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# Acute coronary syndromes with high thrombotic burden: therapeutic innovations

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#### **KEYWORDS**

Acute coronary syndrome; Antithrombotic therapy; antiplatelet therapy

Antiplatelet agents represent one of the cornerstones of drug therapy for acute coronary syndromes (ACS). In the last decade, the arrival of prasugrel and ticagrelor, faster and more powerful oral platelet receptor P2Y12 inhibitors compared to clopidogrel, significantly improved platelet inhibition in patients with ACS. However, the reduction of thrombotic risk came at the cost of increased bleeding risk. Despite having similar indications, prasugrel and ticagrelor have different characteristics and methods of use, essentially due to a different design of the trials in which they have been studied. The optimal use of these antiplatelets in clinical practice should therefore be tailored in individual patients. In the acute phase of ACS with high thrombotic burden, all oral P2Y12 inhibitors have limitations, mainly due to the delay of onset of action related to oral administration. In this scenario, parenteral antiplatelet agents (glycoprotein inhibitors IIb/IIIa and cangrelor) may play a key role in case of percutaneous coronary interventions of high thrombotic coronary lesions and in the prevention of early thrombotic complications. Cangrelor, an intravenous inhibitor of the P2Y2 receptor, has peculiar pharmacokinetic and pharmacodynamic characteristics that make it particularly suitable to be used as an antiplatelet during coronary angioplasty as it achieves a rapid and powerful antiplatelet effect in patients not pretreated with oral medications, and has a favourable safety profile in relation to the bleeding risk.

#### Introduction

Acute coronary syndromes (ACS) comprise a series of clinical scenarios characterized by acute myocardial ischaemia following a complication of coronary atheromatous plaque (rupture, ulceration, fissure, and dissection) with intraluminal thrombus formation. Platelet activation and aggregation play a crucial role in the cascade of events that determine intracoronary thrombosis in myocardial infarction and in possible thrombotic complications during revascularization with percutaneous coronary intervention (PCI). For this reason, antiplatelet therapy has been one of the cornerstones of ACS treatment for decades.

In the last century, the ISIS-2 study first documented the effectiveness of acetyl-salicylic acid (ASA, platelet

cyclooxygenase inhibitor COX-1) in reducing mortality in patients with myocardial infarction.<sup>1</sup> Subsequently, it was documented that the addition of clopidogrel (an adenosine P2Y12 platelet receptor inhibitor) further reduces the risk of thrombotic events in these patients.<sup>2</sup> However, in patients at high thrombotic risk, clopidogrel has some drawbacks: the slow onset of action in the acute phase and the inability to obtain adequate platelet inhibition in a significant portion of patients due to individual drug response variability related to cytochrome P450 activity.

The arrival of newer, faster, and more powerful oral P2Y12 receptor inhibitors (prasugrel and ticagrelor) has allowed a further reduction of the thrombotic risk in patients with ACS, at the price of an increased haemor-rhagic risk.<sup>3,4</sup> Prasugrel and ticagrelor currently represent the oral antiplatelet of choice to be associated with ASA in patients with ACS, unless contraindicated.<sup>5</sup> Although they have been studied in similar scenarios, prasugrel and

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ticagrelor have different characteristics and methods of use, the latter mainly due to the different design of the trials in which they were studied. Until a few months ago, there were no studies that directly compared prasugrel and ticagrelor.<sup>3,4</sup> The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) study 5 sought to directly compare these two antiplatelets for the first time.<sup>6</sup>

#### The ISAR-REACT study 5

ISAR-REACT 5 is a phase 4 randomized open-label study that aimed to evaluate whether a therapeutic strategy with ticagrelor was superior to a therapeutic strategy with prasugrel in patients with ACS and planned invasive therapy. It is correct in this case to speak of 'therapeutic strategy' since in the two study arms not only did the drug used vary but a different strategy was used based on the expected antiplatelet agent. The two different strategies were borrowed from the indications of use of the drugs derived from the previous trials: prasugrel cannot be used in pre-treatment in patients with ACS without ST-segment elevation (NSTE-ACS) before coronary angiography and before PCI indication has been given,<sup>3,7</sup> it cannot be used in patients treated with medical therapy alone,<sup>3</sup> it cannot be used in patients with a history of stroke/TIA and provides for a reduction in dosage in elderly patients (>75 years) and weighing  $< 60 \text{ kg.}^4$ 

Four thousand and eighteen patients with ACS were randomized to prasugrel or ticagrelor in addition to the ASA. Almost half of the patients (41%) had a diagnosis of STsegment elevation myocardial infarction (STEMI). All patients in the ticagrelor group received a loading dose (180 mg) as soon as possible after randomization, followed by a maintenance dose of 90 mg twice a day for 12 months. Patients randomized to prasugrel received an immediate loading dose (60 mg) only in the case of STEMI, while receiving a loading dose only after coronary angiography in the NSTE-ACS, after PCI was planned. Patients in the prasugrel arm received a maintenance dose of 10 mg/day (or 5 mg q.i.d. if they were 75 years of age or older or weighed less than 60 kg) for 12 months. The primary endpoint was death, myocardial infarction, or stroke at 1 year.

The prasugrel-based strategy was superior to a ticagrelor-based strategy in reducing the incidence of primary endpoint at 1 year [6.9% vs. 9.3%, hazard ratio (HR) 1.36 95% confidence interval (CI) 1.09-1.70, P = 0.006]. This result was driven by an absolute 1.8% reduction in the incidence of myocardial infarction, without significant differences between groups in the incidence of major bleeding type BARC (HR 1.12; 95% CI 0.83-1.51, P = 0.46). These unexpected results (researchers themselves did not hide that they would have expected results in favour of the ticagrelor strategy) occurred despite lower than expected event rates.

It is undeniable that in this study the strategy with prasugrel was successful. However, due to the trial design, it is not possible to establish how much the observed benefit is due to prasugrel or to the strategy used in the prasugrel arm. In fact, one of the study's methodological issues is that two drugs and two strategies were tested simultaneously. All patients randomized to ticagrelor were also pretreated and there is no evidence that pre-treatment is useful in patients with NSTE-ACS. Though, the only trial aimed at evaluating pre-treatment in this scenario gave negative results.' Moreover, although the absence of pretreatment with prasugrel may partly explain a better result on bleeding, it can hardly explain the best result in terms of thrombotic events. The same considerations can be made that a dose reduction was expected for prasugrel in elderly or low body weight patients. Other limitations remain, including the absence of a double-blind design, telephone follow-up (with possible underreporting of events) and the fact that approximately 19% of patients (in both groups) did not receive the drug prescribed at discharge.

This study helps to rehabilitate prasugrel, a drug that in the recent past has been relegated to a minority use compared to ticagrelor not only by virtue of a smaller target population but also by limitations due to the design of its approval trial (in particular the contraindication for use in pre-treatment and in non-PCI patients).

Finally, in addition to the methodological limitations mentioned above, this study must be interpreted with caution (especially in terms of translation in clinical practice) also on the basis that the superiority results of one drug over the other struggle to have a clear biological plausibility.

## Acute antithrombotic therapy: when oral antiplatelet agents may not be enough

Several studies have evaluated oral P2Y12 receptor inhibitors in ACS and current guidelines support their use with Class I with level of evidence A in the guidelines.<sup>5</sup> However, these studies are basically secondary prevention studies, where the benefit of therapies is largely due the reduction of ischaemic events in the weeks and months following the acute event.<sup>2-4,6</sup> Despite the introduction of more powerful antiplatelet agents (prasugrel and ticagrelor), periprocedural thrombotic complications during PCI in ACS remain a concern, especially in patients with high thrombotic burden. Oral antiplatelet agents have intrinsic limitations linked to the method of administration, which necessarily implies a delayed onset of action due to absorption and, in the case of clopidogrel and prasugrel, to metabolic activation. The delay of effect of oral anti-aggregation can be further increased during the acute phase of ACS due to the presence of nausea, reduced absorption, inability to swallow, administration of morphine, therapeutic hypothermia and increased platelet activation. Although prasugrel and ticagrelor have a faster onset of action than clopidogrel, they also exhibit suboptimal pharmacokinetics in this scenario.<sup>8</sup> Insufficient platelet inhibition at the time of angioplasty, in cases of high thrombotic burden or complex procedures, is associated with an increased risk of postprocedural major adverse cardiac events (MACEs).<sup>9</sup> However, attempts to administer oral P2Y12 inhibitors early or with increased loading doses have no significant clinical benefit.<sup>7,10,11</sup>

Glycoprotein IIb/IIIa (GPI) inhibitors are the intravenous antiplatelet agents with the largest number of studies in ACSs and include abciximab (high molecular weight monoclonal antibody) and the so-called 'small molecules' tirofiban and eptifibatibe.<sup>12</sup> These drugs work by competing at platelet level with von Willebrand factor and fibrinogen for the binding of the glycoprotein IIb/IIIa receptor resulting in a rapid and powerful antiplatelet effect. GPI therapy has been associated in a number of studies with a decrease in MACE at the expense of slightly increased bleeding and increased risk of thrombocytopenia.<sup>13</sup> However, the clinical benefit of GPIs has been demonstrated mainly in the era of simple balloon angioplasty or old generation stents, before the routine use of the DAPT, the use of new generation stents and thrombus-aspiration. Studies conducted in a more modern therapeutic scenario have shown a no significant benefit of a routine or up-stream use of the GPI.<sup>14,15</sup> Therefore, current guidelines consider the use of these drugs only in cases of high thrombotic burden or procedural thrombotic complications (bail-out).

Cangrelor is a potent direct and reversible inhibitor of P2Y12 for intravenous use, with rapid onset of action (within 2 min), powerful and constant platelet inhibition during infusion and rapid cessation of the effect (30-60 min from suspension). Compared to GPIs, cangrelor has both pharmacokinetic and pharmacodynamic potential advantages, which can determine a better safety profile. First, the rapid reversibility of action (off-set) makes it a more manageable drug than GPI, which have a persistent postsuspension antiplatelet activity: over 4h in the case of small molecules and days in the case of abciximab. Secondly, cangrelor works by inhibiting the same target of ticagrelor, prasugrel and clopidogrel, i.e. the P2Y12 receptor. Therefore, when the acute therapeutic need is rapidity, cangrelor represents an ideal 'bridge' strategy to cover the time interval left uncovered by oral P2Y12 inhibitors, without altering further platelet activation mechanisms. On the contrary, in the case of the use of the GPIs, there is an overlap of three antiplatelet mechanisms (COX-1, P2Y12, and GP IIb/IIIa inhibition) which may last for several hours (or days) after the PCI with possible consequences on safety.

In the CHAMPION-PHOENIX<sup>16</sup> study, cangrelor was compared with clopidogrel in patients undergoing PCI and it reduced the risk of primary endpoint (death, myocardial infarction, stent thrombosis, and urgent revascularization) by 22% (HR 0.78, 95% CI 0.66-0.93, P = 0.005), without a significant increase in major bleeding. The effect on the primary endpoint was mainly driven by reduction of myocardial infarction and stent thrombosis, in particular there was also a reduction in intra-procedural stent thrombosis. These results have been confirmed by further metaanalyses on the CHAMPION trial program.<sup>17</sup> Furthermore, in a further exploratory meta-analysis, cangrelor showed a reduction in ischaemic events similar to GPI but with a lower risk of bleeding.<sup>18</sup>

It is important to consider that the use of cangrelor does not preclude the potential use of the GPI in the case of a thrombotic complication.

In all phase 3 clinical trials, cangrelor was tested against clopidogrel, which is not the preferred oral P2Y12 inhibitor

in patients with ACS, and there is currently no data on the clinical outcomes associated with cangrelor in patients treated with prasugrel or ticagrelor. In addition, the administration of clopidogrel was expected at the end of the cangrelor infusion. Given the slow onset of action of clopidogrel and the rapid off-set of the cangrelor effect, this strategy is theoretically not optimal as it implies a possible 'gap' of post-procedural anti-aggregation. In the recent CANTIC study, the concomitant administration of cangrelor and ticagrelor at the time of angioplasty was studied in patients with STEMI.<sup>19</sup> Cangrelor administered together with ticagrelor (loading dose with crushed tablets to promote the speed of absorption) showed a faster rate and stable platelet inhibition compared to ticagrelor alone. No interactions have been documented between the two drugs. The latter is important because one of the reasons why clopidogrel was not administered at the time of angioplasty in CHAMPION trials was indeed the possible interaction between drugs. Although the small size and mechanistic pharmacodynamics endpoints do not make possible clinical conclusions, the data of this study support the possibility of a simultaneous administration of cangrelor and new generation oral P2Y12 inhibitors at the time of angioplasty in patients with ACS.

#### Conclusions

In the last decade, the arsenal of antithrombotic drugs for the treatment of ACS has been enriched with new antiplatelet agents that allow more powerful and precise control of platelet inhibition. The lack data about direct comparison or combined use of the new drugs makes the choice of the optimal treatment more complex, which must however be customized according to the thrombotic and haemorrhagic risk of the patients. Therefore, the most recent studies have tried to compare different strategies of treatment with new generation drugs. In patients with high thrombotic burden, combined therapy with intravenous and oral antiplatelet agents appears the most reasonable, but further studies are necessary to evaluate the efficacy and safety of this approach.

Conflict of interest: none declared.

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