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The Dual Antiplatelet Therapy study at the American Heart Association meeting: an issue that concerns all of us. Future changes in the paradigm or a look into the past?

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It is unusual for the editor-in-chief to include co-authors in his monthly editorial, with the sole exception of Paul Cummins (Managing Editor) who, by the way, is a wonderful editorialist and, together with me, writes most of the editorials. However, in this present case, I was coming out of the late breaking clinical trials section in the main arena of the American Heart Association meeting during which the Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-eluting Stents (DAPT) study was presented, and bumped into two of my young colleagues who immediately started to ask me questions. These two young colleagues were Felipe Albuquerque from New York and Yoshinobu Onuma from Rotterdam. Their first question was "Professor, what is your opinion about the DAPT study?" and I replied that this was a complex question - what specifically would they like to know?

We had a very interesting discussion, which concentrated on several important topics. First, we focused on the patient population of the DAPT study. This was an interesting point, since the investigators primarily enrolled patients who had already completed twelve months of dual antiplatelet therapy (DAPT) without any ischaemic, thrombotic or bleeding events. This may represent a selection bias and may not represent the all-comers population in whom we prescribe DAPT without completely knowing the risks, despite careful physical examination and history taking. The second important point was that, historically, the DAPT study was conducted following a request from the Food and Drug Administration, a few years ago, to elucidate the optimal DAPT duration which was, at that time, a critical question which remains valid even today.

It is crucial to highlight the technological improvements which have occurred in the meantime in the field of interventional cardiology. Currently, the European guidelines recommend the use of drug-eluting stents for patients with an acute myocardial infarction with a Class Ia indication. As a matter of fact, this represents a recommendation against the use of bare metal stents. In the DAPT study, patients were treated with the CYPHER® stent (Cordis, Johnson & Johnson, Warren, NJ, USA) which has a well-known "unfavourable biological effect of the methacrylate compound", the TAXUS stent (Boston Scientific, Natick, MA, USA), with its "SIBS" coating which elutes only one percent of the drug in thirty days (the long-term amount of drug that remains in the coating has still not been fully elucidated), along with the "light zotarolimus-eluting stent" (Endeavor; Medtronic, Minneapolis, MN, USA). These three stents belong to the past, which clearly indicates the fast pace of progress in the field and how difficult it is to anticipate and have a visionary projection of a trial in interventional cardiology.

The next point is that DAPT represents a historical development which emerged decades ago with the work of Andreas Gruentzig, who used aspirin, a cyclooxygenase inhibitor, as an antiplatelet agent for a short duration, since it was the only agent available. After the development of coronary artery stents, aspirin was found to be a weak agent, and ticlopidine, a medication that was initially designed for prevention of restenosis, was found to be a more specific antiplatelet therapy agent and was the first thienopyridine used. When Michel Bertrand and colleagues associated ticlopidine with aspirin after stent implantation, there was a dramatic reduction of thrombotic events. From Baraghan in Marseille to Jean Marco in Toulouse and Marie-Claude Morice in Paris, DAPT then started to cross borders. Its use progressed to Germany and, finally, crossed the Atlantic and was tested, by our American colleague Martin Leon, in a trial of anticoagulation versus antiplatelet therapy. This is the brief history of DAPT.

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When we designed the first-in-man trial testing the CYPHER stent, we initially planned two months of DAPT. It is important to remind the readers that in the RAVEL trial[1] we used only two months of DAPT. Then the duration of therapy increased to three months with the SIRIUS trial[2] and six months with the TAXUS trial. The current European guidelines recommend continuing DAPT for at least six months after percutaneous coronary intervention (PCI) in patients with stable coronary artery disease, while the American Heart Association/American College of Cardiology recommend at least 12 months of DAPT. However, the need for aspirin, which has been the main trigger for gastrointestinal bleeding, has never been completely challenged. Ticlopidine fell out of favour, mainly due to its side effects such as leukopenia and aplastic anaemia, which occurred mostly in the first 15-30 days. It was replaced by clopidogrel, a pro-drug requiring pre-metabolisation that produced a significant improvement in mortality in the CURE study[3], but also had issues with polymorphisms and drug-drug interactions, so its efficacy was not systematically guaranteed in every individual. Following clopidogrel, there was the development of more potent $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor. The DAPT study included patients who received therapy with clopidogrel, prasugrel, ticagrelor, bare metal stents, Endeavor, TAXUS, CYPHER and PROMUS Element (Boston Scientific) stents. So there is a great element of heterogeneity in this trial.

In our opinion, the most striking aspect is the fact that, if you analyse carefully the curves of major adverse cardiovascular events (MACCE), such as myocardial infarction, death and target lesion revascularisation, it is clear that there is a significant difference between the two groups throughout the duration of the trial. However, the slope of the curves also suggests that there is a significant increase in the incidence of events between zero and three months after randomisation in the group which discontinued DAPT and continued monotherapy with aspirin. This appears to be very similar to the rise in the slope of the curve between 18 and 21 months after randomisation in patients who discontinued the prolonged duration of the thienopyridine. This raises a major question which is – are we really interrogating the therapeutic effect of the prolonged duration of DAPT or are we testing the cessation of DAPT on two different occasions, in a sequential and crossover way? The increased incidence of events observed after the two sequential discontinuations of DAPT may be secondary to a rebound effect, which could have triggered the events after thienopyridine discontinuation. To what extent did an individual become susceptible to an ischaemic event when that therapy was stopped? These findings suggest that we may need an efficient continuous protective agent against atherothrombotic events which does not generate high rates of bleeding. The GLOBAL LEADERS trial, an ongoing, prospective, randomised, multinational trial is currently investigating a novel DAPT regimen, consisting of aspirin for one month associated with ticagrelor for 24 months, compared to standard DAPT with clopidogrel/ticagrelor associated with aspirin monotherapy for 12 months. This trial will continue to pursue the search initiated by the DAPT study. Approximately 8,000 patients in an all-comers population have been enrolled. Its results are eagerly awaited and may help to elucidate important remaining questions on optimal DAPT regimen and duration.

It is not the first time in medicine that we have observed a rebound phenomenon on the interruption of a drug. In the LIPS study, which investigated the effect of statins on mortality prevention, the interruption of compliance with a statin therapy post PCI led to a 2.5-fold increase in the risk of adverse events[4]. Are we facing the same phenomenon? Certainly in the past we have studied the effect of DAPT cessation after bare metal stent implantation and, from a biochemical point of view, there was an increase in CD-40 and p-selectin, so certainly there was a biological effect which could not be ignored. Therefore, for all the above reasons, it is important to remind the readership that, despite extensive research in this field, the clinical decision-making process, assessing the optimal duration, risks and benefits of DAPT for each individual patient, will not soon vanish.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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