

Antithrombotic Treatment in Acute Coronary Syndrome and Atrial Fibrillation

Tratamiento antitrombótico en los síndromes coronarios agudos y fibrilación auricular

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The incidence of patients with chronic atrial fibrillation (AF) who also present with non-ST-segment elevation acute coronary syndrome varies between 10% and 30% according to registries (1, 2). The indication of anticoagulant drugs to reduce systemic embolism poses the need to use dual antiplatelet therapy to prevent recurrent ischemic complications in patients initially treated with a conservative or invasive strategy with percutaneous coronary intervention (PCI). The challenge of individualizing the patient with the most beneficial balance between ischemic and bleeding risk is usually very controversial in this population in daily clinical practice, since there is no evidence with adequate consistency that allows consensus on standardized behaviors. Below we will briefly review the studies performed, placing emphasis on their limitations.

Analysis of studies

The **PIONEER** trial (3) was an open randomized study that assigned 2,124 patients within 72 hours of PCI into groups specified by the administration time of dual antiplatelet therapy (1, 6 or 12 months) and the P2Y12 inhibitor used. Thus, according to these two conditions, patients were randomized in a 1: 1: 1 ratio to 3 groups: 1. Rivaroxaban (15 mg once daily or 10 mg per day if creatinine clearance was between 30 and 50 ml/min) added to a P2Y12 inhibitor for one year, without aspirin; 2. Rivaroxaban (2.5 mg twice daily) added to double antiplatelet therapy with P2Y12 inhibitor and 75-100 mg aspirin according to the specified scheduled time of 1, 6 and 12 months. Patients who received treatment for 1 to 6 months, then continued with rivaroxaban plus aspirin for 1 and 3 years. Warfarin (once daily maintaining INR between 2 and 3 U plus a P2Y12 inhibitor and 75/100 mg aspirin, was also administered according to the established times. Patients who received treatment for 1 and 6 months continued with warfarin plus aspirin for 1 year. In 93% of the cases clopidogrel was the P2Y12 inhibitor used. Group 1 patients had a lower incidence of clinically significant bleeding vs. Group 3

patients (HR 0.59 95% CI 0.47-0.76; $p < 0.0001$), a result that was similar between Group 2 vs. Group 3 (HR 0.63 95% CI 0.50-0.80; $p < 0.001$), without differences in major bleeding. There were no differences in the secondary endpoints among the three groups, although the study was not designed for this purpose.

Limitations

1) The number of patients needed to demonstrate superiority or non-inferiority of ischemic events was not contemplated. A total of 40,000 patients would have been needed (i.e. 13,300 per group) to demonstrate superiority, 2) Half of PCIs were performed in scheduled stable patients where 65% received stents, while the other half were unstable angina (20%), non-ST-segment elevation myocardial infarction (non-STEMI) (18%) and STEMI patients (13%). Thus, we can deduce that it was a population of low to moderate ischemic risk and, therefore, its results are difficult to extrapolate to a higher risk population. 3) The dose of rivaroxaban used in the ROCKET-AF study (4) was 20 mg and 15 mg in kidney failure patients. In the PIONEER study, the rivaroxaban dose used was not useful in preventing stroke in AF or ischemic cardiac events. 4) There were confounding variables regarding the discretion of the researcher in the choice of antiplatelet treatment administration time, which could have impacted in the selection of the included patient. 5) The different stages of treatment duration for 1, 6 and 12 months do not allow any comparison since they were not randomized to evaluate the efficacy between the periods analyzed as well as the antiplatelet strategy used. We might ask whether: a) The lower incidence of bleeding was due to patient selection, administration time or use of low doses of rivaroxaban; b) If the "background" of this study was the WOEST trial, why was there not a comparative arm of warfarin plus clopidogrel?; c) The ratio of patients who discontinued the drug due to bleeding or adverse effects is not mentioned in the study.

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The **RE-DUAL PCI** trial (5) was an open study that randomized 2,725 patients within 120 hours (preferable <72hs) of angioplasty into 3 groups **1)** Dabigatran 110 mg twice daily plus clopidogrel or ticagrelor, **2)** Dabigatran 150 mg twice daily plus clopidogrel or ticagrelor and **3)** Triple scheme with warfarin plus aspirin and clopidogrel or ticagrelor. Patients were randomized into three groups. Those older than 80 years were randomized in a 1: 1 ratio to treatment with dabigatran 110 mg twice daily plus a P2Y12 inhibitor or triple scheme with aspirin. In this latter group, aspirin was discontinued at 1 month in those with bare-metal stents and at 3 months in those with drug-eluting stents. Drug-eluting stents were used in 82% of cases and the most commonly used P2Y12 inhibitor was clopidogrel (88%). The average follow-up period was 14 months. Patients with dual treatment with dabigatran 110 mg or 150 mg had a significantly lower incidence of clinically relevant major or non-major bleeding vs. triple scheme with warfarin (HR 0.52 95% CI 0.42-0.63, $p < 0.001$ and HR 0.72 95% CI 0.58-0.88; $p < 0.002$, respectively). Dual treatment with dabigatran was not inferior for the incidence of thromboembolic events, death or unplanned revascularization, both with the dose of 110 mg: 15.2% vs. 13.4% (HR 1.13 95% CI, 0.90-1.43; $p: 0.30$) or with 150 mg: 11.8% vs. 12.8% (HR 0.89 95% CI 0.67-1.19; $p: 0.44$).

Limitations

1) This was an open study. **2)** PCI was performed for an acute coronary syndrome in 51% of cases and the rest in stable patients. **3)** The population over 80 years of age was underrepresented. **4)** The rate of thrombotic events or death with dabigatran was not lower than with warfarin, but with a higher and worrying risk for dabigatran: 11% vs. 8.5% (HR: 1.30; 95% CI, 0.98 to 1.73; $P < 0.07$). **5)** It is interesting to note that despite the increase in the rate of major bleeding observed with the triple scheme the average treatment discontinuation rate for bleeding was similar in the three schemes: gastrointestinal bleeding 0.6%; hematuria 0.4%, epistaxis 0.3%; anemia 0.2%; hematoma 0.2%, and gingival bleeding 0.2%. There were no differences in mortality, life-threatening bleedings or ischemic events. In my opinion, this implies that most major hemorrhages were defined with soft criteria mainly based on laboratory values (drops in hematocrit or hemoglobin levels, or need for transfusion), **6)** did patients bleed less due to the benefit of dabigatran or for the non-use of aspirin in that group?

The **AUGUSTUS** trial (6) was a study including 4,614 patients randomized in a 2×2 factorial design (median of 6 days) comparing the safety of apixaban vs. warfarin (open-label) and the administration of aspirin vs. placebo (double blind), all treated with a

P2Y12 inhibitor (clopidogrel in 93% of cases) for a 6-month follow-up period. Apixaban proved to be superior to warfarin in the reduction of the primary endpoint (major or non-major clinically relevant hemorrhage (HR 0.69 95% CI 0.58-0.81; $p < 0.001$), while the addition of aspirin had a higher incidence of this primary endpoint compared with placebo (HR 1.89 95% CI 1.59-2.24; $p < 0.001$). There was a lower incidence of death and hospitalization in the apixaban group compared with warfarin (HR 0.83 95% CI 0.74-0.93; $p 0.002$ (superiority) at the expense of lower rehospitalization (HR 0.83 95% CI 0.74-0.93), without differences in this composite endpoint between aspirin and placebo (HR 1.08 95% CI 0.96-1.21, $p=ns$). It is noteworthy that the study was not designed to assess significant differences in the secondary endpoints of death or ischemic events.

Limitations

1) The study was open-label in the comparison of anticoagulant treatments. **2)** The benefit of apixaban vs. warfarin was based on the reduction of the primary endpoint (clinically relevant major or no major bleeding), without differences in intracranial bleeding or mortality (3.3% vs. 3.2%). **3)** The rate of patients who discontinued anticoagulant treatment before completing the study was 12.7% with apixaban, 13.8% with warfarin, 16.9% with aspirin and 14.8% with placebo. Although bleeding difference was almost double with aspirin vs. placebo, there were no differences in mortality or rehospitalizations. Once again, what type of clinically relevant major or non-major bleeding are we preventing? In my opinion, the definition of this study was also very flexible, given that it takes into account among other conditions, laboratory parameters such as hemoglobin decrease >2g/dl, transfusion of at least 2 units of blood cells or clinical visits outside those established by protocol. As an accessory data, in the WOEST study (7), although the triple scheme had a higher rate of total bleeding, it did not have a higher incidence of TIMI or GUSTO major bleeding at the end of follow-up. **5)** It should be noted that despite the higher incidence of bleeding in the aspirin group, it resulted in a lower prevalence of ischemic events when considering an exploratory composite endpoint of cardiovascular death, stroke, acute myocardial infarction, stent thrombosis and emergency revascularization: 8.3% vs. 10% (OR 0.81 95% CI 0.66-0.99); **6)** Is a 6-month follow-up time enough, given that in classical studies of antiplatelet agents the benefit of double antiplatelet therapy is continuous until up to 1 year?

The **ISAR-TRIPLE** Trial (8) included 614 patients receiving oral anticoagulation with warfarin or acenocoumarol and aspirin (85% due to AF and 33% due to unstable syndromes), who underwent PCI with drug eluting stent (mostly last generation).

Patients were openly randomized to either 6-week or 6-month clopidogrel therapy. There was no difference in the incidence of the primary endpoint of a composite of death, myocardial infarction (MI), stroke, stent thrombosis, or Thrombolysis In Myocardial Infarction (TIMI) major bleeding: 9.8% vs. 8.8% (HR 1.14 95% CI 0.68-1.91; p:0.6) and also of ischemic secondary endpoints. It is noteworthy that the triple treatment scheme for 6 weeks vs. 6 months had no differences in major bleeding due to TIMI or BARC at 9 months, which is explained by half of hemorrhages occurring at 6 weeks when both groups were receiving the triple scheme. This observation is interesting since in the AUGUSTUS study although a greater incidence of major bleeding was observed with aspirin at 6 months, as in the ISAR-TRIPLE Trial, the separation of the curves of the primary endpoint at 1 month is already very evident when comparing warfarin and apixaban and even more ostensible in the group with aspirin. Although this phenomenon is difficult to explain, it is noteworthy that in the AUGUSTUS study randomization could be carried out up to 14 days after the index event, the treatment during that period of time being at the discretion of the attending physician, which could have determined a high possibility that most of the patients were treated with aspirin. An observational study of the BERN registry (9) that included 8,722 patients requiring PCI due to stable and unstable coronary syndromes, analyzed the evolution of 576 patients requiring oral anticoagulation and who, at the discretion of the attending physician, were treated with triple antithrombotic scheme (clopidogrel in 89% of cases) for one month or more (in more than half of the patients for at least 3 months) and followed-up for one year. There were no differences between the groups when comparing ischemic or bleeding events at one year. Obviously, since it is a registry, there are evident selection biases, that would in turn reflect the clinical practice. In fact, patients treated for one month had a higher HAS-BLEED, were mostly stable, received a lower number of stents per lesion and had lower use of drug eluting stents, although no interaction was observed in the subgroup analysis, even with the type of stent used.

After one year, the evidence about the best antithrombotic strategy to be applied in secondary prevention was scarce and the studies were not designed in the context of the need for anticoagulation. Historical studies such as the WARIS 2 (n=3,630) (10) and ASPECT 2 (n=999) (11) trials showed that patients randomized to warfarin alone or its combination with aspirin compared with aspirin alone had a lower incidence of all-cause death, infarction or stroke but at the expense of a twofold risk of major bleeding, with an average follow-up of 4 years. On the other hand in the CHAMP study (n=5,059) (12), there was no difference in ischemic events between aspirin vs. warfarin,

but again warfarin doubled the rate of major bleeding, although in this study the intensity of INR anticoagulation was lower. On the other hand, the analysis of studies that used non-vitamin K antagonist oral anticoagulants (NOACs) in secondary prevention have important limitations. The ATLAS-TIMI 51 study (13) is not applicable to patients with AF because it used doses of rivaroxaban not proven useful in preventing systemic embolism. The APPRAISE 2 study (14) showed no benefit with apixaban when it was associated with double antiplatelet therapy or aspirin alone and instead its use doubled the rate of major bleeding, especially when it was associated with double antiplatelet therapy. Finally, the REDEEM study (15) with dabigatran at different doses also demonstrated a significant increase in major bleeding when it was associated with a double antiplatelet scheme, without differences in ischemic endpoints. In addition, NOACs were administered within one year of the index event, and thus this evidence can hardly be applicable to chronic treatment. (16)

Recommendations.

All the studies mentioned have been designed with the aim of optimizing safety over efficacy. This seems reasonable given the factual impossibility of designing a large study that would provide a broader and definite conclusion. I consider that some points should be highlighted: **1.** Patients' anticoagulation is decided during hospitalization (50% in the AUGUSTUS study) and are already a selected population with lower bleeding risk, **2.** The bleeding complication appears of magnitude since the first month of antithrombotic treatment, and **3.** There is no score that allows predicting the additive bleeding risk of double antiplatelet therapy in anticoagulated patients and in fact the PRECISE-DAPT score (17) used in non-anticoagulated patients is of relative value since its usefulness was not proven in prospective randomized studies (the European guidelines grant a low IIB-A recommendation).

Clinical practice guidelines recommend NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) over warfarin in patients with AF (class I-A). Likewise, the 2019 American guideline (18) confers the same level of recommendation for vitamin K antagonists and the three analyzed NOACs, preferably associated to clopidogrel (class IIa-B) in the population with AF and acute coronary syndromes. The doses of rivaroxaban were lower than those considered useful in AF; therefore, in my opinion, apixaban and dabigatran would be more recommendable. The guideline suggests that if triple antithrombotic therapy is chosen (i.e. with the association of aspirin), it should be indicated for 4-6 weeks after the event to be continued with the chosen anticoagulant with a P2Y12 inhibitor without aspirin for a year (class IIb-B, moderate consistency).

Regarding this last recommendation, the decision to use a triple scheme should only be limited to patients at very high ischemic risk as a form of clinical presentation or due to anatomical complexity, which were poorly represented in the aforementioned studies. In my opinion, this population consists of patients with a GRACE risk score >140 as clinical presentation, left ventricular dysfunction, history of stent thrombosis, coronary trunk or multi-vessel angioplasty, or need to implant multiple stents. For this population, and taking as evidence the one applied to non-anticoagulated patients, (19) a 6-month period of triple scheme seems reasonable, continuing with anticoagulation and clopidogrel for one year. With the same criteria, it seems reasonable to continue after one year only with anticoagulation and associate aspirin in the subgroup of patients at high ischemic risk. (20)

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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