

# Antiplatelet Strategies in Acute Coronary Syndromes

## *Estrategias de antiagregación plaquetaria en síndromes coronarios agudos*

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### ABSTRACT

**Background:** Patients with acute coronary syndrome benefit from the use of antiplatelet agents to reduce the recurrence of ischemic events. For a long time, we have been used to indicate a fixed combination of aspirin plus a P<sub>2</sub>Y<sub>12</sub> receptor inhibitor during a strict period of time. However, the complexity of patients and procedures force us, as physicians, to seek the best possible combinations, both of the type of drugs used as treatment duration, in order to achieve the best balance between ischemic protection and bleeding risk. In recent years, numerous studies carried out in this regard have shown that different strategies may benefit our patients in different settings.

In the following review we provide an overview of the current knowledge about antiplatelet therapies, along with some suggestions on their management.

**Key Words:** Antithrombotic Agents - Acute coronary syndrome - Myocardial Infarction

### RESUMEN

**Objetivo:** Los pacientes que presentan síndrome coronario agudo se benefician de la utilización de antiagregantes plaquetarios para reducir la recurrencia de eventos isquémicos. Durante mucho tiempo estuvimos acostumbrados a indicar una combinación fija de aspirina más un inhibidor del receptor P<sub>2</sub>Y<sub>12</sub> por un tiempo estricto. Sin embargo, la complejidad de los pacientes y de los procedimientos que en ellos se realizan nos obligan, como médicos, a buscar las mejores combinaciones posibles, tanto en lo referido al tipo de fármacos utilizados como a la duración del tratamiento, con el fin de lograr el mejor equilibrio entre protección isquémica y riesgo hemorrágico. En los últimos años, múltiples estudios llevados a cabo en esta línea han mostrado que diferentes estrategias pueden beneficiar a nuestros pacientes en distintos escenarios.

En la siguiente revisión brindamos una descripción general de los conocimientos actuales sobre el tratamiento con antiagregantes plaquetarios, junto con algunas sugerencias sobre su manejo

**Palabras clave:** Antitrombóticos - Síndrome coronario agudo - Infarto de miocardio

### INTRODUCTION

In the last years, several research studies have been published on treatment strategies for patients with acute coronary syndrome (ACS), including risk stratification, optimal time to perform a coronary angiography, more or less potent treatment schemes during the first and second year, and the especially complex scenario of patients with atrial fibrillation and a coronary artery event, which suggest changes with respect to what was reported in previous publications.

The aim of this review is to make a critical analysis on the evidence available in these areas.

### RISK STRATIFICATION

Once the diagnosis of ACS is established, ischemic and hemorrhagic risk stratification is essential for decision-making regarding treatment.

The available tools to assess these risks depend on the evolutionary moment of each patient (Figure 1).

Initial ischemic risk can be assessed by:

- Clinical variables: Persistence, recurrence or refractoriness of chest pain, hemodynamic or electrical instability and/or signs of heart failure.
- Electrocardiogram: Transient ST-segment elevation or depression, extent of ischemic changes.

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ISCHEMIC RISK		HEMORRHAGIC RISK	
GRACE score	>40	Crusade score	>40 points
Clinical variables	Persistent ST descent Refractory angina Heart failure Ventricular arrhythmia	PRECISE DAPT score	>25 points
Echocardiographic variables	Great extension of new motility abnormalities	ARC-HBR risk variables	Age>75 years Kidney failure Liver disease Active cancer Anemia Thrombocytopenia Stroke Hemorrhagic diathesis Prior bleeding Anticoagulation Use of NSAID or corticoids Elective surgery
Biochemical variables	Troponin >1000 ng/mL BNP >80 ng/L NT-proBNP >1170 ng/L men and >2150 ng/L women		
Angiographic variables	Stent length >30 mm Stent diameter <3 mm Bifurcation with 2 stents Left main disease or venous graft Stent thrombosis		

Fig. 1.

- Biomarkers: Troponins or natriuretic peptide (BNP / NT-proBNP).
- Imaging studies: The identification of segmentary motility abnormalities, their extent or the detection of mitral valve reflow probably due to an ischemic mechanism have prognostic value when the study is performed during the episode of acute chest pain or associated to ECG changes. Coronary computed tomography, in case it is the initial study, provides anatomical information associated with risk, and chest X-rays with signs of flow redistribution indicate increased risk.
- Risk scores: Many of the aforementioned risk-detecting variables are included in the GRACE score, which in addition incorporates kidney function. This score has good discrimination power and its calculation can be made online. Its use is recommended together with the rest of the mentioned risk factors. (2-4)

Once the coronary anatomy is known, the assessment of ischemic risk is defined with the following data:

- Angiographic variables: Lesions with high thrombotic component, multiple lesions, lesions in main arteries at a proximal level or in bifurcations indicate a high ischemic risk. (5, 6)
- Treatment variables: Bifurcation treatments, left main coronary artery lesions, venous grafts, multiple implanted stents, stent length >30 mm or diameter <3 mm are markers of thrombotic risk. (7-10)
- The PRECISE DAPT or the PARIS scores can be useful to define the ischemic and hemorrhagic risk balance during the first year after the angioplasty. The DAPT score was designed to evaluate the treatment benefit after a year of dual antiplatelet therapy (DAPT), taking into account clinical and angiographic factors. (11, 12)

To assess hemorrhagic risk:

- In the initial stage, in addition to clinical variables including age, previous bleeding, previous stroke, low body mass index (BMI) or kidney failure, use of risk scores is recommended, such as the CRUSADE and the HBR-ARC scores. (13)

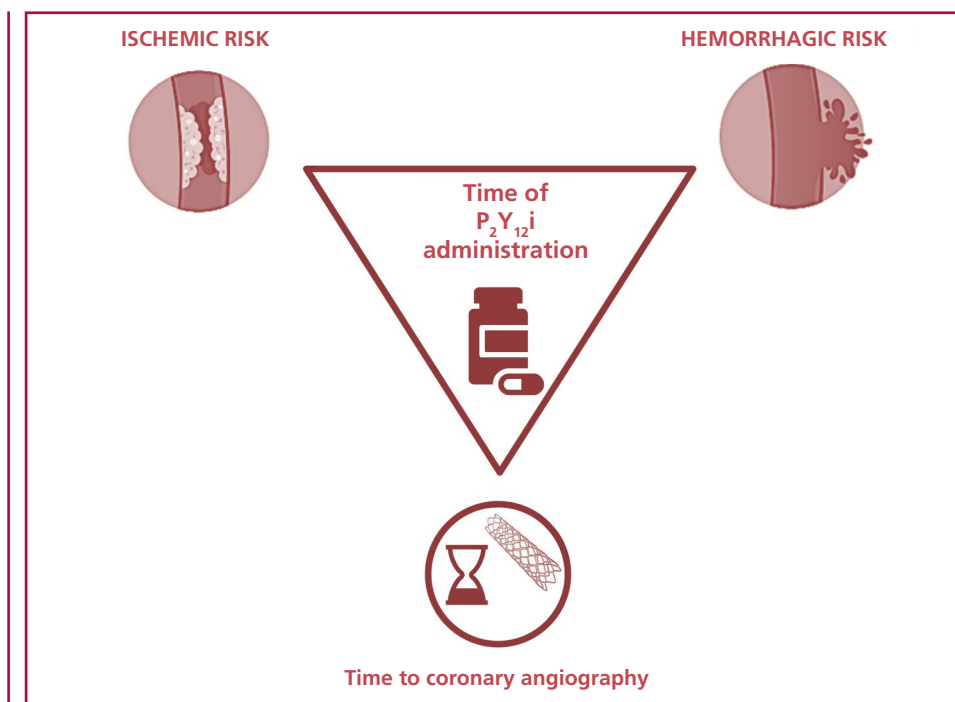
#### TIMING OF CORONARY ANGIOGRAPHY

The initial treatment strategy will depend on risk assessment and resource availability. Different meta-analyses have shown initial invasive strategy to be superior to conservative strategy when the risk of thrombotic events is moderate or high. If the ischemic risk is low, initial invasive and conservative strategies seem to have similar results.

When a coronary angiography is decided, it is important to balance the ischemic and hemorrhagic risk, also considering a third variable, which is time to an eventual angioplasty (Figure 2). The TIMACS study showed a relative risk reduction of 28% in the secondary endpoint of death, acute myocardial infarction (AMI) or refractory ischemia in the early intervention group (9.5%), compared with the late intervention group (12.9%) (HR; 0.72; 95% CI: 0.58-0.89; p=0.003). (14) Prespecified analyses showed that early intervention improved the primary outcome in 33% of patients at greater risk, with a GRACE score above 140 (HR: 0.65; 95% CI: 0.48-0.89). The RIDDLE-NSTEMI study showed that the immediate invasive strategy in patients with non-ST-segment elevation AMI (NSTEMI) was associated with lower death rates or new AMI compared with the late invasive strategy at early and mid-term follow-up, mainly due to a decrease in the risk of new AMI in the period prior to catheterization. (15) So, if thrombotic risk is high, an early angioplasty would avoid ischemic events that might occur in the first hours.

Despite we systematically used pretreatment with

Fig. 2.



P<sub>2</sub>Y<sub>12</sub> inhibitors for many years, evidence from registries and randomized studies as the ACCOAST trial seem to indicate lack of benefit when this conduct is adopted systematically. (16-19) Therefore, considering pharmacokinetics, pharmacodynamics and the results of recent studies, it is suggested to initiate immediate treatment with aspirin and anticoagulation, and indicate a second antiplatelet agent once the coronary anatomy is known (Figure 3). Thus, a potent antiplatelet therapy will be avoided in patients who, eventually, could have a surgical anatomy or another differential diagnosis (for example, aortic dissection).

Once the angioplasty is defined, a potent, quick action antiplatelet agent will be preferred, which can be administered in the cath lab. Prasugrel seems to be the first choice, except contraindications or risk factors for bleeding (history of stroke, patients over 70 years of age, low weight or female sex) force the search of other options. Ticagrelor has similar potency and onset of action and is the second option after the results of the ISAR-REACT 5 trial, except in case of contraindications (respiratory disease or conduction abnormalities). (20) Clopidogrel has an action latency time of at least 6 hours (depending on the loading dose), so if contraindication for more potent antiplatelet agents is detected and thrombotic risk is very high during the initial evaluation, it is recommended to indicate this drug as pretreatment, except that the service has the possibility of treatment with IIB/IIIa inhibitors in the cath lab, immediately after knowing the coronary anatomy, to have the patient with antiplatelet effect at the time of stent implantation.

When there is no possibility of performing a coro-

nary angiography within the first 24 hours in patients with considerable ischemic risk, the possibility of ischemic events increases while waiting for an angioplasty, so it would be beneficial to initiate treatment as soon as possible. (21) There is a continuous line of ischemic and bleeding risk. The greater the ischemic risk with lower bleeding risk, the more potent antiplatelet agents should be preferred. When pretreatment is indicated, ticagrelor is the only potent antiplatelet drug that could be used, as prasugrel has not shown benefit and has been associated with greater bleeding risk. When bleeding risk is very high, the preferred drug should be clopidogrel.

The evaluation of very elevated bleeding risk associated with high ischemic risk should accelerate the coronary angiography to avoid the need of a triple scheme (DAPT + anticoagulation) for a prolonged time.

#### TREATMENT STRATEGIES DURING THE FIRST YEAR

Aspirin, combined with a P<sub>2</sub>Y<sub>12</sub> receptor inhibitor (clopidogrel, prasugrel or ticagrelor) is still the cornerstone of treatment for patients with ACS. Standard treatment lasts 12 months, but we will discuss in subsequent sections shorter and longer duration scenarios.

Clopidogrel is the first P<sub>2</sub>Y<sub>12</sub> inhibitor used, evaluated more than 25 years ago in randomized clinical trials (RCT) and still recommended in patients undergoing coronary angioplasty due a chronic coronary syndrome. In the setting of ACS, more potent P<sub>2</sub>Y<sub>12</sub> inhibitors, as ticagrelor and prasugrel, have shown superiority to prevent ischemic events, with an increase of hemorrhagic events.

Ischemic risk	Hemorrhagic risk	Time to coronary angiography	
		<24 h*	>24 h*
↑	↓	In-hospital prasugrel #	Ticagrelor pretreatment
↑	↑	Clopidogrel pretreatment	Clopidogrel pretreatment
↓	↑	In-hospital ticagrelor	Ticagrelor pretreatment
↓	↓	In-hospital prasugrel #	Clopidogrel pretreatment
		In-hospital ticagrelor #	Ticagrelor pretreatment
			Clopidogrel pretreatment

\* The 24 h period is lower in case of patients at very high ischemic risk (2 h)  
# In case ticagrelor or prasugrel cannot be administered to patients at high ischemic risk, treatment with clopidogrel is recommended.

Fig. 3.

The CURE trial, the main clopidogrel study, demonstrated that in patients with risk criteria (most with ECG changes and/or positive biomarkers) that the association of clopidogrel and aspirin reduced the incidence of the composite endpoint of cardiovascular death and non-fatal AMI or stroke by 20% (9.3% vs. 11.4%;  $p < 0.001$ ) compared with aspirin alone. Seventy percent of event prevention was due to a lower incidence of AMI (15 less cases per 1000 treated patients), especially Q wave type AMI (13 out of 15), which represent the worse prognosis infarcts. (22)

Prasugrel irreversibly blocks  $P_2Y_{12}$  platelet receptors, faster and more effectively, and with less individual response variability than clopidogrel. The TRITON-TIMI 38 trial evidenced 19% reduction in the composite endpoint of death, non-fatal AMI and stroke (9.9% vs. 12.4%;  $p < 0.001$ ). (23) Prasugrel also reduced the incidence of stent thrombosis (ST) (1.1% vs. 2.4%;  $p < 0.001$ ). These results confirm the benefit of prasugrel with respect to clopidogrel in ACS with thrombotic events associated to angioplasty. However, it also increases the risk of fatal hemorrhage (1.4% vs. 0.9%;  $p < 0.01$ ). Taking into account the association with greater hemorrhagic risk, it should not be used in patients with history of cerebrovascular disease (stroke or transient ischemic attack), age over 75 years or body weight below 60 kg, as the post hoc analysis showed that prasugrel, at the doses used in the TRITON study, did not provide benefit and was even harmful in those subgroups. In case of use in this subgroup of patients without absolute contraindications (older than 75 years or body weight  $< 60$ kg), it is suggested to reduce by half the maintenance dose (5 mg/day) as derived from the evidence of the TRILOGY and ISAR-REACT studies. (24)

Ticagrelor reversibly inhibits (non-covalent) the  $P_2Y_{12}$  receptor, with fast action onset, as it does not

need to be activated by the cytochrome system (CYP2C19), and presents low variability of interindividual response. In the PLATO study, ticagrelor showed 1.9% absolute reduction and 16% relative reduction of the composite primary endpoint of cardiovascular death, and non-fatal AMI and stroke. (25) Ticagrelor reduced AMI (5.8% vs. 6.9%;  $p = 0.005$ ), ST (1.3% vs. 1.9%;  $p = 0.009$ ) and vascular mortality (4.0% vs. 5.1%;  $p = 0.001$ ), but was associated with an increase of major bleeding events (4.5% vs. 3.8%;  $p = 0.03$ ), including a higher rate of intracranial bleeding.

Both prasugrel and ticagrelor are more potent and fast antiplatelet agents than clopidogrel, and above all, prevent ST. This has been reflected in several guideline recommendations. Ticagrelor has been compared directly with prasugrel in the ISAR-REACT 5 trial. (20) The primary endpoint was the composite of death, AMI or stroke at one year and occurred in 9.3% of patients in the ticagrelor group and 6.9% in the prasugrel group (HR: 1.36; 95% CI 1.09-1.7;  $p = 0.006$ ). The rate of all-cause death was similar with both drugs. The rate of AMI was greater in the ticagrelor group compared with prasugrel (4.8% vs. 3.0%; HR: 1.63; 95% CI: 1.18-2.25), with no difference in stroke. No differences were observed in major bleeding, defined by the BARC scale (5.4% vs. 4.8%, respectively;  $p = NS$ ). Contrary to what was expected by the investigators, use of prasugrel was associated with a lower rate of major cardiovascular events without increasing bleeding.

The POPular AGE study including patients  $\geq 70$  years with diagnosis of non-ST-segment elevation ACS (NSTEACS) compared clopidogrel versus ticagrelor or prasugrel. (26) The primary endpoint was total bleeding (major and minor by the PLATO study criteria) and the secondary endpoint was the composite of AMI, stroke, all-cause mortality and major and



based on patient age, creatinine clearance, hemoglobin, white blood cell count, and history of spontaneous bleeding. (31, 32) This score was validated in the PLATO trial cohorts of the BernPCI registry and it confirmed its ability to predict bleeding events in the first 12 months. The score was evaluated to analyze the net benefit of using DAPT for a longer (12-24 months) vs. a shorter (3-6 months) period. Patients stratified as high hemorrhagic risk according to the PRECISE-DAPT score (score  $\geq 25$ ) had a significant increase in bleeding after a longer course of DAPT, without obtaining any reduction in ischemic events. Longer treatment in this subgroup resulted in 1 major bleeding for every 38 patients treated. In contrast, in patients with a low PRECISE-DAPT score (score  $< 25$ ), the extension of DAPT duration was not associated with an increase in bleeding events, but was instead associated with a significant reduction in the composite of AMI, ST, stroke and revascularization of the treated vessel. Dual antiplatelet treatment in this subgroup prevented 1 ischemic event per 65 patients treated. It is important to note that the results of this decision-making remained robust when the analysis was restricted to patients with ACS at the time of stent implantation.

Understanding which strategy carries the greatest net clinical benefit, in terms of the absolute rate of ischemia and bleeding, is of utmost importance for optimal decision-making. It is important to note that, despite extensive validation, tools such as scores can never replace case-by-case evaluation and clinical judgment, and none have been prospectively tested, so more research is required to individualize patients and select the optimal strategy.

#### De-escalation of $P_2Y_{12}$ inhibitors within the year

The increase in platelet reactivity during ACS is mainly observed in the first days or first weeks after the index event. For this reason, in recent years, clinical studies have investigated strategies using an early potent antiplatelet treatment in the acute phase, followed by a lower potency antiplatelet regimen. This hypothesis is also supported by the post hoc analysis of the PLATO and TRITON-TIMI 38 studies showing greater ischemic benefit of more potent antiplatelet drugs in the early phase of ACS, whereas bleeding events generally occurred throughout follow-up, including the chronic phase.

In the TROPICAL-ACS study, 2610 patients with coronary percutaneous coronary intervention (PCI) due to ACS were randomized to receive standard treatment with prasugrel for 12 months or a staggered regimen (1 week of prasugrel followed by 1 week of clopidogrel and maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge). (33) In the de-escalation group, clopidogrel patients who had had high platelet reactivity (HPR) were switched back to prasugrel (39%), and HPR-free patients were maintained on clopidogrel for 1 year. At one year, the composite pri-

mary endpoint (cardiovascular death, AMI, stroke and BARC bleeding  $\geq 2$ ) occurred in 95 patients (7%) in the guided de-escalation group and in 118 patients (9%) in the control group (non-inferiority  $p=0.0004$ ; HR: 0.81; 95% CI: 0.62-1.06; superiority  $p=0.12$ ). The ischemic components of the primary endpoint occurred in 32 patients (3%) in the guided de-escalation group and in 42 patients (3%) in the control group (HR: 0.77; 95% CI: 0.48-1.21;  $p=0.25$ ), which indicates that early de-escalation, with the statistical limitations of the study, did not lead to an increased risk of ischemic events (non-inferiority  $p=0.0115$ ). The study also showed a non-significant trend towards a reduction in bleeding events.

The TOPIC trial was a single-center study that compared DAPT strategies with aspirin and a potent  $P_2Y_{12}$  antagonist (ticagrelor or prasugrel) vs. the combination of aspirin plus clopidogrel, in patients who had completed one month after PCI for ACS without ischemic or bleeding events. (34) In this case, no platelet aggregability test was used to guide behavior. The results of the main study showed that the de-escalation strategy reduced the incidence of BARC  $\geq 2$  bleeding (4% vs. 14.9%; HR: 0.30; 95% CI: 0.18-0.50;  $p < 0.01$ ), while ischemic events were not different between the two groups (9.3% vs. 11.5%; HR: 0.80; 95% CI: 0.50-1.29;  $p=0.36$ ).

Overall, the TROPICAL ACS and TOPIC studies suggest that de-escalation from a potent  $P_2Y_{12}$  inhibitor to clopidogrel after an ACS reduces the risk of bleeding complications without an apparent increased risk of ischemic events. This strategy could be an alternative to a potent 12-month platelet inhibition, especially for highly selected patients, considered at high risk of bleeding.

#### Monotherapy with $P_2Y_{12}$ inhibitors within the first year, withdrawing aspirin

With the arrival of more potent drugs such as prasugrel and ticagrelor, monotherapy with these agents began to be considered, with the subsequent suspension of aspirin after the acute period of greatest thrombotic risk. This hypothesis is supported by in vitro tests showing that with this type of potent antiplatelet agents, the addition of aspirin does not improve platelet anti-aggregation.

The STOP-DAPT study sought to test the non-inferiority hypothesis of 1-month DAPT compared with the standard 12-month DAPT for a composite endpoint of cardiovascular and bleeding events. (35) Patients were randomly assigned to 1-month DAPT with clopidogrel followed by monotherapy with clopidogrel or to 12-month DAPT with aspirin and clopidogrel. The primary endpoint was a composite of cardiovascular death, AMI, ischemic or hemorrhagic stroke, definitive ST, or major or minor bleeding at 12 months, with a relative non-inferiority margin of 50%. The results showed that 1-month DAPT was both not inferior and superior to 12-month DAPT for the primary endpoint, which occurred in 2.36% of patients

with 1-month DAPT duration and in 3.70% of patients with 12-month DAPT (HR: 0.64; 95% CI: 0.42-0.98). The composite of ischemic events occurred in 1.96% with 1-month DAPT and in 2.51% with 12-month DAPT, and met non-inferiority ( $p=0.005$ ), but not superiority ( $p=0.34$ ) criteria. The endpoint of major bleeding occurred in 0.41% with 1-month DAPT and 1.54% with 12-month DAPT (HR: 0.26;  $p=0.004$  for superiority).

It is important to highlight that in this study, the optimization rate of stent implantation was high (85% guided by IVUS and 15% by OCT), so its result must be evaluated in this context, which is very different from our daily practice.

The SMART-CHOICE trial was a non-inferiority, randomized, open-label study that included 2993 patients undergoing PCI with drug-eluting stents. (36) Patients were randomly assigned to receive aspirin plus a P<sub>2</sub>Y<sub>12</sub> inhibitor for 3 months and subsequently, a P<sub>2</sub>Y<sub>12</sub> inhibitor alone or DAPT for 12 months. The primary endpoint was a composite of cardiac and cerebrovascular events (all-cause death, or non-fatal AMI or non-fatal stroke) at 12 months after the index procedure. Secondary endpoints included the primary endpoint components and BARC bleeding type 2 to 5. The non-inferiority margin was 1.8%. At 12 months, the primary endpoint occurred in 42 patients of the monotherapy group and in 36 patients of the DAPT group (2.9% vs. 2.5%,  $p=0.007$  for non-inferiority). The bleeding rate was significantly lower in the P<sub>2</sub>Y<sub>12</sub> inhibitor monotherapy group compared with the DAPT group (2.0% vs 3.4%,  $p=0.02$ ).

The TWILIGHT study evaluated the effect of ticagrelor as monotherapy compared with ticagrelor plus aspirin in patients undergoing scheduled or urgent PCI after overcoming the first 3 months of treatment with ticagrelor plus aspirin without complications. (36) The primary endpoint was BARC bleeding type  $\geq 2$ . The incidence of the primary endpoint was 4% among patients in the ticagrelor plus placebo group and 7.1% in the ticagrelor plus aspirin group (HR: 0.56, 95% CI 0.45-0.68;  $p < 0.001$ ). The risk difference between groups was significant for BARC bleeding type 3 or 5 (1% vs. 2%; HR: 0.49; 95% CI: 0.33-0.74). The incidence of all-cause death, non-fatal AMI or non-fatal stroke was 3.9% in both groups. The study presented pre-specified sub-analyses in the populations with ACS, diabetes and complex angioplasty, and consistently showed a reduction in bleeding events and no sign of an increase in ischemic events. (36-38)

The TICO study included 3056 ACS patients treated with drug-eluting stents. Patients were randomized to ticagrelor monotherapy (90 mg twice daily) after 3-month DAPT or 12-month DAPT with ticagrelor. (39) The primary outcome was called 1-year net clinical adverse event, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events (death, AMI, ST, stroke, or target vessel revascularization). The primary endpoint occurred

in 59 patients (3.9%) who received ticagrelor monotherapy and in 89 patients (5.9%) who received DAPT (HR: 0.66; 95% CI: 0.48-0.92);  $p=0.01$ ). Major bleeding occurred in 1.7% of patients on ticagrelor monotherapy after 3 months of DAPT and in 3% of patients on DAPT with ticagrelor at 12 months ( $p=0.02$ ). The incidence of severe cardiac and cerebrovascular events was similar between groups, 2.3% with 3-month DAPT and 3.4% with 12-month DAPT (HR: 0.69; 95% CI: 0.45-1.06;  $p=0.09$ ).

The GLOBAL LEADERS trial evaluated the effects of 24-month monotherapy with ticagrelor (associated with aspirin only for the first month) versus standard 12-month DAPT in 15 991 patients undergoing PCI. (40) The primary outcome, a composite of all-cause death or non-fatal AMI with new Q wave at 24 months, was similar in both study arms (3.81% vs. 4.37%; RR: 0.87;  $p=0.073$ ). The safety endpoint, BARC type 3 or 5 bleeding at 24-month follow-up, was similar in both arms (2.04% vs. 2.12%; RR: 0.97;  $p$  NS). however, a substantial lack of adherence to the experimental treatment may have affected the statistical power of the study. Death from cardiac and non-cardiac causes was similar in both groups.

Two meta-analyses based on these studies have recently been published to evaluate the safety and efficacy of early suspension of aspirin, continuing monotherapy with a P<sub>2</sub>Y<sub>12</sub> inhibitor. (41, 42) In them, shortening DAPT to 1-3 months and continuing thereafter with P<sub>2</sub>Y<sub>12</sub> inhibitor monotherapy was associated with a significant reduction in major bleeding, without an increase in ischemic events.

Sung-Jin Hong and co-authors performed a meta-analysis based exclusively on the three randomized studies that evaluated monotherapy with ticagrelor, with aspirin suspension after 1-3 months, compared with DAPT for one year, in patients with coronary PCI with last generation drug eluting stents. (42) The safety endpoint was clinically relevant bleeding, BARC type 3 or 5, less frequent in the ticagrelor monotherapy group compared with conventional management (RR: 0.67; 95% CI: 0.49-0.92;  $p=0.01$ ). No significant differences were found in myocardial infarction, ST or ischemic stroke.

This information raises the need to deeply analyze whether all patients should continue with DAPT for one year, or whether we are already in a position to put aside aspirin no later than in the third month in some cases, which reduces clinically significant bleeding, without risk of increasing ischemic events. In the referred meta-analysis, monotherapy with a potent P<sub>2</sub>Y<sub>12</sub> inhibitor, such as ticagrelor, is analyzed, so its results are not applicable to monotherapy with aspirin alone or other inhibitors. The same concept can be extended to PCI with bare-metal stents (BMS) or older generation drug-eluting stents; with them, there is no evidence to shorten DAPT. In these studies, last generation stents have been used, which have significantly lower thrombosis rates and, the implantation

of the device has been optimized, reducing short and long-term complications, a fact that allows to shorten DAPT without risk of ST.

### TREATMENT STRATEGIES AFTER ONE YEAR

Despite the success of DAPT in reducing thrombotic events 12 months after an ACS, the risk of cardiovascular events after this period remains significant. In the first year, 35% of deaths occur; however, at 5 years 1 in 5 patients will experience an event in the next 3-4 years. By virtue of trying to reduce this residual risk, strategies have been evaluated based fundamentally on prolonging DAPT beyond one year or with the addition of low-dose anticoagulants.

The DAPT trial evaluated DAPT prolongation with aspirin plus a P<sub>2</sub>Y<sub>12</sub> inhibitor beyond 12 months of an ACS vs. conventional aspirin therapy after that period. (12) Patients with drug-eluting stent PCI were included (43% due to ACS) after having completed 12 months of treatment with clopidogrel or prasugrel and aspirin, without presenting ischemic or hemorrhagic events. Continuous treatment with thienopyridines, compared with placebo, reduced ST rates (0.4% vs. 1.4%; HR: 0.29; 95% CI: 0.17-0.48; p < 0.001), as well as the composite of ischemic events (4.3% vs. 5.9%; HR: 0.71, 95% CI: 0.59-0.85; p < 0.001). The rate of AMI was significantly lower with P<sub>2</sub>Y<sub>12</sub> inhibitor treatment than with placebo (2.1% vs. 4.1%; HR: 0.47; P < 0.001), but the rate of moderate or severe bleeding increased with continuous treatment (2.5% vs. 1.6%; p = 0.001).

The PEGASUS-TIMI 54 study included patients with a history of myocardial infarction of more than one year evolution treated with aspirin, who were randomized to receive ticagrelor or placebo. (43) Three groups were randomized, ticagrelor at a dose of 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo. All patients had to receive low-dose aspirin and were followed-up for a median of 33 months. Compared with placebo, the two doses of ticagrelor reduced the rate of the primary efficacy endpoint (composite of cardiovascular death, AMI or non-fatal stroke) at 3 years: the incidence was 7.85% in the group that received 90 mg of ticagrelor twice daily; 7.77% in the group that received 60 mg of ticagrelor twice daily and 9.04% in the placebo group (HR: 0.85, 95% CI: 0.75-0.96, p = 0.008; HR for ticagrelor 60 mg vs. placebo: 0.84; 95% CI: 0.74-0.95; p = 0.004). TIMI major bleeding rates were higher with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than with placebo (1.06%) (p < 0.001 for each dose vs. placebo); the rates of intracranial bleeding or fatal bleeding in the three groups were similar: 0.63%, 0.71%, and 0.60%, respectively. Given the similar benefit of reducing ischemic events between ticagrelor 90 mg and 60 mg, and the significant difference in bleeding events, the authors recommend the use of the 60 mg dose of ticagrelor in combination with aspirin over the 90 mg dose.

In the COMPASS trial, two strategies with rivaroxaban (with and without aspirin) were compared

with chronic use of aspirin for the secondary prevention of atherothrombotic events in patients with history of stable cardiovascular disease (90.6% with coronary artery disease and 27.3% with peripheral vascular disease). (44) Patients were randomized to rivaroxaban 2.5 mg twice daily plus aspirin, rivaroxaban 5 mg twice daily, or aspirin alone 100 mg daily. At a mean follow-up of 23 months, the primary efficacy endpoint (a composite of cardiovascular death or non-fatal stroke or AMI) occurred in 4.1% of the group of patients with rivaroxaban 2.5 mg and aspirin, in 4.9% of the group of patients with rivaroxaban alone and in 5.4% of the group of patients with aspirin alone (rivaroxaban + aspirin vs. aspirin, HR: 0.76; 95% CI: 0.66-0.86; p < 0.001; rivaroxaban alone vs. aspirin, HR: 0.90; 95% CI: 0.79-1.03; p = 0.12). The benefit was driven by the reduction in the rate of cardiovascular death and stroke, without a significant reduction in the risk of AMI (although it was numerically reduced). Major bleeding was more frequent in the rivaroxaban + aspirin group than in those who received aspirin alone (3.1% vs. 1.9%; HR: 1.70; 95% CI: 1.40-2.05; p < 0.001), due mainly to gastrointestinal bleeding, without significant differences in fatal bleeding or intracranial hemorrhage. A sub-analysis identified patients with disease in more than one vascular territory, heart failure, kidney failure, or diabetes as those deriving the greatest net benefit from receiving rivaroxaban treatment. Within the subgroup of patients with peripheral vascular disease, the combination of rivaroxaban + aspirin significantly reduced the primary efficacy endpoint by 28% (5% vs. 8%; p = 0.0047) and major adverse events in the extremities, including amputation by 46% (1% vs. 2%; p = 0.0037) compared with aspirin alone. (45)

It is important to point out that the PEGASUS trial excluded patients with any prior stroke, while the COMPASS trial only excluded patients with a recent (<1 month), hemorrhagic, or lacunar stroke. Beneficial results from the COMPASS trial were driven by a reduction in the rates of cardiovascular death and stroke, while in the PEGASUS trial, the benefit was driven by a reduction in the rate of AMI. These findings suggest a differential role for DAPT compared with the combination of rivaroxaban and aspirin in the recurrence of ischemic complications, in which the former is probably more effective in arterial thrombotic complications of small vessels and the latter is more effective in cardioembolic events or large vessels.

Based on this information, we believe that it is important to reassess patients once the ischemic event is over, to define how to continue long-term protection. From the "ischemic" point of view, the type of event suffered and the way of resolution, as well as the coexistence of arterial or venous disease in non-coronary territories, influence the decision. From a "hemorrhagic" point of view, tolerance expressed during the first 12 months of initial treatment, bleeding history and patient frailty must be taken into account.

Fig. 5.

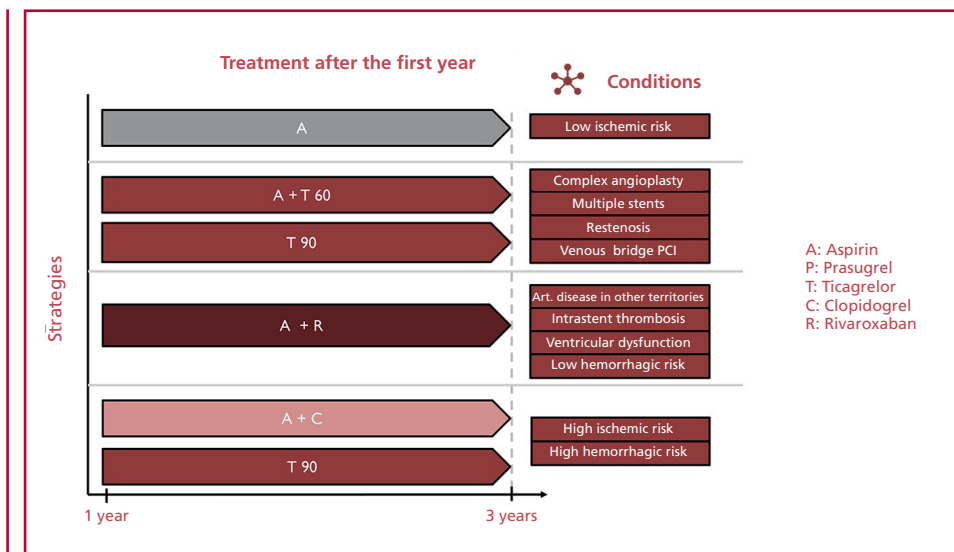
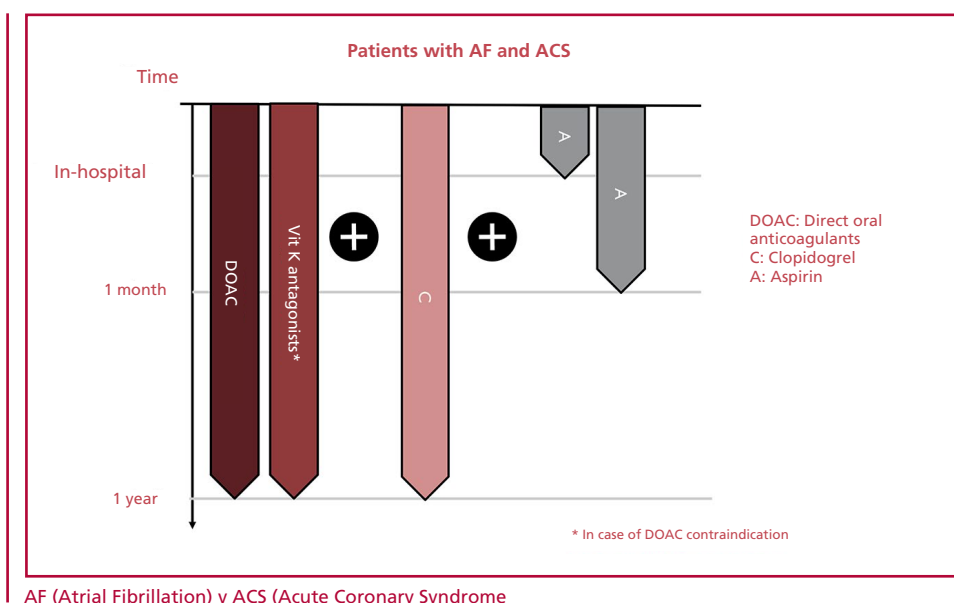


Fig. 6.



Especially in this period we can use scores such as DAPT or PRECISE, or the clinical variables used by the PEGASUS study to make the decision between continuing with some form of antithrombotic regimen or only using aspirin.

Prolonged antithrombotic therapy has demonstrated clinical benefit in patients at high ischemic risk and low bleeding risk who passed the initial 12-month period without major bleeding events. In those patients at low ischemic risk, aspirin treatment would be indicated, regardless of the bleeding risk. Figure 5 shows, based on the evidence, a way of individualizing which would be the most appropriate treatment according to the clinical characteristics and also supported by the scores that can be used.

In patients with a DAPT score >2, without bleeding events in the first year of DAPT, treatment schemes of

aspirin plus ticagrelor 60 mg every 12 h or ticagrelor 90 mg every 12 h would be indicated. In patients in whom peripheral artery disease predominates or have had in-stent thrombosis, or present ventricular dysfunction, the most appropriate treatment should be that of aspirin and rivaroxaban 2.5 mg every 12 hours. If they present high ischemic and hemorrhagic risk, then treatment schemes of clopidogrel 75 mg per day or monotherapy with ticagrelor 90 mg every 12 h should be considered.

**TREATMENT STRATEGIES IN PATIENTS WITH INDICATION OF LONG-TERM ORAL ANTICOAGULATION**

**Patients with atrial fibrillation**

The incidence of atrial fibrillation (AF) in the context of ACS ranges from 6% to 10%. In patients with AF, we are faced with the need to indicate DAPT to avoid

ischemic complications and anticoagulation to avoid embolic events. Assessing ischemic and bleeding risk in this context and making the appropriate therapeutic decision is a great challenge, as most studies were designed with the aim of optimizing safety over efficacy.

In general, in patients with AF without mechanical valve prostheses or with moderate to severe mitral stenosis, the evidence supports the use of direct oral anticoagulants (DOAC) instead of vitamin K antagonists (VKA) in terms of safety (i.e., lower risk of bleeding). In this setting, trials have tested the benefit of using apixaban (AUGUSTUS study), dabigatran (REDUAL-PCI study), and rivaroxaban (ROCKET study). (46-48). However, the doses of rivaroxaban used were lower than those proved useful in AF, so apixaban and dabigatran seem more recommended in this scenario taking into account the proven cardioembolic protection of their doses. VKA would be the treatment of choice in patients with DOAC therapy contraindication.

In patients with AF, after an ACS, dual antithrombotic therapy (DAT) with a DOAC for the prevention of embolic events and a P2Y<sub>12</sub> inhibitor for coronary protection appears to be the strategy with the best balance between ischemic protection and minimization of bleeding. The evidence for the use of oral anticoagulation together with ticagrelor or prasugrel as DAPT is limited, since clopidogrel was used in most of the studies, so the combination with these more potent inhibitors should be administered in very selected cases.

Regarding the use of aspirin, it was used in all the trials during the acute phase (between 2 and 7 days), so there is no evidence to avoid it at this stage. On the other hand, in those patients at high ischemic risk, without high bleeding risk, taking into consideration that the highest rate of events related to the treated vessel occurs in the first 30 days, it seems reasonable to extend it up to 1 month, followed by DAPT until reaching 12 months (Figure 6). (49)

#### Patients with mechanical prosthetic valves

In this group of patients, the indication for anticoagulation is with VKA. In a network meta-analysis, dual therapy (VKA + clopidogrel) was associated with a trend to reduce major bleeding compared with triple therapy (VKA+ clopidogrel + aspirin) by TIMI criteria (OR: 0.58; 95% CI: 0.31-1.08), while no significant difference was observed in major cardiovascular events (OR: 0.96; 95% CI: 0.60-1.46). (49).

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