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Long-term monotherapy with ticagrelor after coronary stenting: the GLOBAL LEADERS study

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Dual antiplatelet treatment is currently the mainstay of pharmacologic treatment for patients after coronary percutaneous interventions for stable or acute coronary syndrome. The treatment decreases the incidence of thrombotic complications, but is responsible for an increased risk of bleeding. The advances in interventional cardiology and the development of new coronary stents, allow for a significant reduction of haemorrhagic complications secondary to antithrombotic treatment by either decreasing their dose or limiting their duration. The GLOBAL LEADERS study failed to demonstrate, after 2 years of follow-up, an advantage for the monotherapy with ticagrelor as compared to standard dual antiplatelet regimen. Nevertheless, focused appraisal of the study results, provide for some positive and promising new considerations. In fact, even though the results of the GLOBAL LEADER trial have not changed the current clinical practice, they provide the starting point for the design of new trials aiming at comparing new antithrombotic regimens which could be not inferior in terms of efficacy, but superior in terms of safety.

The dual antiplatelet therapy (DAPT), consisting of the combination of acetylsalicylic acid (ASA) and a P2Y12 purinergic receptor inhibitor (clopidogrel, ticagrelor, prasugrel), has established itself as the cornerstone of drug treatment in patients with ischaemic heart disease (stable coronary artery disease or acute coronary syndrome) subjected to percutaneous myocardial revascularization (PCI, percutaneous coronary intervention).[1] In this high-risk population, DAPT has been shown to be effective in reducing the rate of acute ischaemic complications related to the presence of stents (intra-stent thrombosis) and ischaemic events affecting stent-free vessel tracts.[1]

However, the price to pay is the predictable increase in the incidence of bleeding (mainly gastrointestinal), which reduces the quality of life and affects the patient's prognosis.[2] Thanks to technological development and greater understanding of the mechanisms underlying the intra-stent thrombosis, the development of drug-releasing stents (DES, drug-eluting stent) of the 'new generation', is associated with a lower rate of thrombotic complications, with consequent permissive effect on the use of 'minor' adjuvant antithrombotic therapy.[3] It is therefore easy to understand why many new trials propose 'experimental' strategies on the associations or duration of post-PCI antithrombotic therapy, with the common goal of minimizing the rate of bleeding complications while ensuring full therapeutic efficacy.

Current European guidelines on myocardial revascularization provide recommendations on antithrombotic therapy specific for clinical presentation.[4] In stable coronary artery disease, the use of DAPT with ASA + clopidogrel for 6 months is recommended (recommendation Class I), followed by a single long-term antiplatelet agent. However, there are exceptions: in selected patients, it is possible to obtain a benefit from the prolongation of the therapy up to 30 months (Class IIb);[5] on the contrary, the DAPT could be reduced to 3 months (Class IIa) or even to 1 month (Class IIb) in patients at high risk of bleeding.[6] In acute coronary syndromes, DAPT with ASA + prasugrel or ticagrelor is recommended for 12 months (Class I), reducible to 6 months in the event of a high risk of bleeding (Class IIa). The pillar of any post-PCI antithrombotic regimen is the ASA, whose role is sometimes called into question. A potential concern

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arising from the early discontinuation of ASA could be linked to the renunciation of its possible additive effects (e.g. prevention of venous thromboembolism, reduced neurocognitive impairment, prevention of colorectal tumours).[7] Clopidogrel is traditionally the drug more commonly used in association with ASA within the DAPT, but its main limitation is the high inter-individual variability. Prasugrel and ticagrelor, also antagonists of the platelet P2Y12 receptor, exert a faster, more powerful, and more constant anti-aggregating effect than clopidogrel; ticagrelor also showed further effects mediated by the inhibition of the adenosine transporter ENT1 (Type 1 equilibrative nucleoside transporter), which hinders the transport and therefore the intracellular metabolism of endogenous adenosine, with favourable repercussions on coronary flow and platelet aggregation, but also with potential adverse effects such as dyspnoea.[8]

The addition of ASA to other antithrombotic agents increases the incidence of bleeding, while its contribution to anti-ischaemic efficacy is questionable; for this reason, the so-called 'aspirin-free' strategies are having initial credit in recent years.[7]

The first attempt to renounce aspirin in the setting of ischaemic heart disease was in patients undergoing PCI and with indication for long-term anticoagulation, so as to avoid the negative effects of a triple antithrombotic therapy. The WOEST trial, conducted on a population relatively small and before the advent of new oral anticoagulants, compared the combination of clopidogrel + anti-vitamin K with the classic triple therapy (ASA + clopidogrel + anti-vitamin K), demonstrating a significant reduction in bleedings, with no increase in major adverse cardiovascular events.[9] Subsequently, in the PIONEER AF-PCI and RE-DUAL PCI trials, the combination of a P2Y12 receptor inhibitor with a new oral anticoagulant (rivaroxaban or dabigatran, respectively) demonstrated a significant reduction in safety endpoint, although the effect of ASA on bleeding in control groups is difficult to determine in the presence of a triple therapy with vitamin K antagonist[10,11]

Subsequently, strengthened by the greater anti-aggregation power of ticagrelor, it was decided to evaluate aspirin-free strategies even in patients subjected to angioplasty without indication to the anticoagulant.

This is how the GLOBAL LEADERS study was born (Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy vs. Current-Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use), published by Vranckx *et al.*[12] in 'The Lancet' in September 2018. This is a trial of superiority, randomized, multicentre (130 sites in 18 countries), and open-label. Between July 2013 and November 2015, 15 968 patients undergoing PCI were enrolled and implantation of BioMatrix, a Biolimus A9 releasing stent (umirolimus), derived from sirolimus with similar anti-inflammatory and antiproliferative activity, but with a better pharmacokinetic profile. Patients were randomized (1:1) to DAPT (ASA 75–100 mg/day + ticagrelor 90 mg bid) for 1 month and subsequent monotherapy with ticagrelor 90 mg bid for 23 months, or to standard DAPT (ASA 75–100 mg/day + clopidogrel 75 mg/day in stable coronary heart disease or ASA 75–100 mg/day + ticagrelor 90 mg bid in acute coronary syndromes) for 12 months followed by monotherapy with ASA 75–100 mg/day for an additional 12 months.

The primary endpoint at 2 years was defined as a composite of death from all causes and non-fatal Q wave myocardial infarction. The secondary safety endpoint included Type 3 or 5 bleeding according to the BARC (Bleeding Academic Research Consortium) criteria.

The intention-to-treat analysis at 2 years, despite a trend in favour of experimental treatment, showed no significant differences for the primary endpoint [3.81% in the experimental group vs. 4.37% in the control group; rate ratio (RR) 0.87, 95% confidence interval (CI) 0.75–1.01; $P = 0.073$] nor for the secondary (2.04% vs. 2.12%; RR 0.97, CI 0.78–1.20; $P = 0.77$).

Considering only patients with acute coronary syndrome and therefore using ASA + ticagrelor as a control, an advantage emerged in favour of the experimental group (RR 0.73, 95% CI 0.54–0.98; $P_{interaction} = 0.007$). On the contrary, the experimental therapy proved to be disadvantageous in patients with stable coronary artery disease, in which the comparison was conducted against DAPT with ASA + clopidogrel (RR 1.32, 95% CI 0.97–1.81; $P_{interaction} = 0.007$).

Furthermore, the 1-year landmark analysis showed a statistically significant reduction in bleeding in patients with acute coronary syndrome undergoing ticagrelor monotherapy (RR 0.64, 95% CI 0.46–0.90), not confirmed in patients with stable coronary artery disease.

The trend in favour of ticagrelor monotherapy (14.35% vs 15.49%; $P = 0.057$) is also interesting for NACCE (Net Adverse Cardiovascular and Cerebrovascular Events).

The GLOBAL LEADERS study is also accompanied by the GLASSY sub-study (GLOBAL LEADERS Adjudication Sub-Study; NCT03231059),[13] created to re-award the events reported by the single centres in order to reduce the variability and heterogeneity caused by the multicentric nature of the study and avoid detection and reporting bias typical of open-label trials.

In conclusion, the main result of the GLOBAL LEADERS study is that, after a 2-year follow-up, ticagrelor monotherapy did not prove superior to the standard DAPT in terms of efficacy and safety.

The GLOBAL LEADERS trial, however, is full of innovative aspects: in fact, it was the first randomized trial to compare a monotherapy with a P2Y12 receptor inhibitor to the standard DAPT; first to renounced ASA in patients not receiving anticoagulant therapy; second, it also had the primacy in comparing a very-short DAPT (duration of 1 month) to the standard duration of DAPT, not only in stable patients but also in the setting of acute coronary syndromes.

The rationale of this study is very clear: after an initial period of 30 days characterized by an elevated risk of intra-stent thrombosis, an attempt was made to avoid the greater risk of bleeding potentially associated with the addition of ASA (although at low dose) to the antithrombotic regimen, while maintaining a full anti-aggregating effect thanks to a powerful drug such as ticagrelor.[14] The design of the study is one of its strengths: patients undergoing PCI

were included both in election and for acute coronary syndrome; no restrictions were placed on the type of coronary lesion or on the number and length of implanted DES. A valuable aspect is the removal of important confounding factors by standardizing the intra-procedural use of bivalirudin and especially the use of a single stent in all patients.

Noteworthy is the execution of landmark analysis and analysis by subgroups (based on the characteristics of the patients or the use of ticagrelor or clopidogrel) for both the primary and secondary endpoints.

However, the interpretation of the GLOBAL LEADERS also passes through the consideration of some less positive aspects. The trial was conducted with an open-label design, a potential cause of assessment bias or reporting bias. The source of concern and potential confounding effect is the simultaneous comparison of different durations (1 month vs. 12 months) and different regimens (ticagrelor vs. ASA + clopidogrel or ASA + ticagrelor) of DAPT. Only an intention-to-treat analysis was conducted, which therefore ignored any protocol violations, such as early drug withdrawal or high crossover frequency between groups. The latter was remarkably asymmetric, occurring almost exclusively in favour of the control group. The treatment was completed as per protocol in 77.6% of patients in the experimental group and in 93.1% of controls, with a drop in the rate of adherence to experimental therapy during the 2nd year. If the trial had been interrupted after only 1 year of follow-up, probably today we would talk about an extremely positive study in favour of ticagrelor monotherapy. Despite being in line with the previously conducted trials, the low adherence to ticagrelor may have influenced the results and the lack of an 'as-treated' analysis makes us lose any information on what happened after the randomization (e.g. also introduction of other therapies prohibited by the exclusion criteria, e.g. anticoagulant therapy): the presence of the intention-to-treat analysis alone reflects the consequence of randomization to a treatment rather than the effect of the treatment itself. It is essential to note a peculiarity in the design of the study: during the 1st year, after the 1st month of DAPT, the monotherapy with ticagrelor (experimental) and the DAPT with ASA + ticagrelor or clopidogrel (control) were compared, with a resulting benefit in terms of safety in the subgroup with acute coronary syndrome; in the 2nd year, instead, the comparison concerned ticagrelor monotherapy and ASA monotherapy and the absence of significant differences reduced the overall significance in favour of the experimental strategy. The choice of the primary endpoint is also questionable: all-cause mortality and Q wave myocardial infarction are clinically relevant and easy to determine, but the inclusion of other traditional endpoints would probably have increased the ability to identify differences between the two treatment regimens.

Considerations on the statistical power of the study also deserve attention. The expected frequency of the primary endpoint (5% at 2 years in the control group) was determined based on the LEADERS trial,[15] in which, however, all patients took clopidogrel and not ticagrelor: the lower rate of events reduced the statistical power of the study, even more in subgroup analyses, for example, in patients with acute coronary syndrome. Perhaps, to overcome this problem, a choice of the event-driven sample size would have been useful. Furthermore, the expected reduction in ischaemic risk was determined on the basis of the PLATO trial,[16] conducted in patients with acute coronary syndrome: 53% of patients included in the GLOBAL LEADERS had instead a stable coronary artery disease (in which the ticagrelor did not shown overt benefits), so the expected reduction in the frequency of ischaemic events may have been too optimistic and therefore the superiority of the experimental treatment too difficult to prove.

Finally, it should also be noted that, despite the formally negative result in terms of superiority, there are some numerical trends in favour of ticagrelor monotherapy, so a longer follow-up could have shown a significant benefit.

The GLOBAL LEADERS trial was not designed to demonstrate the non-inferiority of the experimental treatment, which, however, seems to be confirmed on the basis of safety data (upper limit of 95% CI of the primary endpoint close to unity), making it promising further study of a monotherapy with a powerful antiplatelet agent in patients with acute coronary syndrome, especially in the presence of bleeding events during DAPT.

Among the trials already in progress (Table), TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; NCT02494895)[17] includes only patients with acute coronary syndrome, randomized after 3 months of DAPT with ASA + ticagrelor without adverse events, with ticagrelor monotherapy or with continuation of standard DAPT. The objective is the comparison between the two groups in terms of major adverse cardiovascular events and major bleeding in the 12 months after PCI. The results are expected by May 2023.

Another ongoing trial is TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention; NCT02079194),[18] which included high-risk patients undergoing PCI for either acute coronary syndrome (population similar to that of PEGASUS trial,[19] certainly at a higher risk than that of GLOBAL LEADERS) and, after 3 months of DAPTwith ASA + ticagrelor in the absence of adverse events, randomized them in double-blind to continue DAPT with ASA + ticagrelor or to placebo + ticagrelor. Unlike the GLOBAL LEADERS, the primary endpoint concerns safety (Type 2, 3, or 5 bleedings according to the 12-month BARC criteria) and is therefore easier to achieve following ASA removal. Non-inferiority will also be established with regard to ischaemic events. The results are expected by August 2019.

In conclusion, the standard pharmacological treatment for patients undergoing PCI with the preferred DES implant or for acute coronary syndrome is DAPT. Thanks to the introduction of better and better coronary stents, today it is possible to use antithrombotic therapies of lesser duration, so as to reduce the haemorrhagic events that these involve. Studies conducted in patients undergoing anticoagulant therapy have already shown that, even after PCI, ASA is not always indispensable. Thanks to this and to the advent of more potent and constant P2Y12 receptor inhibitors compared to clopidogrel, the improvement of the efficacy and safety profiles of the therapy through the 'drop-out' of the ASA in favour of a monotherapy with a receptor

antagonist of the P2Y12 seems to be a viable route. Since the choice of therapy should not be based only on the pharmacological effect but on an overall balance of the risks and benefits obtainable, pending positive results from trials of superiority, the current clinical practice will not be influenced by the GLOBAL LEADERS and probably nor it would have been even if this had been a non-inferiority trial and had shown a positive result. In fact, ticagrelor is a more expensive drug than clopidogrel, it requires a double daily administration, causes more side effects (primarily dyspnoea) and is associated with less therapeutic compliance.

However, the GLOBAL LEADERS study maintains a key role as a forerunner, as it is innovative, especially with regard to some concepts that until recently were well established, such as the role of the ASA in secondary prevention and the minimum duration of 6 months of post-DAPT PCI (12 months in the case of acute coronary syndrome).

Pending the results of the trials still in progress, the optimal strategy remains the DAPT with ASA + P2Y12 receptor inhibitor, however, individualized on the basis of demographic, clinical, and angiographic variables of the single patient, so as to obtain the maximum benefit by minimizing the risk.

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