Antiplatelet therapy in acute coronary syndromes: what is the optimal therapy with the current generation of drug-eluting stents?

Tratamiento antiplaquetario en síndromes coronarios agudos: ¿cuál es la terapia óptima con la actual generación de stents farmacológicos?

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ABSTRACT

The managementof patients with acute coronary syndrome has progressedsignificantly over the past few decades primarily due to technological advancements made in interventional cardiology with the arrival of new drug-eluting stents, early reperfusion strategies, and a deeper understanding of anti-thrombotic therapy.
The development and addition of more effective antiplatelet drugs to the therapeutic armamentarium along with the use of dual antiplatelet therapy with more potent P2Y12 receptor inhibitors (ticagrelor and prasugrel) have shown a significant reduction in the number of acute ischemic events following percutaneous revascularization. However, over time, careful assessmentof scientific studies and real-world practice registries has revealed that these more aggressive antiplatelet regimens are associated with a significant increase in bleeding complications that jeopardize the patient's life.
Different alternatives and treatment strategies were evaluated to determine the most suitable therapeutic approach that keeps a balance between preventing ischemic events (stent thrombosis, acute myocardial infarction or cardiovascular mortality) without increasing bleeding complications. This is how the concept of "de-escalation" and individualized antiplatelet treatment was born.

Keywords: *antiplatelet drugs, prasugrel, ticagrelor, acute coronary syndroms, de-escalation*

RESUMEN

El tratamiento de pacientes con síndromes coronarios agudos ha evolucionado significativamente en las últimas décadas, principalmente debido al avance tecnológico de la cardiología intervencionista con los nuevos stents farmacológicos, las estrategias de reperfusión temprana y el entendimiento más profundo de la terapia antitrombótica.
El desarrollo e incorporación de drogas antiplaquetarias más eficaces en el armamentarium terapéutico y el uso de doble antiagregación plaquetaria con inhibidores del receptor P2Y12 más potentes (ticagrelor y prasugrel) han demostrado una significativa disminución de eventos isquémicos agudos post revascularización percutánea. Sin embargo, con el tiempo, la evaluación más cuidadosa de los estudios científicos, como también la evidencia en registros de la práctica diaria, demostró que estos esquemas de antiagregación más agresivos se asociaron a un incremento significativo en la incidencia de complicaciones de sangrado que ponían en riesgo la vida del paciente. Diferentes alternativas y estrategias de tratamientos fueron evaluadas con la intención de determinar el esquema terapéutico más adecuado que mantuviera un equilibrio entre la prevención de eventos isquémicos (trombosis del stent, infarto agudo de miocardio o mortalidad cardiovascular) sin el aumento de las complicaciones por sangrado. Así nació el concepto de de-escalation y el concepto del tratamiento antiplaquetario personalizado. Este esquema lo estaremos analizando en esta revisión.

Palabras clave: *drogas antiplaquetarias, prasugrel, ticagrelor, clopidogrel, síndromes coronarios agudosm de-escalation.*

Revista Argentina de Cardioangiología Intervencionista 2023;14(2):67-70. https://doi.org/10.30567/RACI/202302/0067-0070

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The development and addition of more effective antiplatelet drugs to the therapeutic armamentarium along with the use of dual antiplatelet therapy with more potent P2Y12 receptor inhibitors (ticagrelor and prasugrel) have shown a significant reduction in the number of acute ischemic events following percutaneous revascularization. However, over time, careful assessment of scientific studies and real-world practice registries has revealed that these more aggressive antiplatelet regimens are associated with a significant increase in bleeding complications that jeopardize the patient's life. The net benefit of using these agents was therefore questioned. Concurrently, the development of second and third-generation drug-eluting stents has reduced the risks of the feared acute and subacute stent thrombosis significantly with a more rapid and complete re-endothelialization process. These advancements also questioned the need for prolonged aggressive antiplatelet treatment.
Different alternatives and treatment strategies were evaluated to determine the most suitable therapeutic approach that keeps a balance between preventing ischemic events (stent thrombosis, acute myocardial infarction or cardiovascular mortality) without increasing bleeding complications. This is how the concept of "de-escalation" and individualized antiplatelet treatment was born.

CONCEPT OF "DE-ESCALATION"

De-escalation refers to those strategies used to reduce antiplatelet effects to decrease bleeding complications without compromising ischemic events. These strategies include: 1) reducing the duration of dual antiplatelet therapy to shorter periods, 2) reducing the intensity of antiplatelet effects by switching to less potent agents, and 3) reducing the number of antiplatelet agents used to a one agent only. Additionally, the concept of adjusting the degree of antiplatelet therapy based on genetic studies or antiplatelet response known

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No conflicts of interest whatsoever.

Received: 29/04/2023 | Accepted: 16/05/2023

TABLE 1.

Events (3 or 6 monthsvs 12 months)	HR (95% CI)
Death/Infarction/ST-segment elevation	1,14 (0,88-1,49)
Stent thrombosis (ST)	1,30 (0,77-2,27)
Bleeding	0,65 (0,45-0,92)
Major bleeding	0,52 (0,30-0,93)

HR: hazard ratio. 95% CI: 95% confidence interval.

as "individualized antiplatelet therapy" was evaluated. These strategies and their clinical response will be described further.

SHORTER DURATION OF ANTIPLATELET THERAPY

The first question that arose was whether the shorter duration of dual antiplatelet therapy (DAPT) with more aggressive agents (aspirin + ticagrelor or aspirin + prasugrel) could be shortened to reduce the risk of bleeding without compromising the risk of ischemic events. For over a decade now, multiple randomized clinical trials have been conducted to determine the optimal duration of more aggressive DAPT. In other words, whether the duration can be shortened from 12 months. Initially, treatment durations of 6 months vs 12 months or even 3 months only vs 12 months were evaluated in former studies with a significant number of patients. More recently, with the addition of third-generation drug-eluting stents, trials with just 1 month of more aggressive treatment have been conducted. Most of these studies have shown that a shorter and more aggressive antiplatelet treatment is associated with a significant reduction in the risk of bleeding without more ischemic events. A meta-analysis of the early randomized clinical trials of 8100 patients demonstrated that the shorter 3-6 month course of treatment was superior to the 12-month course with a 35% to 45% reduction of bleeding events and no increase in the risk of ischemic events (**Table 1**)[1]. More recently, the MASTER DAPT trial of 4500 patients with acute coronary syndrome and high bleeding risk randomized to only 30 days of aggressive DAPT showed similar results reduced bleeding (6.5% vs 9.4%; < .001) and no increase in ischemic risks (5.9% vs 6.1%, *P* = NA) in patients treated with DAPT therapy for 30 days compared to 6 months[2].

SWITCHING TO A LESS POTENT ANTIPLATELET AGENT

The second concept studied was the switch from a more potent P2Y12 inhibitor (prasugrel or ticagrelor) to a less potent agent either low-dose prasugrel (5 mg) or clopidogrel. Several studies were conducted to research this hypothesis. One of the most important studies that included patients at the highest ischemic risk such as those with ST-segment elevation myocardial infarction is the TALOS-AMI trial. This study randomized 2700 patients to receive aspirin and ticagrelor for 30 days followed by aspirin and clopidogrel for the remaining 11 months vs guideline-recommended strategy of aspirin and ticagrelor for 12 months as advised by both the American and European guidelines. The study showed a 45% reduction in the composite primary endpoint of death, myocardial infarction, stent thrombosis, and bleeding (BARC type 2, 3, or 5) with rates of 4.6% vs 8.2%, respectively, HR, 0.55 [95%CI, 0.40-0.76][3]. The HOST-REDUCE-POLYTECH-ACS trial assessed another form of switching or de-escalation (the reduction of prasugrel from 10 mg down to 5 mg after the initial 30 days of treatment with aspirin and full-dose prasugrel. The trial demonstrated a significant decrease in bleeding events with dose reduction (HR, 0.25; 95%CI, 0.10-0.61) without an increased ischemic risk (HR, 0.88; 9% CI, 0.47-1.66)[4].

TABLE 2.

Study	Patients	Strategy	Ischemic events	Bleeding events
GLOBAL Leaders	16,000	DAPT 1 mes	No difference	Fewer
TWIGHLIGHT	8,200	DAPT 3 meses	No difference	Fewer
TICO	3.000	DAPT 3 meses	No difference	Fewer
SMART CHOICE	3.000	DAPT 3 meses	No difference	Fewer
STOP DAPT 2 (*)	3.000	DAPT 1 mes	No difference	Fewer

Ischemic events: myocardial infarction, death, stent thrombosis. Bleeding: BARC type 2, 3, and 5. The STOP DAPT 2 trialused clopidogrel as a single agent vs continuing with a 9-month course of aspirin + ticagrelor.

DE-ESCALATION TO A SINGLE ANTIPLATELET THERAPY. DISCONTINUE ASPIRIN

Five randomized clinical trials specifically examined the use of dual antiplatelet therapy for 1-3 months followed by discontinuation of aspirin and continuation of a single antiplatelet agent. Most trials used ticagrelor as the sole antiplatelet agent. The 2 most important and largest studies were the GLOBAL LEADERS trial (16 000 patients randomized to 1 month of DAPT followed by ticagrelor for 23 months vs continuing with aspirin + ticagrelor for 11 months) and the TWILIGHT trial (8200 patients randomized to 3 months of DAPT followed by a 9-month course of ticagrelor)[5,6]. **Table 2** shows the main characteristics of these studies and the results of ischemic and bleeding events in each of them. A meta-analysis of all these trials showed that discontinuing aspirin and continuing with the P2Y12 receptor blocker only was associated with a 45% reduction in the rate of major bleeding (HR, 0.55; CI, 0.28-1.0), with a trend towards fewer acute or subacute stent thrombosis (HR, 0.6; CI, 0.32-1.12) and myocardial infarction (HR, 0.82; CI, 0.58-1.16). We should mention that the trials that assessed the discontinuation of the P2Y12 receptor inhibitor leaving the patient on aspirin alone were associated with a significant increase in the risk of stent thrombosis (HR, 1.55; CI, 1.02-2.36) and a trend towards an increased risk of myocardial infarction (HR, 1.28; CI, 0.97-1.68), which means that it would be ill-advised for the patient to continue with aspirin as the sole antiplatelet agent[7].

GUIDED ANTIPLATELET THERAPY ALSO KNOWN AS "INDIVIDUALIZED" THERAPY

The main reason for the higher ischemic risk associated with clopidogrel is its antiplatelet effect variability. This is so because clopidogrel is a prodrug that requires dual hepatic metabolism to generate an active metabolite. This hepatic metabolic step is determined by the enzyme of the CYP2C19 system. Genetic variations of this enzyme are associated with a decreased antiplatelet effect of clopidogrel, leading to an increased risk of ischemic events in these patients. By conducting genotype studies, we can determine whether patients have this genetic alteration and if they will respond to clopidogrel therapy. Patients with loss

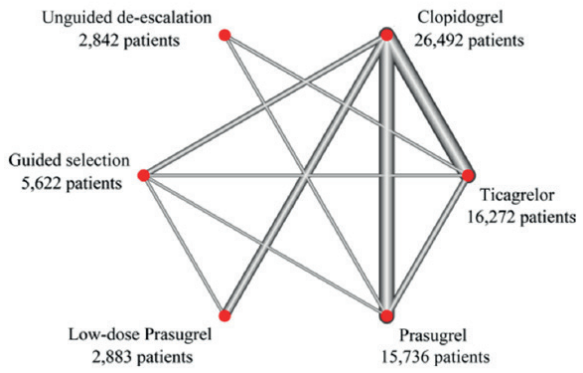

Figure 1. *Randomized clinical trials assessing different antiplatelet therapy regimens.*

of the two function alleles, homozygous genotype, have an almost zero response to clopidogrel while those with one allele present and the other one absent have an intermediate response. Instead of determining the genotype, another alternative is to measure the anti-P2Y12 effect of clopidogrel using platelet aggregation studies. Based on this concept, we hypothesized that if the presence of genetic modification or demonstration of non-response to clopidogrel were measured and more aggressive anti-P2Y12 drugs were used only in these unresponsive patients while continuing clopidogrel in the responders, the anti-ischemic profile would improve without a higher risk of bleeding. Multiple randomized studies were conducted to put this concept to the test. Although initial studies did not validate this concept, most of them showed a favorable trend to guided therapy. The TAILOR-PCI trial, probably the most important one regarding the number of patients, included 5235 patients and assessed the use of genetic studies to guide the use of clopidogrel (or ticagrelor in those with genetic loss of function) vs clopidogrel without evaluation of antiplatelet effect. The study showed a significant trend towards fewer ischemic events with guided therapy (HR, 0.66; CI, 0.43-1.02) without changes to the rate of bleeding events (HR, 1.22; CI, 0.60-2.51)[8]. A meta-analysis of 11 randomized trials that assessed multiple treatment options, guided vs non-guided therapy (based on genetic studies or platelet aggregation studies) of 27 000 patients demonstrated that guided was superior to non-guided therapy with a significantly lower ischemic risk (HR, 0.78; CI, 0.63-0.95) and a trend towards a lower risk of bleeding (HR, 0.88; CI, 0.77-1.01)[9].

GUIDED DE-ESCALATION USING GENETIC OR PLATELET FUNCTION TESTS VS DE-ESCALATION FOR ALL PATIENTS

Although based on the previous section, guided therapy appears to be safer and as effective as conventional more aggressive DAPT, it is not clear whether guided therapy should be given to all patients or instead upfront de-escalation for all patients. Although no randomized clinical trials studied these 2 strategies directly, evidence from randomized trials on different strategies suggests that genetic or platelet function testing should not be necessary to de-escalate antiplatelet therapy. Upfront de-escalation to all patients is the best therapeutic alternative. Kuno et al. evaluated data from 19 randomized trials of almost 70 000 patients treated with different antiplatelet regimens (**Figure 1**)[10]. Compared to selection based on genetic or platelet function testing, blind de-escalation of all patients was linked to a trend towards fewer ischemic events (HR, 0.82; CI, 0.53-1.28) and very few bleeding events (HR, 0.48; CI, 0.33-0.72).

SPECIAL TREATMENT GROUP

These strategies may have an even more significant application in specific clinical groups. Defining the effect of more or less aggressive antiplatelet therapy in patients at high compared to low risk of bleeding, treatment in patients at high ischemic risk, and an increasingly important group such as elderly patients with a well-known higher risk of bleeding, is of significant clinical importance. Multiple trials have been conducted to determine the benefit of de-escalation with different alternatives in high-risk bleeding and elderly patients, all showing that shorter DAPT courses (1 to 3 months) or less aggressive agents (prasugrel 5 mg or clopidogrel) are associated with very few bleeding events without an increase of ischemic events. This benefit was also seen in patients undergoing more complex procedures and a higher ischemic risk as demonstrated by the HOST-REDUCE-POLYTECH-ACS trial that randomized patients with ACS and complex procedures to a 1-month course of DAPT with prasugrel 10 mg followed by de-escalation down to a 12-month course with 5 mg and then 10 mg. There were no differences in ischemic events (HR, 0.81; 95% CI, 0.45-1.46). However, there were significanty fewer bleeding events with the reduced dose (HR, 0.25; CI, 0.10-0.61)[11]). Similarly, in elderly patients, the POPULAR AGE trial randomized patients older than 70 years to DAPT with ticagrelor vs DAPT with clopidogrel. Patients treated with clopidogrel had lower rates of bleeding (HR, 0.71; CI, 0.54-0.94) without more ischemic events (HR, 0.92; CI, 0.64-1.34)[12]. This demonstrates that in patients at higher risk of bleeding due to clinical characteristics or advanced age, less aggressive treatment was associated with fewer bleeding complications with even a trend towards fewer ischemic events.

CONCLUSIONS

The addition of second and third-generation drug-eluting stents, the understanding of the need for more advanced anti-ischemic therapies, but mainly the recent demonstration of the clinical implications of bleeding risks have led us to develop a more elaborate and individualized antiplatelet therapy to balance their positive effects of reducing the rate of ischemic events without more bleeding complications. Aggressive treatments seem necessary, but mainly within the first 30 to 90 days. In those at very high risk of bleeding or elderly patients, 30 days seem to be sufficient. After this period, de-escalation regimens should be used. While there is no single regimen and combinations of aspirin + clopidogrel or aspirin + prasugrel 5 mg are possible alternatives, based on more recent studies, the most effective de-escalation therapy would be to reduce the degree of antiplatelet

therapy by using one single agent with potent and predictable antiplatelet effects (ticagrelor or prasugrel) while discontinuing aspirin. The use of genetic or platelet function tests is not superior to discontinuing aspirin in all patients and continuing with ticagrelor or prasugrel. If, for economic or adverse events reasons, neither one of these two agents can be used, genetic or platelet function tests would be indicated to determine and confirm the response to clopidogrel.

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