REVIEW ARTICLE

Antiplatelet Strategies in Acute Coronary Syndromes

Estrategias de antiagregación plaquetaria en síndromes coronarios agudos

JUAN PABLO COSTABEL[1], ERNESTO DURONTO[2], SEBASTIÁN NANI[3], HERNÁN COHEN ARAZI[4], JAVIER GUETTA[5]

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_2Y_{12} 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_2Y_{12} 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.

Rev Argent Cardiol 2021;89:140-150. http://dx.doi.org/10.7775/rac.v89.i2.19703

Address for reprints: Dr. Juan Pablo Costabel - Av. del Libertador 6302 - C1428 CABA, Argentina – Tel: +54 11 4787-7500 - E-mail: jpcostabel@icba.com.ar

[1] Coronary Care Unit, ICBA.
[2] Coronary Care Unit, Fundación Favaloro.
[3] Cardiology Department, Clínica Olivos.
[4] Coronary Care Unit, Sanatorio Trinidad Mitre.
[5] Cardiology Department, CEMIC

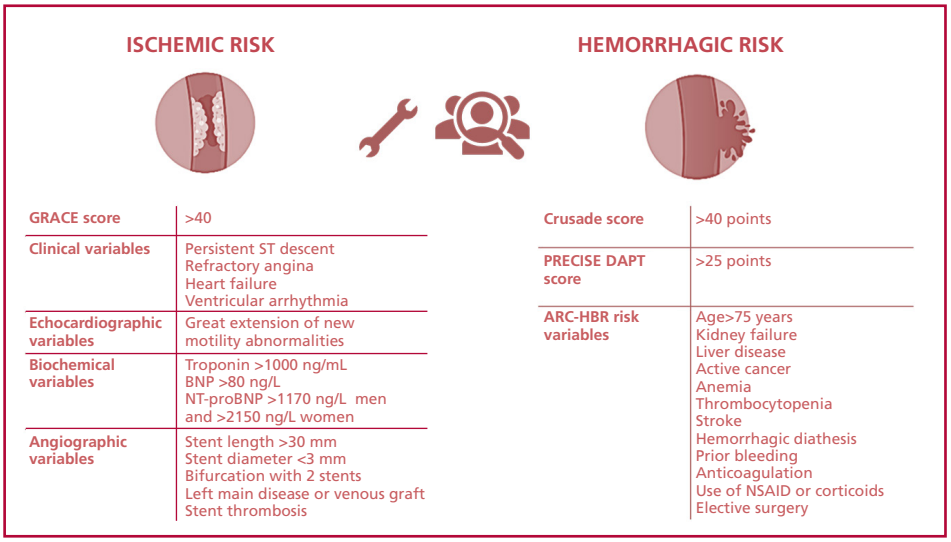


Fig. 1.

- 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)

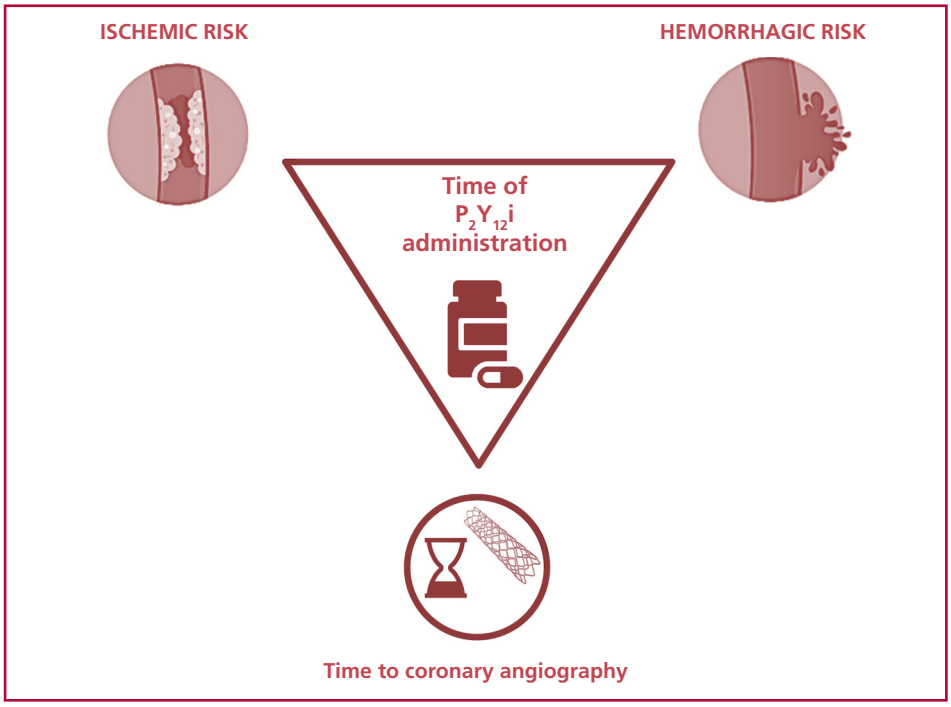
TIMING OF CORONARY ANGIOGRAPHY

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_2Y_{12} 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 IIbIIIa 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 coronary 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_2Y_{12} 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_2Y_{12} 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_2Y_{12} inhibitors, as ticagrelor and prasugrel, have shown superiority to prevent ischemic events, with an increase of hemorrhagic events.

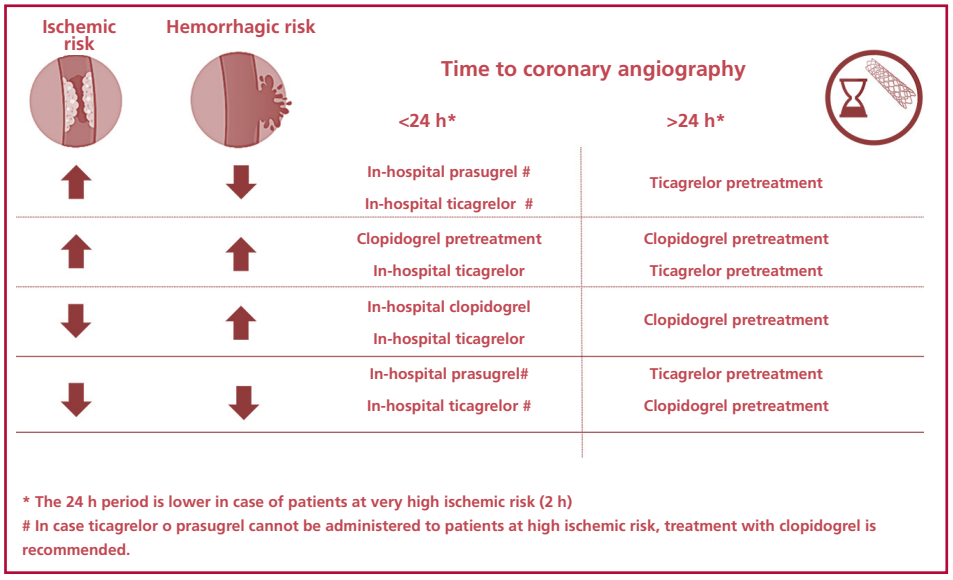


Fig. 3.

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 <60kg), 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 ≥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

minor bleeding. Major and minor bleeding occurred in 23.1% of patients in the ticagrelor/prasugrel group versus 17.6% in the clopidogrel group (HR: 0.74; 95% CI: 0.56-0.97; p=0.03). The composite endpoint of net clinical benefit was 30.7% with ticagrelor/prasugrel versus 27.3% with clopidogrel, without significant differences. No significant differences were either found in death for AMI and stroke (12.8% with clopidogrel and 12.5% with ticagrelor/prasugrel (HR: 1.02; 95% CI: 0.72-1.45; p=0.91). This trial suggests that clopidogrel would be more beneficial in patients over 70 years of age, as it reduces bleeding without a higher rate of thrombotic events, although due to the low number of patients included, it did not have sufficient power to detect them.

Figure 4 summarizes the general strategies.

Strategies to reduce bleeding events

Most large DAPT studies have used DAPT for 12 months, following which the P_2Y_{12} inhibitor was discontinued and aspirin was continued for life. The benefit of DAPT is dual, reducing the risk of ST and the clinical events associated with new coronary plaque accidents. However, bleeding events clearly increase the longer the time of DAPT and negatively impact the prognosis of our patients. That is why strategies are constantly being sought to reduce hemorrhagic events, without losing anti-ischemic protection, shortening the DAPT time.

Regarding the risk of ST, the development of new devices has reduced the dependence on DAPT for long periods. (27-29) Thinner platforms, as well as the use of less pro-inflammatory or re-absorbable polymers, allow a faster re-endothelialization, reducing the risk of ST as a result of less metal exposure. While with the first-generation of drug-eluting stents, 1 year of DAPT has been recommended to prevent long-term ST, with the latest-generation drug-eluting stents, DAPT duration can be significantly reduced.

On the other hand, improvements in coronary stent implantation techniques reduce the risk of complications. The correct device deployment guided by intravascular ultrasound (IVUS) or optical coherence tomography (OCT) reduces the interventions of the treated lesion. New techniques for treating bifurcations with a single device or with the minimum necessary apposition of two stents also contribute to reduce events.

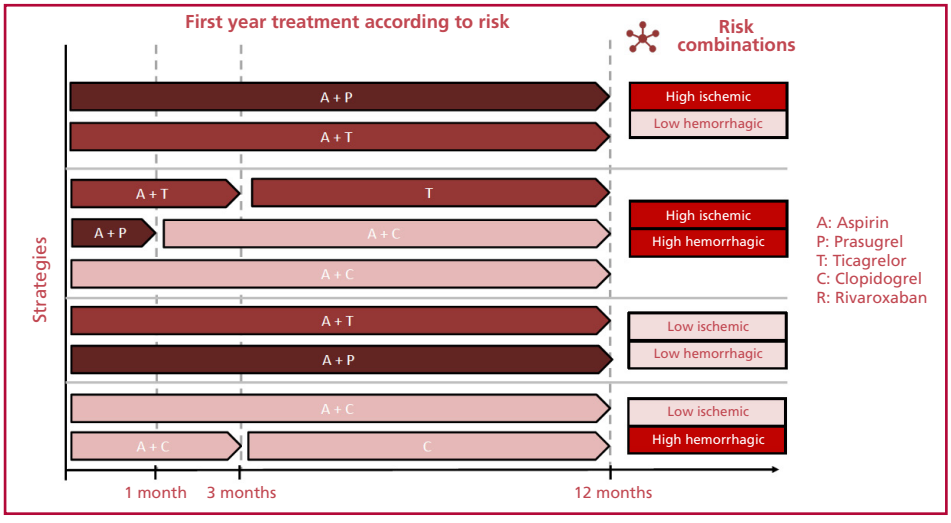
In this context, there have been three strategies to reduce the risk of bleeding: 1) to reduce the time of DAPT and continue with aspirin alone, 2) to reduce the potency "de-escalating" the P_2Y_{12} inhibitor, and 3) to reduce DAPT duration and continue monotherapy with P_2Y_{12} inhibitors.

Reduction of treatment time with P_2Y_{12} inhibitors to less than 1 year

Today there are more than 20 randomized controlled trials that test different DAPT duration strategies and thus challenge the recommended 12-month standard. These studies can be grouped into two classes: those that prove the non-inferiority of reducing DAPT duration to 3 or 6 months and those that prove the superiority of extending DAPT duration beyond 12 months. (30) In conclusion, the results seem to show that longer DAPT treatment is associated with a significant benefit in terms of stent-related (ST) and non-stent-related ischemic events (plaque accidents with clinical impact), but also with a significant increase in bleeding. On the contrary, shortening DAPT to less than 1 year is associated with a significant reduction in bleeding events, with more thrombotic events. The impact of these strategies in terms of total mortality or cardiovascular mortality remains controversial.

In recent years, different scores have been developed to estimate the individual risk of suffering adverse events, aimed at assisting the decision of DAPT duration. The PRECISE-DAPTT score assigns points

Fig. 4.



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 ≥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 primary endpoint (cardiovascular death, AMI, stroke and BARC bleeding ≥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 ≥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_2Y_{12} inhibitor for 3 months and subsequently, a P_2Y_{12} 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_2Y_{12} 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 ≥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_2Y_{12} inhibitor. (41, 42) In them, shortening DAPT to 1–3 months and continuing thereafter with P_2Y_{12} 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_2Y_{12} 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_2Y_{12} 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_2Y_{12} 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.

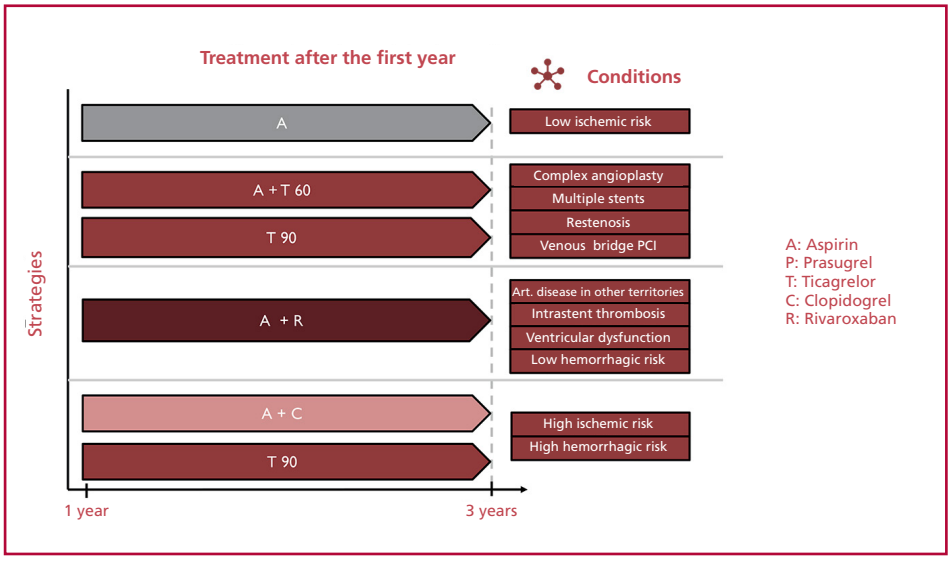
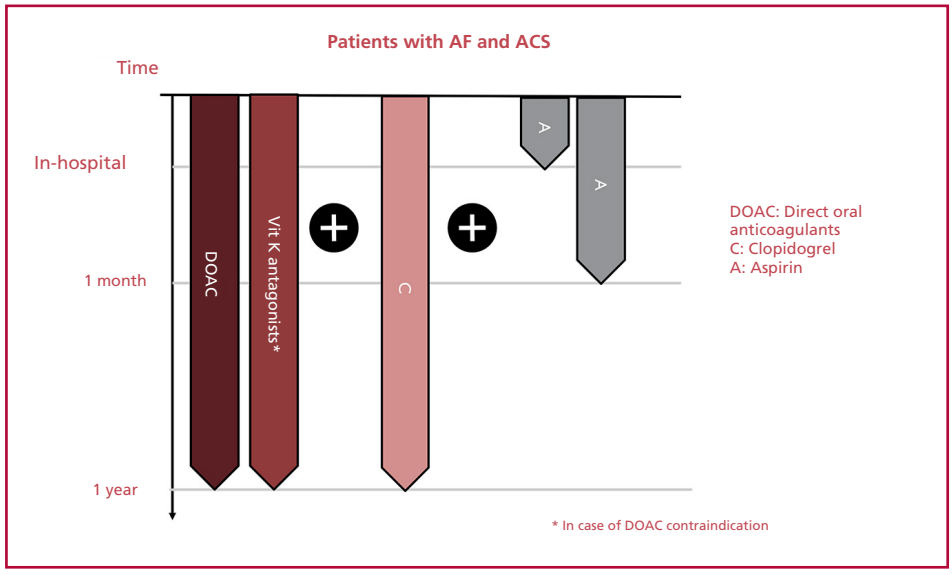


Fig. 6.



AF (Atrial Fibrillation) y ACS (Acute Coronary Syndrome

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 P2Y12 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).

REFERENCES

1. Mueller C. Biomarkers and acute coronary syndromes: an update. Eur Heart J 2014;35:552–6. https://doi.org/10.1093/eurheartj/eht530

2. Burgos L, Garmendia C, Giordanino E, Godoy Armando C, Cigalini I, García Zamora S, et al. Validación y comparación de dos modelos de estratificación de riesgo en infarto de miocardio con elevación del segmento ST. Rev Argent Cardiol 2019;87:118–24. http://dx.doi.org/10.7775/rac.es.v87.i2.13339

3. Poldervaart JM, Langedijk M, Backus BE, Dekker IMC, Six AJ, Doevendans PA, et al. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. Int J Cardiol 2017;227:656–61. https://doi.org/10.1016/j.ijcard.2016.10.080

4. Luo J, Yang M, Han L, Chen L, Chen X, Gao K, et al. Validity of the Global Registry of Acute Coronary Events risk score in prediction of acute myocardial infarction mortality in hospitalised Chinese patients aged 80 and over. Australas J Ageing 2014;33:E1–5. https://doi.org/10.1111/ajag.12044

5. Kastrati A, Schömig A, Elezi S, Dirschinger J, Mehilli J, Schühlen H, et al. Prognostic Value of the Modified American College of Cardiology/American Heart Association Stenosis Morphology Classification for Long-Term Angiographic and Clinical Outcome After Coronary Stent Placement. Circulation 1999;100:1285–90. https://doi.org/10.1016/j.amjcard.2014.09.003

6. Oduncu V, Erkol A, Turan B, Akgün T, Karabay CY, Tanboğa IH, et al. Predictors and long-term prognostic significance of angiographically visible distal embolization during primary percutaneous coronary intervention. Turk Kardiyol Dern Ars 2013;41:486–94. https://doi.org/10.1016/j.ijcard.2009.01.026

7. Kastrati A, Schömig A, Elezi S, Dirschinger J, Mehilli J, Schühlen H, et al. Prognostic value of the modified American College of Cardiology/American Heart Association stenosis morphology classification for long-term angiographic and clinical outcome after coronary stent placement. Circulation 1999;100:1285–90. https://doi.org/10.1161/01.CIR.100.12.1285

8. Bechiri MY, Souteyrand G, Lefèvre T, Trouillet C, Rangé G, Cayla G, et al. Characteristics of stent thrombosis in bifurcation lesions analysed by optical coherence tomography. EuroIntervention 2018;13:e2174–81. https://doi.org/10.4244/EIJ-D-17-00794

9. Iakovou I, Kadota K, Papamentzelopoulos S, Pavlides G, Mitsudo K. Is there a higher risk of stent thrombosis in bifurcation lesion or is it related to the technique? EuroIntervention 2010;6 Suppl J:J107-11. https://doi.org/10.4244/EIJV6SUPJA17

10. Kamenik M, Widimsky P. Stent thrombosis in acute coronary syndromes: Patient-related factors and operator-related factors. Anatol J Cardiol 2020;24:274–9. https://doi.org/10.14744/AnatolJCardiol.2020.69679

11. Palmerini T, Stone GW. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: Conceptual evolution based on emerging evidence. Eur Heart J 2016;37:353–64. https://doi.org/10.1093/eurheartj/ehv712

12. Ueda P, Jernberg T, James S, Alfredsson J, Erlinge D, Omerovic E, et al. External Validation of the DAPT Score in a Nationwide Population. J Am Coll Cardiol 2018;72:1069–78. https://doi.org/10.1016/j.jacc.2018.06.023

13. Ariza-Solé A, Salazar-Mendiguchía J, Lorente V, Sánchez-Salado JC, Romaguera R, Ferreiro JL, et al. Predictive ability of bleeding risk scores in the routine clinical practice. Eur Heart J Acute Cardiovasc Care 2015;4:205–10. https://doi.org/10.1177/2048872614538405

14. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand J-P, Faxon DP, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165–75. https://doi.org/10.1056/NEJMoa0807986

15. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, Marinkovic J, Vukcevic V, Stefanovic B, et al. Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients: The RIDDLE-NSTEMI Study. JACC Cardiovasc Interv 2016;9:541–9. https://doi.org/10.1016/j.jcin.2015.11.018

16. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369:999–1010. https://doi.org/10.1056/NEJMoa1308075

17. Tarantini G, Mojoli M, Varbella F, Caporale R, Rigattieri S, Andò G, et al. Timing of Oral P_2Y_{12} Inhibitor Administration in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. J Am Coll Cardiol 2020;76:2450–9. https://doi.org/10.1016/j.jacc.2020.08.053

18. Dworeck C, Redfors B, Angerås O, Haraldsson I, Odenstedt J, Ioanes D, et al. Association of Pretreatment With P_2Y_{12} Receptor Antagonists Preceding Percutaneous Coronary Intervention in Non-ST-Segment Elevation Acute Coronary Syndromes With Outcomes. JAMA Netw Open 2020;3:e2018735. https://doi.org/10.1001/jama-

networkopen.2020.18735
19. Camaro C, Damman P. Antithrombotic PreTreatment and Invasive Strategies in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome. J Clin Med 2020;9:2578. https://doi.org/10.3390/jcm9082578
20. Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019;381:1524–34. https://doi.org/10.1056/NEJMoa1908973
21. Steinhubl SR, Berger PB, Brennan DM, Topol EJ, CREDO Investigators. Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention. J Am Coll Cardiol 2006;47:939–43. https://doi.org/10.1016/j.jacc.2005.10.047
22. Investigators TC in UA to PRET. Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. N Engl J Med 2001;345:494–502. https://doi.org/10.1056/NEJMoa010746
23. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15. https://doi.org/10.1056/NEJMoa0706482
24. Roe MT, Armstrong PW, Fox KAA, White HD, Prabhakaran D, Goodman SG, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012;367:1297–309. https://doi.org/10.1056/NEJMoa1205512
25. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med 2009;361:1045–57. https://doi.org/10.1056/NEJMoa0904327
26. Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. Lancet 2020;395:1374–81. https://doi.org/10.1016/S0140-6736(20)30325-1
27. Ullrich H, Münzel T, Gori T. Coronary Stent Thrombosis- Predictors and Prevention. Dtsch Arztebl Int 2020;117:320–6. https://doi.org/10.3238/arztebl.2020.0320
28. McKavanagh P, Zawadowski G, Ahmed N, Kutryk M. The evolution of coronary stents. Expert Rev Cardiovasc Ther 2018;16:219–28. https://doi.org/10.1080/14779072.2018.1435274
29. Gori T, Polimeni A, Indolfi C, Räber L, Adriaenssens T, Münzel T. Predictors of stent thrombosis and their implications for clinical practice. Nat Rev Cardiol 2019;16:243–56. https://doi.org/10.1038/s41569-018-0118-5
30. Belley-Côté E, Eikelboom J. Review: After PCI with DESs, long- and standard-term DAPT increase some adverse outcomes vs short-term DAPT. Ann Intern Med 2019;171:JC54. https://doi.org/10.7326/ACPJ201911190-054
31. Guerrero C, Ariza-Solé A, Formiga F, Martínez-Sellés M, Vidán MT, Aboal J. Applicability of the PRECISE-DAPT score in elderly patients with myocardial infarction. J Geriatr Cardiol 2018;15:713–7. https://doi.org/10.11909/j.issn.1671-5411.2018.12.003
32. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389:1025–34. https://doi.org/10.1016/S0140-6736(17)30397-5
33. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390:1747–57. https://doi.org/10.1016/S0140-6736(17)32155-4
34. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J 2017;38:3070–8. https://doi.org/10.1093/eurheartj/ehx175
35. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI. JAMA 2019;321:2414 -27. https://doi.org/10.1001/jama.2019.8145
36. Hahn J-Y, Song Y Bin, Oh J-H, Chun WJ, Park YH, Jang WJ, et al. Effect of P_2Y_{12} Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention. JAMA 2019;321:2428-37. https://doi.org/10.1001/jama.2019.8146.
37. Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, et al. Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. Eur Heart J 2020;41:3533–45. https://doi.org/10.1093/eurheartj/ehaa670
38. Angiolillo DJ, Baber U, Mehran R. Ticagrelor monotherapy in patients with diabetes mellitus undergoing percutaneous coronary interventions: insights from the TWILIGHT trial. Cardiovasc Res 2020;116:e70–2. https://doi.org/10.1093/cvr/cvaa120
39. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, et al. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome. JAMA 2020;323:2407. https://doi.org/10.1001/jama.2020.7580
40. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940–9. https://doi.org/10.1016/S0140-6736(18)31858-0
41. Ho AC, Egolum U, Parker S, Dimmel J, Hawkins A, Ling H. P_2Y_{12} Inhibitor Monotherapy After a Short Dual Antiplatelet Therapy Versus Standard-Term Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention: A Contemporary Meta-Analysis. Clin Drug Investig 2020;40:799–808. https://doi.org/10.1007/s40261-020-00947-x
42. Hong SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, et al. Effect of ticagrelor monotherapy on mortality after percutaneous coronary intervention: a systematic review and meta-analysis of randomized trials including 26 143 patients. Eur Hear J Cardiovasc Pharmacother 2020; pvaa119. https://doi.org/10.1093/ehjcvp/pvaa119.
43. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-Term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791–800. https://doi.org/10.1056/NEJMoa1500857
44. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;377:1319–30. https://doi.org/10.1056/NEJMoa1709118
45. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, et al. Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease: The COMPASS Trial. J Am Coll Cardiol 2018;71:2306–15. https://doi.org/10.1016/j.jacc.2018.03.008
46. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513–24. https://doi.org/10.1056/NEJMoa1708454
47. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380:1509–24. https://doi.org/10.1056/NEJMoa1817083
48. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt F, Wildgoose P, et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin k antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). Am Heart J 2015;169:472-8.e5. https://doi.org/10.1016/j.ahj.2014.12.006
49. Alexander JH, Wojdyla D, Vora AN, Thomas L, Granger CB, Goodman SG, et al. Risk/Benefit Tradeoff of Antithrombotic Therapy in Patients With Atrial Fibrillation Early and Late After an Acute Coronary Syndrome or Percutaneous Coronary Intervention: Insights From AUGUSTUS. Circulation 2020;141:1618–27. https://doi.org/10.1161/CIRCULATIONAHA.120.046534