Worthy of mention in this regard is the TWILIGHT trial, which included 7000 patients with a complex ischemic procedure and high bleeding risk and showed a significant reduction in bleeding with the short 3-month DAPT regimen.[17]

The implications of procedure complexity have already been analyzed in depth in a meta-analysis published in 2016 by Giustino et al.[21] This was recently updated and completed by a second meta-analysis by Costa el at.[22] in 2019, which analyzed 14 893 patients from 8 randomized trials, with regimens from 1 to 6 or 12 months, in which they also defined high bleeding risk with a PRECISE-DAPT score $\geq$ 25. Both analyses showed that the incidence of ischemic events was significantly higher in patients with complex percutaneous coronary intervention (PCI). The presence of more than 1 PCI complexity factor was associated with an even higher incidence of events. In addition, bleeding risk factors were also associated with a higher incidence of ischemic events. The incidence of major or minor bleeding was some 3 times higher in the groups with high bleeding risk and, interestingly, PCI complexity was not associated with increased bleeding risk.

Analysis of DAPT duration showed that, in patients on DAPT with a PRECISE-DAPT score $\geq$ 25, longer DAPT showed no benefit in efficacy, independently of procedural complexity, and there was an increase in bleeding events. In patients with a score $<$ 25, the longer regimen did not lead to an increase in bleeding risk and did show a reduction in ischemic events, especially in complex patients. Finally, if ischemic and hemorrhagic events were considered as a net composite variable, the long DAPT regimen was only superior in patients with complex procedures and without high bleeding risk. This finding was even clearer when the authors analyzed patients with PCI in the context of ACS. Essentially, both analyses confirmed that high bleeding risk determines the benefit of shorter regimens, and the benefit from longer, 12-month regimens is limited to patients with complex PCI and without high bleeding risk.

In the coming months, the results of the MASTER DAPT[23] clinical trial will be available for analysis. This study has randomized patients with high bleeding risk to 1-month or 12-month DAPT and is certain to provide evidence that will shine more light on this question. It appears increasingly clear though, with all this cumulative evidence, and with the strength that the present meta-analysis indicates, that 3-month DAPT regimens could become standard for patients at high bleeding risk; for certain devices, in situations of noncomplex PCI with intracoronary image guidance, this may even be reduced to 1 month. This treatment strategy will undoubtedly benefit patients in terms of bleeding events. It is likely, and, in our opinion, desirable, that all of these scientific contributions and the evidence that they generate will be reflected in the next update of the American guidelines, and that the level of recommendation in the European guidelines will increase for short and ultrashort regimens in patients with high bleeding risk.

A few days ago, we left behind the legendary mountain The Cloudmaker, we have surpassed practically all the difficulties, the crevasses, and the pressure ridges of the Beardmore glacier, and the polar plateau is within our sight. The South Pole begins to appear within reach, but in such adventures, it is important not only to reach the destination but also to ensure a safe return—as well as preventing ischemia we must consider the other edge of the sword: bleeding.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in relation to the contents of this article.

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