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How should the ticagrelor be used? The point after the TWILIGHT and THEMIS-PCI studies

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The ticagrelor represents a cornerstone of antiplatelet therapy and its use has been supported, over the years, by several clinical trials that have enrolled thousands of patients; while the PLATO study initially demonstrated its effectiveness in the immediate treatment of acute coronary syndromes, the PEGASUS study documented the benefit of prolonging this treatment beyond 12 months from the heart attack. Over the past few months, two new randomized clinical trials have been published that have seen the use of ticagrelor in different clinical settings. The TWILIGHT study showed that in high-risk patients who completed 3 months of double antiplatelet drugs after coronary angioplasty, ticagrelor monotherapy is associated with a 44% reduction in the risk of clinically relevant bleeding in the absence of an increase in the ischaemic risk. The THEMIS study instead concluded that in the population of diabetics with stable coronary artery disease, but without a history of heart attack or stroke, a strategy that involves the addition of ticagrelor to the acetylsalicylic acid is not advisable as in the face of a benefit in the prevention of events ischaemic an increased risk of bleeding has been observed. Only in the subgroup of diabetic patients with a history of previous angioplasty would a more powerful antithrombotic therapy seem to be advantageous.

Introduction

Antiplatelet therapy is the cornerstone of drug treatment for patients with cardiovascular disease, especially in the presence of acute coronary syndrome (ACS). The ticagrelor is the progenitor of a class of platelet inhibitors which through the reversible bond with the P2Y12 platelet receptor prevents its activation and the consequent conformational modification that leads to the activation of the protein G.[1]

The efficacy and safety of ticagrelor were initially evaluated in the PLATO (PLATelet inhibition and patient Outcomes) trial, a randomized, double-blind study that compared ticagrelor with clopidogrel, both added to treatment with acetylsalicylic acid (ASA), in over to 18 000 patients with SCA. In this study, ticagrelor therapy was significantly more effective in reducing ischaemic events (myocardial infarction, stroke, death from all causes and cardiovascular causes) in the face of a significant increase in major bleeding and, in particular, of intracranial haemorrhages.[2]

The efficacy of the prolongation of ticagrelor therapy in patients at high risk of recurrent ischaemic events was instead tested in the PEGASUS TIMI-54 study (PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome-Thrombolysis In Myocardial Infarction Study Group) which enrolled more than 21 000 patients with a history of previous myocardial infarction randomized at least 1 year after the acute event in one of the three arms: ticagrelor 90 mg 2 times a day, ticagrelor 60 mg 2 times a day, or placebo, in addition to the ASA. The ticagrelor, administered in the two different dosages, demonstrated a significant reduction in the primary efficacy endpoint (composite of cardiovascular death, heart attack, stroke), compared to a significant

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increase in bleeding without however any significant difference in terms of fatal or intracranial bleeding. The efficacy of the prolongation of the double antiplatelet therapy with ticagrelor has been maintained in all the pre-specified subgroups and the highest benefit has been documented precisely in subjects at higher risk of ischaemic recurrences (diabetic patients, with renal failure, with multivessel coronary artery disease and with peripheral vascular disease). Overall, treatment with ticagrelor at a dosage of 60 mg × 2 has shown a better risk/benefit profile than the 90 mg × 2 regimen and is therefore what is normally used in clinical practice to prolong dual antiplatelet therapy after the first 12 months.[3]

Over the past few months, two new randomized clinical trials have been published that have seen the use of ticagrelor in different clinical settings: the TWILIGHT study[4] and the THEMIS study[5] with the THEMIS-PCI sub-analysis.[6]

The TWILIGHT study

The TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) study is a randomized, placebo-controlled trial designed to evaluate whether in patients undergoing PCI (percutaneous coronary intervention), at high risk of ischaemic and haemorrhagic events and that have completed the first 3 months of double antiplatelet therapy with ASA and ticagrelor, a ticagrelor strategy in monotherapy compared to continuing the double treatment may be advantageous in terms of protection from clinically relevant bleeding and in the absence of an increased ischaemic risk.[4]

In order to be enrolled, patients had to have undergone successful coronary angioplasty with at least one medicated stent implanted and treated for 3 months with ASA and ticagrelor. They also had to have at least one additional clinical and angiographic feature associated with a high risk of ischaemic or haemorrhagic events. High-risk clinical criteria were considered: age >65 years, diabetes mellitus, chronic renal failure, female sex, troponin-positive ACS, peripheral vascular disease. High-risk angiographic criteria were instead considered: multivessel coronary artery disease, a total length of the implanted stents >30 mm, the presence of thrombus at the target lesion, a bifurcation treated with two stents, obstructive disease of the left main or proximal tract of the anterior descending artery, a calcified target lesion undergoing an atherectomy. Subjects with heart attack with ST-segment elevation, cardiogenic shock, contraindications to taking ticagrelor or ASA or being treated with oral anticoagulants were excluded.

All enrolled patients underwent double antiplatelet therapy with ticagrelor (90 mg twice a day) and ASA (81–100 mg per day) for the first 3 months after the PCI index. Thereafter, patients who had not experienced an ischaemic event (heart attack, stroke, or new revascularization) or major bleeding in the first 90 days were eligible and were randomized double-blinded and with a 1:1 ratio to receive, in addition to ticagrelor, ASA, or placebo in the following 12 months. Failure to adhere to ASA or ticagrelor treatment in the first 3 months made patients unsuitable for randomization. All subjects underwent a telephone follow-up 1 month after the start of the study and a clinical follow-up in the 6th and 12th months. After the 12 months of therapy imposed by randomization, patients were switched to take the antiplatelet therapy which represented the local standard of care and performed a final telephone follow-up 3 months later.[7] The primary endpoint of the study was the occurrence of type 2, 3, or 5 bleeding according to the BARC classification.[8] The key secondary endpoint was the occurrence of death from all causes, myocardial infarction, or non-fatal stroke. Secondary haemorrhagic endpoints included bleeding defined by following different classifications: type 3 or 5 bleeding according to the BARC classification, major or minor bleeding according to the TIMI classification;[9] moderate, severe, or life-threatening bleeding according to the TASTE classification[10] and major bleeding according to the ISTH classification.[11] Other secondary endpoints have included: death from cardiovascular causes, myocardial infarction, ischaemic stroke, definite, or probable stent thrombosis.

From July 2015 to December 2017, a total of 9006 patients were screened following PCI, 7119 were finally randomized after the first 3 months to ticagrelor and ASA (3511) or to ticagrelor and placebo (3496). The occurrence of the primary endpoint was ascertained in 98.4% of cases. The two groups were quite overlapping as regards the main demographic, clinical, and procedural characteristics: the average age was 65 years, 23.8% of the patients enrolled were women, 64.8% underwent percutaneous revascularization for ACS (29.8% for a myocardial infarction without ST-segment elevation). Adherence to ticagrelor treatment after randomization was similar between the two groups: 87.1% for the ticagrelor-placebo arm and 85.9% for the ticagrelor-ASA arm.

The primary endpoint of the study occurred in 141 patients (4%) treated with ticagrelor-placebo and in 250 patients (7.1%) treated with ticagrelor-ASA [hazard ratio, 0.56; 95% confidence interval (CI) 0.45–0.68; $P < 0.001$]. The incidence of BARC type 3 or 5 bleeding was 1% in the ticagrelor-placebo arm and 2% in the ticagrelor-ASA arm (hazard ratio, 0.49; 95% CI 0.33–0.74). The positive effect on the haemorrhagic endpoint for ticagrelor in monotherapy was maintained also by defining bleeding according to the other classifications (TIMI, TASTE, and ISTH) and also in all the pre-specified subgroups.

In contrast, the secondary endpoint of death from all causes, non-fatal heart attack, and stroke occurred in 135 patients (3.9%) treated only with ticagrelor and in 137 patients (3.9%) treated with the dual anti-aggregation (hazard ratio 0.99; 95% CI 0.78–1.25). The ticagrelor-placebo group and the ticagrelor-ASA group also showed a comparable incidence of death from all causes (1.0% vs. 1.3%, respectively), myocardial infarction (2.7% for both groups), and stent thrombosis (0.4% vs. 0.6%, respectively). There were 16 ischaemic strokes in the arm that received only ticagrelor and 8 in the arm that received double antiplatelet therapy (0.5% and 0.2%, respectively). Even for ischaemic endpoints, the efficacy of ticagrelor in monotherapy was observed in all the pre-specified subgroups.

The trial authors therefore concluded that in high-risk patients who underwent PCI and who completed 3 months

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of double antiplatelet therapy, ticagrelor monotherapy is associated with a 44% reduction in the risk of clinically relevant bleeding in the absence of increased probability of encountering an ischaemic event.[4]

THEMIS and THEMIS-PCI studies

THEMIS (The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) study is a randomized, double-blind study designed to test the safety and efficacy of ticagrelor in addition to ASA in the population of patients with diabetes and stable coronary artery disease with no previous history of myocardial infarction or stroke.[5]

The trial population was in fact made up of subjects with type II diabetes, over 50 years of age and with stable coronary artery disease defined as history of previous PCI, history of previous aortocoronary bypass surgery or angiographic documentation of a coronary artery stenosis of at least 50% (criteria not mutually exclusive). The presence of type II diabetes mellitus has been determined when patients were taking hypoglycaemic drugs for at least 6 months. Instead, patients with a known history of myocardial infarction or stroke were excluded, as were patients who were already on dual antiplatelet therapy. Eligible subjects were randomized 1:1 to take ticagrelor or placebo.[12] In the early stages of the study, the ticagrelor dose was 90 mg administered twice a day; after the publication of the PEGASUS-TIMI 54 study[3] the protocol was amended and the dosage of the drug was reduced to 60 mg twice a day, therefore the patients already enrolled were switched to the lowest dose at which they were, instead the new patients are directly randomized.

The primary efficacy endpoint was a composite of death, myocardial infarction and stroke. The secondary efficacy endpoint was assessed hierarchically according to the following sequence: death, myocardial infarction, ischaemic stroke, and death from all causes. The primary safety endpoint was represented by major bleeding defined according to the TIMI classification.[9] For the evaluation of bleeding, the PLATO[4] and BARC[8] classifications were also considered. Finally, the 'net irreversible damage' was defined among the endpoints, defined as the set of death for all causes, myocardial infarction, stroke, fatal bleeding, and intracranial haemorrhages.[12]

From February 2014 to May 2016, a total of 20 108 patients were screened, and finally, 19 220 were randomized: 9619 to ticagrelor and 9601 to placebo. The mean follow-up of the study was 39.9 months, with a maximum of 57 months; vital status data were available for 99.9% of patients (of the 21 missing patients 10 were lost to follow-up and 11 withdrew consent after randomization). Discontinuation of the drug was more frequent in the ticagrelor group than in the placebo group (34.5% vs. 25.4%) and was mainly due to the occurrence of dyspnoea or bleeding. Of the randomized patients, 73.9% were enrolled before the publication of the PLATO, thus before the emended protocol with the reduced dose of 60 mg twice a day. The two groups were quite overlapping as regards the main clinical characteristics, with an average age of 66 years and 31.4% of women. A total of 58.0% of patients had a history of previous PCI (with or without stent placement), 21.8% had a history of coronary artery bypass grafting, 7% had undergone both types of procedures, while 20.2% of the patients had no history of previous coronary revascularization. On average, patients had been diagnosed with diabetes 10 years before randomization and about a quarter had complications related to the disease; most were being treated with two or more hypoglycaemic drugs, with the use of metformin and insulin in over 50% and 20% of the subjects, respectively.

The primary efficacy endpoint occurred in 736 patients in the ticagrelor group (7.7%) and in 818 patients in the placebo group (8.5%); the Kaplan–Meier curves show an incidence of events at 36 months of 6.9% and 7.6%, respectively (hazard ratio 0.90; 95% CI 0.81–0.99; $P = 0.04$), difference mainly due to a reduction in the number of myocardial infarction and stroke in patients treated with ticagrelor. The number needed to treat to prevent an ischaemic event at 36 months was 138.

The secondary safety endpoints were tested hierarchically starting with the evaluation of death from cardiovascular causes; since there were no significant differences between the two groups in relation to this endpoint, the formal analysis was stopped; however, fewer myocardial infarctions and strokes were found in the group of diabetic patients treated with ticagrelor. In addition, a prespecified exploratory analysis showed fewer episodes of acute ischaemia of the lower limb and greater amputations in the ticagrelor arm than in the placebo arm (hazard ratio 0.45; 95% CI 0.23–0.86).

The other side of the coin was represented by a higher incidence of major bleeding according to the TIMI definition in the ticagrelor group compared to the placebo group (2.2% vs. 1.0%; hazard ratio 2.32; 95% CI 1.82–2.94; $P < 0.001$), with a 'number needed to harm' at 36 months equal to 93. There were no significant differences between the two groups in the occurrence of fatal bleeding, however, numerically higher in the ticagrelor arm which also presented a significantly higher number of intracranial haemorrhages compared to placebo (70 vs. 46 events, respectively, 0.7% vs. 0.5%; hazard ratio 1.71; 95% CI 1.18–2.48; $P = 0.005$), result mainly driven by traumatic intracranial haemorrhages (41 vs. 16 events), on the contrary, there were no significant differences in spontaneous intracranial haemorrhages. In general, the incidence of adverse events other than bleeding was higher in ticagrelor patients who most frequently complained of dyspnoea.

Precisely in light of the safety data, the authors of the study conclude that in the population of diabetics with a history of stable coronary artery disease, a strategy that involves the addition of ticagrelor to the ASA is not advisable as it does not have a favourable risk-benefit ratio.[5] However, at the same time as the results of the main trial, those of a sub-analysis, THEMIS-PCI, were published, which involved that 58% of the population (11 154 patients) with a history of previous percutaneous revascularization. This subgroup of patients was then further divided according to whether or not a coronary stent was implanted and based on the time elapsed since the angioplasty procedure (less than 1 year, 1–3 years, and more than 3 years).

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Patients with a history of percutaneous revascularization had different clinical characteristics than those without a history of PCI (lower incidence of multivessel coronary artery disease, peripheral vascular disease and concomitant bypass, higher incidence of angina-like symptoms). Mean duration of diabetes, treatment with hypoglycaemic drugs, and compliance with treatment were similar between the two groups and consistent with the results of the main trial.

Also in the THEMIS-PCI population, ticagrelor treatment resulted in a significantly lower number of events covered in the primary endpoint than in placebo (404 vs. 480, 7.3% vs. 8.6%, hazard ratio 0.85; 95% CI 0.74–0.97, $P = 0.013$) with a 'number needed to treat' equal to 84. This benefit was consistent in all the subgroups examined and was not observed in patients without a history of percutaneous revascularization; in addition, the benefit was independent of the time elapsed since the PCI was performed, although an analysis suggests that the greatest benefit is observed in more recently revascularized patients.

Furthermore, in the THEMIS-PCI study, the use of ticagrelor was associated with a reduced number of strokes and myocardial infarctions including those with ST-segment elevation which had an incidence of 0.3% and 0.9%, respectively in the ticagrelor group and in the placebo group (hazard ratio 0.32; 95% CI 0.18–0.55; $P < 0.0001$). Defined stent thrombosis also occurred less frequently in the ticagrelor group although this difference did not reach statistical significance (0.1% vs. 0.3%, $P = 0.21$). The pre-specified endpoint that included coronary, cerebral and peripheral ischaemic events was significantly reduced in the ticagrelor group compared to placebo; in fact in the THEMIS-PCI population the incidence of the endpoint death from all causes, myocardial infarction, stroke, acute ischaemia of the lower limb, or amputation for vascular causes was 9% in the ticagrelor arm and 11% in the placebo arm, on the contrary, this benefit was not observed in subjects without a history of prior PCI.

Also in this subanalysis, the incidence of bleeding, defined according to all the classifications (TIMI, PLATO, BARC) was higher in the patients treated with the double antiplatelet therapy. Fatal bleeding occurred in six patients in each group (hazard ratio 1.13; 95% CI 0.36–3.50; $P = 0.83$). In patients with a history of prior PCI, 33 patients (0.6%) in the ticagrelor group and 31 patients (0.6%) in the placebo group experienced intracranial haemorrhage ($P = 0.45$), while in the group with no history of PCI this event occurred in 37 ticagrelor patients (0.9%) and in 15 placebo patients (0.4%) ($P < 0.001$).

The authors concluded that in the subgroup of diabetic patients, with no history of heart attack or stroke, but with history of percutaneous revascularization, the addition of ticagrelor to the ASA is associated with a 15% reduction in the risk of a new ischaemic event with an improvement of the net clinical benefit and therefore may be an advisable strategy in this category of patients.[6]

Conclusions

These two new studies certainly represent two other important pieces that add to the complex puzzle of the strategy of antiplatelet therapies. If, on the one hand, the concept remains that in a patient at high risk of recurrence of ischaemic events and who has well tolerated a dual antiplatelet therapy in the first 12 months after ACS this can be prolonged as indicated by PEGASUS, on the other, the TWILIGHT study suggests that after the first 3 months, a ticagrelor-based monotherapy strategy that provides for the suspension of the ASA may represent a valid option, especially in those patients in whom there is fear that the bleeding risk is prevalent. The THEMIS study, on the other hand, probably downsizes that common idea that diabetes in itself represents an element that should always lead us to enhance the inhibition of platelet aggregation, the choice in this case must take into account the presence of concomitant factors, first of all, the history of previous percutaneous revascularization.

Conflict of interest: none declared.

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