Safety and efficacy outcomes among patients with acute coronary syndromes treated with clopidogrel, prasugrel and ticagrelor: insights from randomized clinical trials

Seguridad y eficacia de los resultados del tratamiento con clopidogrel, prasugrel y ticagrelor entre pacientes con síndrome coronario agudo: enseñanzas de los ensayos clínicos aleatorizados

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Abstract

In patients presenting with acute coronary syndromes (with or without ST-segment elevation), dual anti-platelet therapy consisting of aspirin and a platelet ADP-receptor antagonist (P2Y12 inhibitor) is recommended for at least 1 year accorded ACC/AHA guidelines. This recommendation is independent of whether revascularization is performed during the acute hospitalization. The method of revascularization (percutaneous coronary intervention with bare-metal or drug-eluting stents or coronary artery bypass grafting), when performed, does not affect this treatment paradigm either. In the last few years, pivotal randomized clinical trials in patients with acute coronary syndromes compared the first generation agent clopidogrel, with more potent inhibitors (prasugrel and ticagrelor), which have different mechanisms of action and pharmacokinetic properties..The purpose of this review is to compare the study designs and results pertaining to these new compounds and glean insight into the potential advantages and disadvantages of each agent.

Key words: *antiplatelet therapy, acute coronary syndromes, stent thrombosis, thyenopiridines, drug eluting stents.*

Revista Argentina de Cardioangiología Intervencionista 2013;4(3):145-150

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Conflictos de intereses: no existen.

Recibido: 11-4-2013 | Aceptado: 31-5-2013

INTRODUCTION

For patients presenting with acute coronary syndromes (ACS, with or without ST-segment elevation), dual anti-platelet therapy (DAPT), consisting of aspirin and a platelet ADP-receptor antagonist (P2Y12 inhibitor) is recommended for at least 1 year accorded ACC/AHA guidelines.[1-3] This recommendation is independent of whether revascularization is performed during the acute hospitalization for ACS. The method of revascularization (percutaneous coronary intervention with bare-metal or drug-eluting stents or coronary artery bypass grafting), when performed, does not affect this treatment paradigm either. In the last few years, pivotal randomized clinical trials in ACS

patients compared the first generation agent clopidogrel, with more potent P2Y12 inhibitors (prasugrel and ticagrelor), which have different mechanisms of action and pharmacokinetic properties.[4-8]

The purpose of this review is to compare the study designs and results pertaining to these new compounds and glean insight into the potential advantages and disadvantages of each agent, in the absence of a direct comparison between the novel agents.

CLOPIDOGREL IN ACUTE CORONARY SYNDROMES

Clopidogrel is a first generation thienopyridine, which requires extensive metabolism (two oxidative stages) and activation by human carboxylesterase 1 (hCE1) in order to irreversibly inhibit the P2Y12 ADP receptor on the platelet surface.

Because of this complex metabolic pathway, clopidogrel's onset of action is slow (up to 12 hours after a 300 mg loading dose, and 2-6 hours after a 600 mg loading dose) and its effect is significantly affected by genetic factors, such as polymorphism of the 2C19 allele of the cytochrome P450 complex. This results in marked variability in platelet aggregation inhibition as well as a relative modest effect (~40-50% inhibition of platelet aggregation in response to stimulation with 20 μm ADP).

In order to achieve greater platelet inhibition, a larger dose of clopidogrel was tested both for loading (600 mg instead of 300 mg) and for maintenance (150 mg instead of 75 mg). Only marginal increments in platelet inhibition were noted, and a further reduction in clinical events was even less convincing [9].

The need to develop novel P2Y12 inhibitors stemmed from the unmet clinical need of recurrent ischemic events despite first generation DAPT. In the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial [1] 28% of DAPT patients, compared with 11.47% of monotherapy (aspirin) patients had cardiovascular death, myocardial infarction or stroke over a 9-month period (20% relative risk reduction).

PRASUGREL AND TICAGRELOR

Prasugrel is a second generation thienopyridine, an irreversible P2Y12 antagonist, which requires less extensive metabolism (one oxidation) for its transformation into an active drug (hCE2 in viscera and hCE1 in the liver). Compared to clopidogrel (even in higher loading and maintenance does), it exhibits more potent platelet inhibition, more rapid onset of action and substantially less pharmacokinetic variability due to faster generation of the active metabolite.[10,11]

In contrast to clopidogrel and prasugrel, ticagrelor is an oral, reversible, direct-acting inhibitor of the P2Y12 receptor. It is not a thienopyridine, but rather a cyclopentyl-triazolo-pyrimidine (CPTP) with more rapid onset of action and more predictable and pronounced platelet inhibition than clopidogrel. Unlike clopidogrel and prasugrel, it is not a pro-drug, but is directly active in binding to the P2Y12 receptor. It is also a reversible agent, such that after drug discontinuation, as serum levels fall the ticagrelor molecule dissociates from the P2Y12 receptor, restoring normal platelet function. Conversely, clopidogrel or prasugrel irreversibly bind to the platelet P2Y12 receptor, thus requiring bulk replacement of the circulating platelet pool to restore normal hemostatic function.[12] However, ticagrelor, unlike clopidogrel or prasugrel, also increases levels of endogenous adenosine by blocking its reuptake in red blood cells. This phenomenon is likely responsible for the higher incidence of dyspnea and bradycardia observed with this compound.[7,8]

Both prasugrel and ticagrelor demonstrated marked platelet inhibition even in patients who have diminished response to clopidogrel, or high on-therapy residual platelet aggregation.[12-14]

Five randomized trials have assessed the clinical safety and efficacy of clopidogrel in comparison with either prasugrelor ticagrelor,[4-9] PRINCIPLE TIMI 44,[4] JUMBO-TIMI 26,[5] and TRITON-TIMI 38 compared prasugrel versus clopidogrel, while DISPERSE-2[8] and PLATO[7] compared ticagrelor versus clopidogrel. JUMBO[4] and PRINCIPLE[5] will be excluded from this review because they included patients with stable coronary artery disease, for which the novel agents aren't indicated.

TRITON-TIMI 38

The TRITON-TIMI 38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38) enrolled 13,608 patients with ACS (STEMI in 24%) scheduled for PCI.Patients were randomized after coronary angiography demonstrated eligibility for PCI (except for in some primary PCI STEMI patients), 1:1 to prasugrel 60 mg loading dose and 10 mg maintenance dose daily, or clopidogrel 300 mg loading dose and 75 mg maintenance dose daily. Patients with hemorrhagic or ischemic stroke within the previous 3 months, high risk of bleeding, fibrinolytic therapy within 24 hours or any thienopyridine in the last five days were excluded. The primary endpoint was the composite of cardiovascular death, non- fatal MI or stroke. Other important endpoints were stent thrombosis and the composite of cardiac death, nonfatal MI or urgent revascularization. The critical safety endpoints were total TIMI major bleeding and non-CABG related TIMI major bleeding.

At least one stent was deployed in 95% of cases (48% BMS and 47% DES), multivessel PCI was performed in 14% of patients, and in 55% of patients glycoprotein IIb/IIIa inhibitors were used.

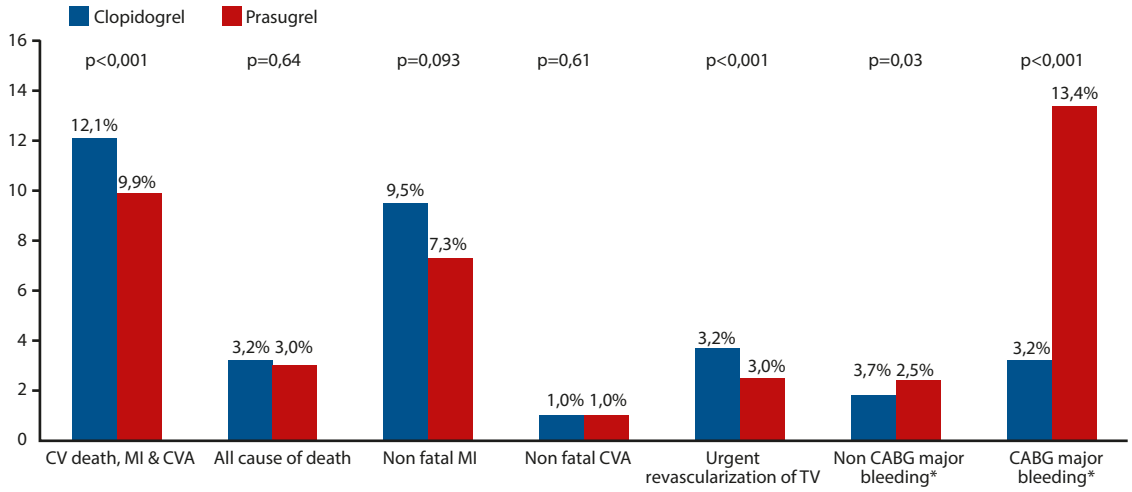

Figure 1. *TRITON-TIMI 38. Results (all ACS).* ****:*** *TIMI (Thrombolysis In Myocardial Infarction) criteria.* ***ACS:*** *acute coronary syndromes.* ***CV death:*** *cardiovascular death.* ***MI:*** *myocardial infarction.* ***CVA:*** *cerebrovascular accident.* ***TV:*** *target vessel.* ***CABG:*** *coronary artery by-pass graft. Modified from Wiviott SD, et al. N Engl J Med 2007;357:2001-15.*

Patients randomized to prasugrel had a significant reduction in the composite primary endpoint from 12.1% for clopidogrel to 9.9% (HR 0.81; 0.73-090; p<0.001) at an average follow-up of 15 months. The benefit was observed as early as day 3, representing the effect of the loading doses (HR 0.82; p=0.01), and persisted throughthe end of the study (HR 0.80; p=0.003) **(Figure 1).**

Of interest, the benefit of prasugrel tended to be more pronounced in diabetic patients (p<0.001) than in non-diabetic patients (p=0.02) and in patients with STEMI rather than with NSTEMI or unstable angina **(Figure 2)**. However, the interaction effects for these subgroups were not significant, and thus these observations should not be over-interpreted; i.e. the results were consistent in all 4 of these subgroups.

Other endpoints such as non-fatal MI, and stent thrombosis were also significantly reduced with prasugrel compared to clopidogrel. In patients with BMS, early stent thrombosis (within 30 days) was significantly reduced (p=0.0009) whereas with DES stent thrombosis was reduced both during the first 30 days (p=0.0001) and up to study completion (p=0.04) **(Figure3).**[15]

In contrast, TIMI major bleeding episodes either related or not to CABG were significantly more common in the prasugrel arm; bleeding risk was especially increased with prasugrel in patients undergoing CABG: 13.4% vs. 3.4% for prasugrel and clopidogrel, respectively (p=0.001). There was also a significant increase in life-threatening and fatal bleeding with prasugrel compared to clopidogrel. There was no difference between the 2 agents in all-cause or cardiovascular mortality.

Post-hoc analysis of the trial showed that prasugrel was harmful in patients with a history of stroke or TIA. For patients older than 75 years and in those weighing less than 60 kg the reduction in ischemic events was offset by an increase in bleeding. In all other subgroups prasugrel demonstrated a net clinical benefit compared to clopidogrel.

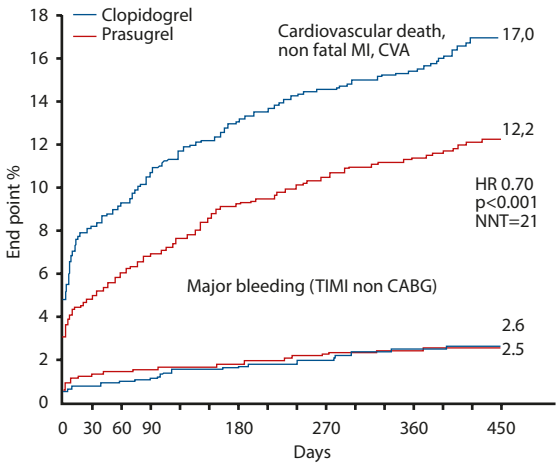

Figure 2. *Subgroup analysis from TRITON-TIMI 38. Diabetics.* ***MI:*** *myocardial infarction.* ***CVA:*** *cardiovascular accident.* ***TIMI:*** *thrombolysis in myocardial infarction.* ***CABG:*** *coronary artery by-pass grafting.* ***HR:*** *hazard ratio.* ***NNT:*** *number needed to treat. Modified from Antman EM, et al. American Heart Association Scientific Sessions 2007, Nov 4-7, Orlando, FL.*

In summary, substituting prasugrel for clopidogrel in patients with known coronary anatomy about to undergo PCI resulted in a significant net clinical benefit for most patients undergoing PCI in the setting of ACS. This agent should not be used in patients with prior stroke or TIA, and caution should be applied in elderly and low body weight patient to make sure that the risks are overweighed by the benefits. The benefits of prasugrel may be enhanced in some groups, such as those with STEMI, diabetes or with prior MI, although more study is required in this regard.

DISPERSE

Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST segment Elevation myocardial infarction (DISPERSE-2) study[7] was a phase 2 study comparing two doses of ti-

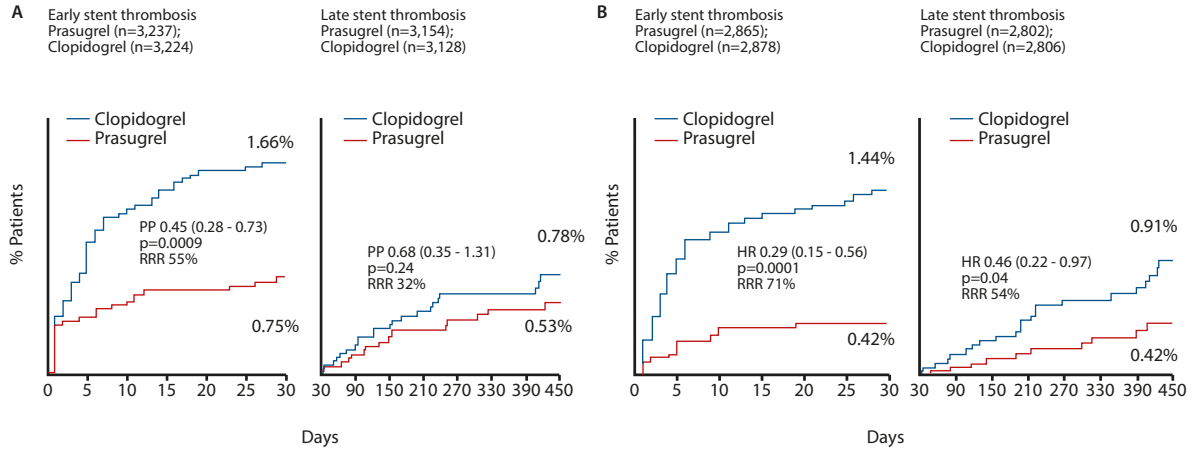

Figure 3. *Analysis of probable/definitive stent thrombosis at 30 days (ARC definition).* ***A.*** *BMS.* ***B.*** *DES.* ***ARC:*** *Academic Research Consortium.* ***HR:*** *hazard ratio.* ***RRR:*** *relative risk reduction. Modified from Wiviott SD et al. N Engl J Med 2007;357:2001-15.*

cagrelor with clopidogrel in 984 patients with ACS without ST-segment elevation. Patients with chest pain within 48 hours and were randomly allocated to ticagrelor 90 mg twice daily, 180 mg twice daily or clopidogrel 75 mg daily. Half the ticagrelor patients received a loading dose of 270 mg, while clopidogrel patients received a 300 mg loading dose. The primary endpoint was major and minor bleeding at 4 weeks. The composite endpoint occurred in 9.6%, 7.7% and 8.0% (p=NS) of the three groups, respectively. The composite 90-day clinical endpoint of death, MI or stroke was numerically lower in the high dose ticagrelor arm, while the rate of MI was significantly lower in this group (2.5% vs. 3.8% for lower dose ticagrelor and 5.6% for clopidogrel; p<0.05). There was a dose-response relationship with respect to dyspnea and ventricular pauses >2.5 seconds.

PLATO

PLATO (PLATelet inhibition and patient Outcomes) was a double-blind, randomized trial comparing ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) to clopidogrel (300-600 mg loading dose, 75 mg daily thereafter) in 18,624 patients admitted to the hospital with ACS, with or without ST-segment elevation. Randomization occurred prior to coronary angiography, and patients treated with an intended early conservative strategy were enrolled in the trial (~35%). Importantly, nearly of all patients had received clopidogrel prior to angiography.

Major exclusion criteria of the study were any contraindication to clopidogrel, fibrinolytic therapy within 24 hours before randomization, a need for concomitant oral anticoagulation therapy, an increased risk of bradycardia and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer.

Because of the trial design, only 64% of patients had PCI and fewer patients than in TRITON-TIMI 38 received DES (18%) or use of glycoprotein IIb/IIIa inhibitors. At 12 months, the primary endpoint, a composite of cardiovascular death, MI or stroke, occurred in 9.8% of patients receiving ticagrelor vs. 11.7% of those receiving clopidogrel (HR=0.84; 0.77-0.92; p<0.001). Other endpoints such as MI alone (5.8% vs. 6.9%; p=0.005), death from vascular causes (4.0% vs. 5.1%; p=0.001), death from any cause (4.5% vs. 5.9%; p<0.001) and definite stent thrombosis (p=0.009) were also similarly reduced by ticagrelor. There were no significant differences in the rates of total major bleeding (using the PLATO definition, including CABG as well as non-CABG bleeding) between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; p=0.43); ticagrelor was associated with a higher rate of major bleeding not related to CABG (4.5% vs. 3.8%; p=0.03), without a significant increase in intracranial bleeding (0.3% vs. 0.2, respectively) or fatal bleeding (0.2% in both groups) although intracranial fatal bleeding was higher with ticagrelor (p=0.02); PLATO major and minor bleeding (not related to CABG) were also more common with ticagrelor (8.7% vs. 7.0%, respectively).**(Figure 4).** The results were comparable in patients treated with an early invasive vs conservative strategy.

Of interest, ticagrelor was associated with a greater incidence of dyspnea than clopidogrel (p<0.001), although the rate of drug discontinuation was similar and very low (0.9% vs. 0.1%, respectively). Most of these episodes of dyspnea were mild and resolved within a few hours to days.

SUMMARY OF INDIVIDUAL AND POOLED DATA

It is clear that based on the results from the above mentioned pivotal trials,[6-8] both prasugrel and ticagrelor are superior to clopidogrel in reducing major adverse events in patients with ACS with or without ST-seg-

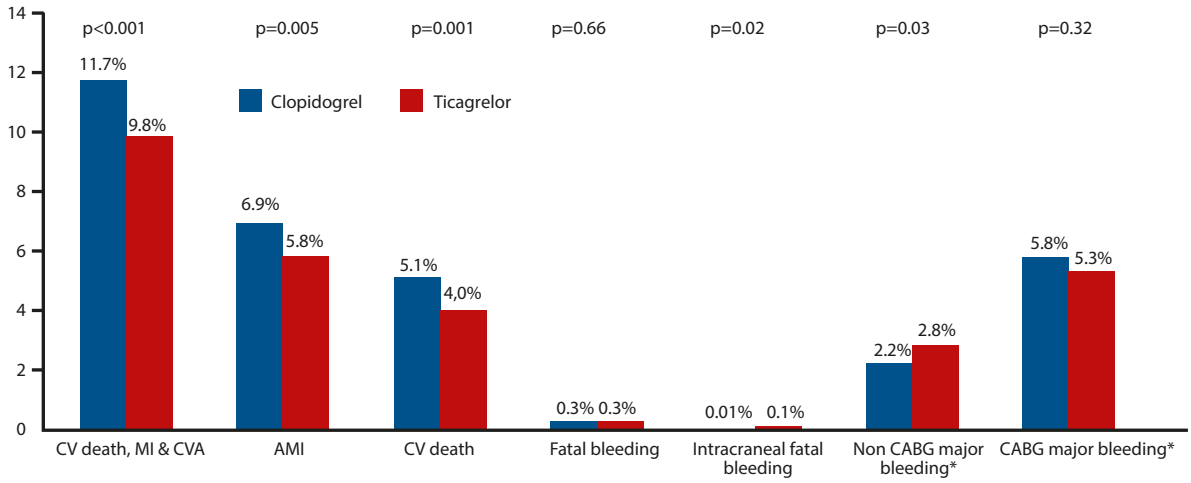

Figure 4. *PLATO results (all ACS).* ****:*** *TIMI (Thrombolysis In Myocardial Infarction) criteria.* ***ACS:*** *acute coronary syndromes.* ***CV death:*** *cardiovascular death.* ***AMI:*** *myocardial infarction.* ***CVA:*** *cerebrovascular accident.* ***CABG:*** *coronary artery by-pass graft. Modified from Wallentin L, et al. N Engl J Med 2009;361:1045-57.*

ment elevation. This benefit may be explained by their rapid onset of action and more pronounced and stable platelet inhibition.[16]

Recently, an adjusted indirect meta-analysis[17] from 32.893 patients included in DISPERSE 2, PLATO and TRITON-TIMI 38, showed that when compared with clopidogrel, prasugrel or ticagrelor as a class appeared superior with respect to the 12-months risk of composite death/MI/stroke (p<0.001), death (p=0.001), MI (p<0.001) or stent thrombosis (p<0.001) without any significant difference in non-fatal stroke or total major bleeding.

An indirect comparison between prasugrel and ticagrelor suggested **(Figure 5)** no significant differences in the risk of overall death (p=0.11), non-fatal MI (p=0.20), non-fatal stroke (p=0.49), or their composite endpoint (p=0.86). However, the risk of definite or probable stent thrombosis was lower with prasugrel (OR=0.64; 0.43±0.93; p=0.02), but at the expense of a higher risk of any major bleeding (p=0.007) and major bleeding associated with cardiac surgery (OR=4.30; 1.73±10.6; p=0.002). The two drugs were associated with similar risks of major bleeding unrelated to CABG (OR=1.06; 0.77±1.45; p=0.34), minor bleeding (p=0.65), and drug discontinuation (p=0.73).

However, this indirect comparison between prasugrel and ticagrelor should be interpreted with caution because of the significant trial design differences, such as the lack of medically managed patients and high use of glycoproteins IIb/IIIa inhibitors in TRITON-TIMI 38, and the inclusion of patients previously treated with clopidogrel in PLATO. Arguably the largest differences in the results between the pivotal TRITON-TIMI 38 and PLATO trials were the reductions in all-cause and cardiovascular mortality with ticagrelor in PLATO, and the increase in life threatening and fatal bleeding with prasugrel in TRITON-TIMI 38.

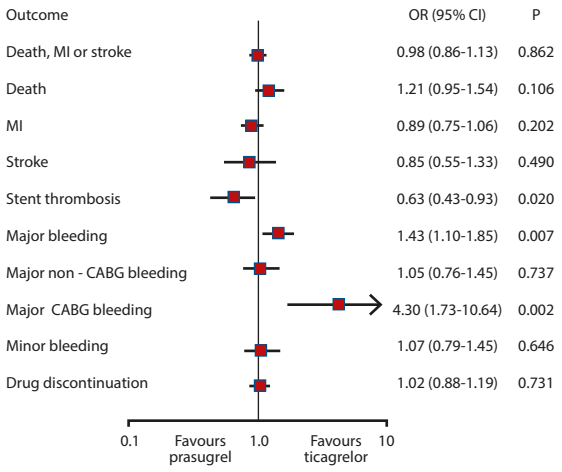

Figure 5. *Forest plots comparing prasugrel vs. ticagrelor for the risk of key clinical events.* ***CABG:*** *coronary artery bypass grafting.* ***CI:*** *confidence interval.* ***MI:*** *myocardial infarction.*

Whether these differences are due to differences in study design, patient selection, drug properties and timing of administration, or play of chance cannot be known for certain without an adequately powered controlled randomized trial.

CONCLUSIONS

The new platelet ADP P2Y12 receptor antagonists prasugrel and ticagrelor, while sharing some similarities, belong to different classes of drugs and have substantially different properties. They both exhibit significantly more potent platelet aggregation inhibition when compared to clopidogrel and offer an ~20% reduction in the clinically meaningful composite outcome of cardiovascular death, MI or stroke for up to 1 year of treatment. However, only ticagrelor was shown to reduce mortality. Both drugs cause more major bleeding not related to CABG than clo-

pidogrel, and prasugrel increased fatal and life threatening bleeding in the TRITON-TIMI 38 trial, although this adverse effect may be mitigated by excluding the highest risk patients for bleeding, especially those with prior stroke and TIA, and elderly and low body weight patients. Both drugs are preferred to clopidogrel in ACS in patients with an appropriate clinical profile.

RESUMEN

El uso de drogas antiplaquetarias en los sindromes coronarios agudos en pacientes coronarios ha sido de uso creciente en los ultimos diez años y ha reducido sensiblemente las complicaciones hospitalarias y en el seguimiento alejado, independientemente de si los pacientes se efectuaban o no un procedimiento de revascularización y también del tipo de intervención: angioplastia coronaria con *stent* convencional, *stent* medicamentoso y/o cirugía de revascularización miocárdica.
El uso de tienopiridinas de última generación ha contribuido a mejorar la evolución clínica de estos pacientes, a pesar de que presentan limitaciones en su uso clínico.
En esta revisión se analizan las ventajas/desventajas de estas drogas en pacientes con síndromes coronarios agudos, de acuerdo con los hallazgos recientes de estudios aleatorizados, mediante comparación de una droga de 1ra generación (clopidogrel) con las de 2da generación (prasugrel/ticagrelor) y estas dos últimas entre sí a pesar de no existir todavía estudios comparativos entre ambas.

Palabras clave: *tratamiento antiplaquetario, síndromes coronarios agudos, trombosis del stent, tienopiridinas, stents liberadores de drogas.*

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