

# Dual Antiplatelet Therapy Under Scrutiny: Real Benefit and Risk Subgroups

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## ABSTRACT

CURE, TRITON-TIMI 38 and PLATO studies have demonstrated clinical benefit with the use of dual antiplatelet therapy with clopidogrel, prasugrel or ticagrelor in addition to aspirin in patients with acute coronary syndrome, and have contributed to exponentially increase their prescription. The publication of new randomized trials with findings contrasting with the benefits obtained in these studies and of some opinion articles which have questioned the validity of the results, make it necessary, at least, to reassess the general indication and actual clinical benefit of these drugs. In this article we discuss the results of these three trials as well as the methodological objections that have been posed to them, focusing on the real clinical benefit of these drugs. The probability of preconception in certain subgroups is also discussed and a simple scheme that allows the selection of patients most likely to benefit from these treatments is postulated.

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## Key words

> Antiplatelet drugs - p2 and 12 receptor antagonists - Acute coronary syndrome

## Abbreviations

> ACEI	Angiotensin-converting enzyme inhibitors	CPK-MB	Creatine phosphokinase-MB fraction
ACS	Acute coronary syndrome	FDA	Food and Drug Administration
CPK	Creatine phosphokinase	t-PA	Tissue plasminogen activator

## INTRODUCTION

The decision of prescribing dual antiplatelet therapy in acute coronary syndromes is increasingly becoming more common despite persisting doubts concerning risks and benefits of the three commonly used drugs (clopidogrel, prasugrel and ticagrelor). Almost all scientific information on this subject is focused on three clinical trials: the CURE (clopidogrel vs. placebo in patients with ACS without ST-segment elevation, n = 12562), TRITON-TIMI 38 (prasugrel vs. clopidogrel in patients with ACS with and without ST-segment elevation undergoing percutaneous coronary intervention, n = 13608) and PLATO (ticagrelor vs. clopidogrel in patients with ACS with and without ST-segment elevation, n = 18624) studies. (1-3)

The three trials have reported a significant benefit

in the reduction of cardiovascular events, mainly acute myocardial infarction, at the expense of greater bleeding. Since the publication of the CURE study, use of this group of drugs has continuously increased. Publication of new randomized trials with findings contrasting the benefits obtained in the first studies and some opinion articles questioning the validity of their results, pose the need to, at least, reassess the generalized indication and real clinical benefit of these drugs. (4-7)

Overall, the benefits provided by these drugs are small. The main weakness of these trials is that their greatest impact has been the reduction in the incidence of myocardial infarction, many of which were periprocedural, and characterized according to controversial, permanently changing definitions. Conversely,

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hemorrhagic risks are more tangible. The clinical benefit of these drugs, as shown in the TRITON study, seems to focus on patients without certain comorbidities. To assess these hypotheses, we will first analyze the overall real benefit of dual antiplatelet therapy in ACS, and then the risk-benefit relationship in subgroups of patients. One of the major challenges is building a logic model that allows contrasting the magnitude of benefit with risk according to specific demographic aspects and clinical presentation.

#### **REAL BENEFIT OF DUAL ANTIPLATELET THERAPY AFTER AN ACUTE CORONARY SYNDROME**

The benefits of large clinical trials are increasingly less significant and on events of questionable relevance. Reduction of mortality is undeniably a very solid major benefit, but different authors have observed that when the impact is less than 1% absolute reduction, the amount has scarce community acceptance. The relevance of the decrease in the incidence of myocardial infarction is much more questionable due to its difficult definition. For example, authors of the FRISC II, RITA-3 and ICTUS studies observed in a joint analysis that periprocedural myocardial infarction was associated with an unexplained lower mortality than in patients without that complication. (8)

There is no uniform criterion to establish the clinical relevance of benefit or damage, nor for what we have termed as net benefit. We will analyze from a quantitative point of view the information about drug effects provided by these trials to get better insight of their clinical significance.

#### **Clopidogrel in the CURE study**

Placebo-controlled clopidogrel treatment was associated with 20% reduction in the primary end point (cardiovascular mortality, myocardial infarction, stroke: 9.3% vs. 11.4%; RR 0.80, 95% CI 0.72 to 0.90;  $p < 0.001$ ). A 38% increase in major bleeding (own definition of bleeding) (3.7% vs. 2.7%; RR 1.38, 95% CI 1.13 to 1.67;  $p < 0.001$ ) but not of fatal bleeding was observed. Balancing the 2.1% absolute reduction of cardiovascular events with the 1% increase in bleeding, the net clinical benefit was 1.1%, that is, 1.1 events per 100 patients.

The benefit of clopidogrel was mainly infarct reduction, without impact on overall or cardiovascular mortality, or stroke. Compared with placebo, clopidogrel reduced 1.5 non-fatal myocardial infarctions and increased 1 major bleeding and 3.5 major or minor bleedings per 100 patients.

From a critical approach, we could state that clopidogrel reduced myocardial infarctions that had no impact on mortality. Overall, mortality in patients with ACS entering the trials was very low, and studies lacked adequate power to assess it. The CURE study defined myocardial infarction as the presence of two or three of the following signs: ischemic pain, elevated marker levels (CPK, CPK-MB or troponin twice above

their normal upper level, or a threefold increase after a percutaneous coronary intervention) and associated electrocardiographic changes. In many cases, especially in the periprocedural period according to the criterion adopted, myocardial infarctions may have been of scarce clinical relevance.

#### **Prasugrel in the TRITON study**

The TRITON trial compared prasugrel with clopidogrel in ACS with and without ST segment elevation in patients referred for percutaneous coronary intervention. Prasugrel was associated with 2.2% absolute reduction in the primary end point (cardiovascular mortality, myocardial infarction, and stroke: 9.9% vs. 12.1%; HR 0.81, 95% CI 0.73 to 0.90;  $p < 0.001$ ) and 0.6% increase in major non-surgical bleeding (TIMI bleeding definition) (2.4% vs. 1.8%; HR 1.32, 95% CI 1.03 to 1.68;  $p < 0.03$ ) with a net clinical benefit of 1.6% in the overall population of patients. It should be pointed out that prasugrel was the only one of the three studied drugs associated to a significant increase in fatal bleeding (0.4% vs. 0.1%; HR 4.19, 95% CI 1.58 to 11.11;  $p < 0.002$ ).

In the TRITON study, benefit was also based on infarct reduction, whose definition was even more flexible than in the CURE study, in agreement with the new general definition of myocardial infarction that had to be reviewed later. (9) Myocardial infarction was defined as elevated CPK or troponin above the normal upper limit in addition to one of the following signs: ischemic pain or more than 1 mm ST-segment elevation. The criterion for post-coronary percutaneous intervention was a threefold increase above the upper normal limit. Again, a definition was made favoring the reduction of less significant clinical events, without impact on mortality. A substudy of the TRITON trial revealed that almost 50% of myocardial infarctions were periprocedural. (10) Compared to clopidogrel, prasugrel reduced 2 fatal myocardial infarctions and increased one major or minor bleeding per 100 patients. An interesting result arises from the detailed analysis of results: prasugrel reduction of cardiovascular events did not impact on mortality, but a subanalysis showed that major or minor bleeding was significantly associated with a sixfold increase in mortality (HR 5.8) within 40 days of the hemorrhagic episode. (11)

#### **Ticagrelor in the PLATO study**

The trial compared ticagrelor with clopidogrel. Ticagrelor was associated with 1.9% absolute decrease in the primary end point (cardiovascular mortality, myocardial infarction, stroke) (9.8% vs. 11.7%; HR 0.84, 95% CI 0.77 to 0.92;  $p < 0.001$ ) and 0.7% increase in major non-surgical bleeding (own bleeding definition) (4.5% vs. 3.8%; HR 1.19, 95% CI 1.02 to 1.38;  $p = 0.03$ ) with 1.3% clinical benefit (1.5% when total major bleeding is considered).

Compared with previous studies, ticagrelor evidenced two distinctive effects:

- a) Half of the events prevented were myocardial infarctions and the other half were deaths, while the other two trials only reduced myocardial infarction.
- b) The net clinical benefit was similar in the main subgroups.

In the PLATO study, definition of acute myocardial infarction was similar to that in the TRITON study. Again, myocardial infarctions with lower clinical involvement were considered. Despite a lower reduction of myocardial infarctions than in the CURE and TRITON studies, there was a significant decrease in overall and cardiovascular mortality, similar or slightly greater than reduction of myocardial infarction. Ticagrelor increased bleeding was lower than in the other studies. Compared with clopidogrel, ticagrelor reduced one non-fatal myocardial infarction and increased 0.5 major or minor bleeding per 100 patients. The lower increase in bleeding could favor mortality reduction despite its association with less infarct reduction than the other drugs. This clinical phenomenon, in which lower increase in bleeding is associated with lower mortality despite similar reduction in cardiovascular events, was also seen in the OASIS 5 study, comparing fondaparinux with heparin. (12)

Table 1 shows the necessary number of patients to be treated in the three trials.

The clinical benefit with the new drugs, which was evident in the studies, was overshadowed by an opinion article reporting the information submitted by the authors to the Food and Drug Administration (FDA) concerning the participation of event adjudication committees in the TRITON and PLATO trials. (6) The authors compared the number of myocardial

infarctions reported by the participating centers with the number of myocardial infarctions readjudicated by these committees which, theoretically, are blinded to treatment assigned to each patient. As shown in Table 2, after intervention of the TRITON study adjudication committee, the number of myocardial infarctions doubled with respect to those reported by the participating centers, so that the study passed from having a no-significant primary end point (negative study) to a significant reduction of both final end points.

Something more striking happened in the PLATO study. The committee, through readjudication of myocardial infarctions, added 45 events in the clopidogrel group without modifying the number of events in the ticagrelor group, and similarly to the TRITON study, it passed from a negative to a positive result (see Table 2). According to the authors of this article, the probability that this asymmetrical readjudication were by chance is 0.0000000000002. The study should have to be repeated 5 billion times to readjudicate again, by chance, 45 events in a single group.

These authors also question the mortality analysis of the PLATO study. Mortality reduction was not observed in the United States, but was observed in Eastern European countries, where follow-up experienced significant losses and monitoring was only performed by the industry. (6)

In summary, we are in the presence of drugs with a clinical benefit that might be quantified (which, as said, is debatable) as mild or moderate. This benefit is far behind that found with thrombolytics in myocardial infarction, or betablockers or ACEI in heart failure. Death decrease with ticagrelor in the PLATO study,

**Table 1.** Necessary number of treated patients to avoid an event or induce an adverse effect.

	CURE (Clopidogrel)	TRITON (Prasugrel)	PLATO (Ticagrelor)
Combined event	48	44	48
Myocardial infarction	48	46	91
Q type myocardial infarction	85	NR	NR
Cardiovascular death	250 (NS)	550 (NS)	71
Increased major or minor bleeding	29*	83#	200* (NS)
Increased major bleeding	100*	167#	167#
Avoid stent thrombosis	NR	77	167

Table description: With clopidogrel, for example, 48 patients should be treated to prevent a combined event or myocardial infarction, and a major bleeding will be induced per 100 treated patients. NR: not reported. NS: not significant, indicating those events in which the benefit or damage was not significant.

\* Major bleeding is surgical and non-surgical bleeding as defined in the study.

# Major bleeding is nonsurgical bleeding as defined by TIMI.

**Table 2.** Event readjudication in the TRITON and PLATO studies.

Study	Events reported by treating physicians		HR	p	Events readjudicated by the Study Committee		HR	p
	Study drug	Clopidogrel			Study drug	Clopidogrel		
TRITON-TIMI 38	226	298	0.76	0.08	475	620	0.76	< 0.001
PLATO	504	548	0.92	0.095	504	593	0.84	< 0.001

A twofold increase in the number of readjudicated events is seen in the TRITON study and a concentration of readjudicated events in the clopidogrel group is observed in the PLATO study.

even disregarding the mentioned issues, was reduced in absolute terms and similar to that obtained with the t-PA fibrinolytic compared with streptokinase in the GUSTO I study, (13) and even with this benefit it has not massively replaced streptokinase for the treatment of myocardial infarction, at least in our latitudes. The clinical benefit has emerged from studies with questionable points, as the definition of infarction and readjudication of events by the corresponding committees. Drugs were associated with increased bleeding that, in many cases, are more severe than the myocardial infarctions they reduce. Reduction of events in general, as will be seen in the following paragraphs, is focused on patients without comorbidities. We will see that a generalized indication has limitations, and the analysis of effects in subgroups is a feasible exploration to improve decision making criteria.

**Subgroup analysis of the risk-benefit relationship**

The risk-benefit relationship will be analyzed in each study population and in subgroups with comorbidities that may alter this relationship: female gender, advanced age, chronic renal failure and prior stroke. In the analysis “risk” and “benefit” are respectively considered as major bleeding and reduction of the study primary end point (cardiovascular death, myocardial infarction and stroke).

**Clonidogrel. Subgroup effects**

The net clinical benefit was not homogeneous. Women presented an increase of 0.4% net risk, i.e. no benefit since the increase in bleeding was greater than the reduction in the primary end point. All the benefit, 2.1 % in absolute values, corresponded to males. (14) (Table 3, Figure 1).

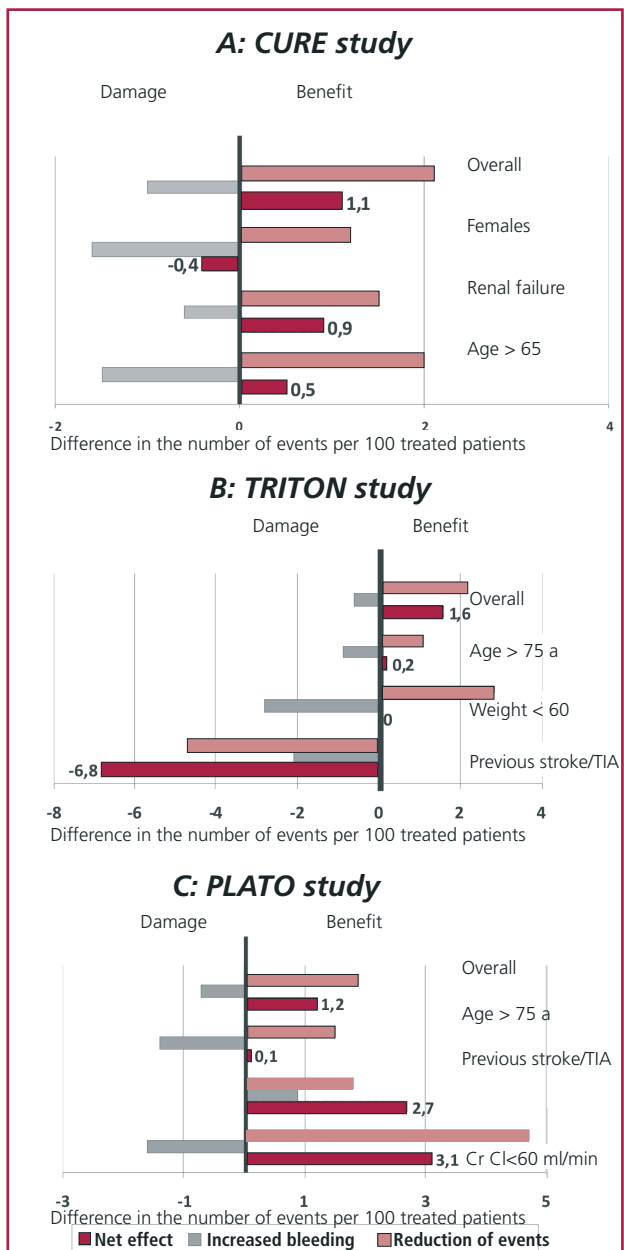
Patients with renal failure (clearance < 64 ml/h) in the placebo group had approximately twice as many cardiovascular events during follow-up than patients with normal renal function (clearance > 81 ml/h) (14.9 % vs. 8.8%). Event reduction with clopidogrel was in relative terms higher in the subgroup with normal renal function. (15) In patients with renal failure, clopidogrel was associated with a threefold increase of overall bleeding vs. the control group (1.7 % vs. 0.6 %) and the net clinical benefit was lower in patients with this condition (Table 3).

Advanced age was also associated with an increase in major cardiovascular events and major bleeding at follow up. Again, older patients had a lower clinical benefit than the young population (see Table 3 and Figure 1).

In conclusion, the benefit with clopidogrel was focused on patients without the mentioned comorbidities, as these were associated with lower net clinical benefit and, in some cases, injury.

**Prasugrel. Subgroup effects**

In a post- hoc analysis of the TRITON study, the authors identified three subgroups with increased risk



**Fig. 1.** Risk-benefit balance in the total population and in patients with comorbidities. Figure description: the net effect (or net clinical benefit) is the difference between the reduction of events (primary end point) and increased bleeding (major bleeding) per 100 treated patients. TIA: transient ischemic attack. Cr Cl: creatinine clearance.

of cardiovascular events and major bleeding, without net clinical benefit: age > 75, weight < 60 kg and history of stroke or transient ischemic attack. In Table 3, a phenomenon similar to that observed in the CURE study is repeated: the presence of these comorbidities markedly increased the risk of cardiovascular events and bleeding compared with patients not presenting them, regardless of the assigned treatment group. Net profit tended to be neutral or negative in all these subgroups.

**Table 3.** Net clinical benefit in subgroups

Trial	Subgroup	Primary end point					Major bleedings					Clinical benefit
		% T	% C	ARR	RR or HR	p	% T	% C	ARR	RR or HR	p	
CURE*	Total	9.3	11.4	2.1	0.80	< 0.001	3.7	2.7	-1	1.38	0.001	1.1
	Female	9.5	10.7	1.2	0.89	NS	4	2.4	-1.6	1.68	S	-0.4
	Male	9.1	11.9	2.8	0.76	S	3.5	2.8	-0.7	1.24	NS	2.1
	Age > 65	13.3	15.3	2	0.87	S	5.2	3.7	-1.5	1.4	NR	0.5
	Age < 65	5.4	7.6	2.2	0.71	S	2.4	1.8	-0.6	1.33	NR	1.6
	Cr Cl < 64	13.4	14.9	1.5	0.89	NS	2.3	1.7	-0.6	1.37	NS	0.9
	Cr Cl > 81	6.6	8.8	2.2	0.74	S	1.2	0.6	-0.6	2	S	1.6
TRITON- TIMI 38#	Total	9.9	12.1	2.2	0.81	< 0.001	2.4	1.8	-0.6	1.32	0.03	1.6
	Female	11	12.6	1.6	0.87	NS	NR	NR	-	-	-	-
	Male	9.5	11.9	2.4	0.80	S	NR	NR	-	-	-	-
	Age ≥ 75	17.2	18.3	1.1	0.94	NS	3.8	2.9	-0.9	1.31	0.2	0.2
	Age < 75	8.4	10.5	2.1	0.80	S	19	1.8	-0.1	1.05	NS	2
	Weight < 60	NR	NR	≈ 2.8	NR	NR	5.9	3.1	-2.8	NR	NR	≈ 0
	Weight ≥ 60	NR	NR	-	-	-	2	1.5	-0.5	1.33	NR	-
	Previous stroke/TIA	19.1	14.4	-4.7	1.37	0.15	5	2.9	-21	2.46	0.06	-6.8
	Without previous stroke/TIA	9.5	12	2.5	0.79	< 0.001	2.3	1.8	-0.5	1.26	0.08	2
	Age ≤ 75 or weight < 60 or previous stroke/TIA	16.1	16	-0.1	1.02	0.83	4.3	3.3	-1	1.42	0.10	-1.1
	Age < 75, weight ≤ 60 and without previous stroke/TIA	8.3	11	2.7	0.74	< 0.001	2	1.5	-0.5	1.24	0.17	2.2
PLATO‡	Total	9.8	11.7	1.9	0.84	< 0.001	4.5	3.8	-0.7	1.19	0.03	1.2
	Female	11.2	13.2	2	0.83	< 0.05	NR	NR	-	-	-	-
	Male	9.2	11.1	1.9	0.85	< 0.05	NR	NR	-	-	-	-
	Age ≥ 75	16.8	18.3	1.5	0.94	NS	8.3	6.9	-1.4	1.16	NS	0.1
	Age < 75	8.6	10.4	1.8	0.82	S	3.8	3.2	-0.6	1.22	0.05	1.2
	Previous Stroke/TIA	19	20.8	1.8	0.87	NS	5.9	6.8	0.9	0.88	NS	2.7
	Without previous stroke/TIA	9.2	11.1	1.9	0.84	< 0.05	4.4	3.6	-0.8	1.22	0.05	1.1
	Cr Cl < 60	17.3	22	4.7	0.77	S	8.5	6.9	-1.6	1.28	NS	3.1
	Cr Cl ≥ 60	7.9	8.9	1	0.90	NS	3.4	2.8	-0.6	1.21	NS	0.4

\* Major bleeding is surgical and non-surgical bleeding as defined in the study.

# Major bleeding is nonsurgical bleedings as defined by TIMI.

‡ Major bleeding is surgical and non-surgical bleedings as defined in the study.

T: Treatment group: clopidogrel in CURE, prasugrel in TRITON and ticagrelor in PLATO studies. C: Control group: placebo in the CURE study and clopidogrel in the TRITON and PLATO studies. ARR: Absolute risk reduction. HR: Hazard ratio. NR: not reported. NS: Not significant, with no reported p-value. RR: Relative risk. S: Significant with no reported p-value. Cr Cl: creatinine clearance. TIA: transient ischemic attack

Prasugrel showed greater benefit in patients without comorbidities that negatively influenced the net clinical benefit obtained with the drug. Even in the absence of comorbidities and excluding the three highest risk groups mentioned, prasugrel was associated with 24% increase in major bleeding.

In conclusion, the benefit with prasugrel compared

with clopidogrel, focused on patients without comorbidities (see Table 3 and Figure 1).

#### *Ticagrelor. Subgroup effects*

Although it differs from clopidogrel and prasugrel due to its benefit on mortality and lower interaction in the main subgroups (16-18) (see Table 3), some test

results indicated the need to reassess the genuine benefit of this drug, even in certain subgroups:

- Subgroup analysis showed that patients enrolled in the United States presented a marked, though not significant, increase in the primary end point associated with ticagrelor (HR 1.25, 95 % CI 0.93 to 1.67). Although it was not a very large subgroup, an editorial suggests that audits in this country were stricter and more independent from the sponsor and that, for these reasons, the data obtained in this country would be more reliable. (5) In another editorial, the main author of the PLATO study justified these results, creating a still ongoing debate. (19)
- The mechanism that led to a reduction in mortality is unclear. The degree of reduction in myocardial infarction with ticagrelor is less than with other drugs that did not reduce mortality. (5)
- The information submitted to the FDA for the approval of this study evidenced questionable handling of major events by the adjudication committee, as was previously pointed out. (6)

In conclusion, although ticagrelor had a beneficial effect on a more demanding end point than the other drugs, there are still methodological issues concerning the PLATO trial.

#### **Benefit in subgroups according to the clinical risk of the event**

The clinical risk of ACS is a variable that influences the benefit obtained with dual antiplatelet therapy. After the incorporation of the first 3000 patients, inclusion criteria were modified in the CURE study due to the low rate of events. Thereafter, only patients with elevated troponin or ST changes were enrolled, thus, confirming that the benefit focused on patients with risk indicators. (1) The TRITON and PLATO studies only randomized patients with elevated biomarkers or ST changes. In the PLATO study, patients with myocardial infarction with or without ST-segment elevation obtained more benefit than patients with unstable angina. This seems to confirm that benefit with dual antiplatelet therapy is only manifested when patients exceed a certain clinical risk threshold.

All the evidence described above raises some important concepts for decision-making:

- The aforementioned comorbidities are associated both with increased risk of cardiovascular events and higher risk of bleeding.
- The increased risk of cardiovascular events associated with these comorbidities did not result in greater clinical benefit with the addition of a second antiplatelet drug due to a greater increase in hemorrhagic events. While this seems to contradict an “axiom” of modern medicine indicating that higher risk patients benefit most with more aggressive treatment, it is in agreement with the observation of parallelism between cardiovascular risk and increased bleeding with aspirin in primary prevention. (20)

- The risk of cardiovascular events at follow-up depends on two factors: the clinical risk of the cardiovascular event, dependent on the size of the ischemic area, electrocardiographic changes, myocardial necrosis markers, etc., where greater clinical risk is associated with greater treatment benefit, and the “epidemiological” risk, dependent on the presence of comorbidities, where higher risk (or increased presence of comorbidities) is associated with lower treatment benefit and greater bleeding increase with consequent reduction in net clinical benefit.

#### **IF THE INDICATION SHOULD NOT BE GENERALIZED, HOW SHOULD PATIENTS BE SELECTED FOR TREATMENT?**

The decision must arise from a balance between the patient’s clinical risk associated to the coronary event, and the presence of comorbidities. Figure 2 postulates a tentative outline of clinical management. Although it is impossible to generate an algorithm that accurately discriminates which patients will benefit and which will not, this simple scheme can help decide on the individual patient. As already mentioned, the greatest benefit is focused on patients with higher clinical risk and absence of comorbidities (left of the figure). Those patients with lower clinical risk and more comorbidities were clearly the least benefitted and even damaged by the treatment (right of the figure). The middle part of Figure 2, which concentrates most patients, will probably afford a similar benefit for the three studies (CURE, TRITON and PLATO), and these patients are candidates for a second antiplatelet drug. To the left of the graph are the patients who will benefit most with the new drugs (prasugrel and ticagrelor) and longer treatment, and to the right are patients who have lower clinical risk and increased risk of bleeding who may be better candidates for clopidogrel with less prolonged treatments.

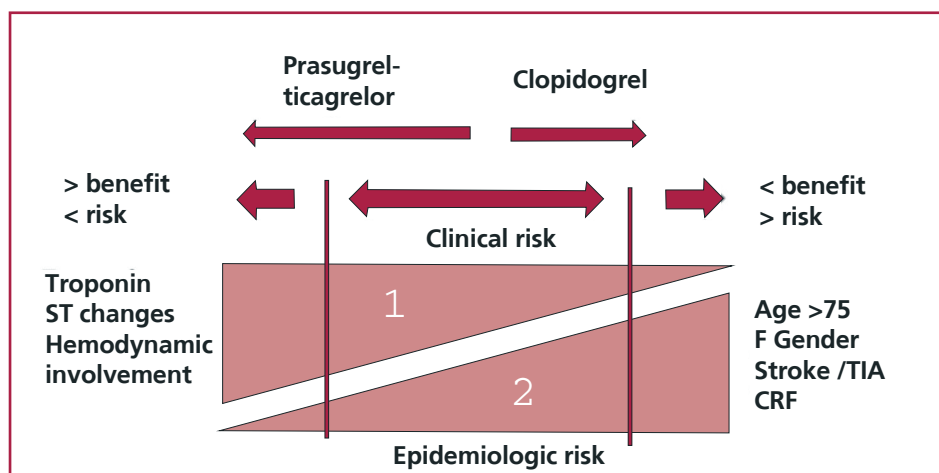
As examples, a 50-year-old man, without prior stroke or renal dysfunction, with coronary syndrome with ST-segment elevation and positive troponin gets the maximum benefit and very low bleeding risk with dual antiplatelet therapy. In the case of a 78-year-old woman with chronic renal failure, previous cerebrovascular disease, with coronary syndrome without high risk enzymatic and electrocardiographic markers, there is more possibility of damage than benefit with dual antiplatelet therapy.

Finally, in patients undergoing angioplasty, the type of stent graft should be considered as it will determine the need for dual antiplatelet therapy and length of treatment. When deciding which type of stent to implant the same comorbidities should obviously be considered, as the implantation of a drug-eluting stent will force us to indicate a dual antiplatelet therapy for a year, increasing the risk of bleeding during follow-up.

#### **CONCLUSIONS**

Adding a second antiplatelet drug to ACS treatment

**Fig. 2.** Antiplatelet therapy: use according to clinical risk (1) and epidemiological risk (2). TIA: Transient ischemic attack. F: Female. CRF: chronic renal failure.



has provided a mild to moderate clinical benefit, focused on patients without comorbidities. This benefit, mainly based on reduction of non-fatal myocardial infarction, is counterbalanced by an increase in bleeding. Considering the clinical risk of coronary events and comorbidities of the individual patient may help better decision making on whether or not to indicate a second antiplatelet drug, which drug and for how long.

## RESUMEN

### Doble antiagregación bajo la lupa: beneficio real y subgrupos de riesgo

Los estudios CURE, TRITON-TIMI 38 y PLATO han demostrado beneficio clínico con el uso de doble antiagregación plaquetaria con clopidogrel, prasugrel o ticagrelor adicionados a la aspirina en pacientes con síndrome coronario agudo y han contribuido a incrementar exponencialmente su prescripción. La publicación de nuevos ensayos aleatorizados con hallazgos que contrastaron con los beneficios obtenidos en estos estudios y de algunos artículos de opinión que han cuestionado la validez de los resultados hace necesario, al menos, replantear su indicación generalizada y el real beneficio clínico de estas drogas. En este artículo se discuten los resultados de estos tres ensayos, como también los cuestionamientos metodológicos que se les han efectuado, focalizando en el real beneficio clínico de estas drogas. Asimismo, considerando que en determinados subgrupos puede existir perjuicio, se discute este punto y se propone un esquema sencillo que permita seleccionar a los pacientes que más se benefician con estos tratamientos.

**Palabras clave** > Antiplaquetarios - Antagonistas del receptor p2y12 - Síndrome coronario agudo

**Conflicts of interest**  
None declared.

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