

TRITON-TIMI 38

The TRITON-TIMI 38 study compared a novel anti-platelet thienopyridine drug, prasugrel, with clopidogrel, the reference standard for this class, in moderate to high risk patients with NSTEMI (unstable angina or NSTEMI), undergoing coronary angiography (CORO) and PCI if needed.

Prasugrel is a pro-drug, just like clopidogrel, that is converted to active metabolite before binding to the P2Y₁₂ platelet receptor; prasugrel's action in inhibiting platelet aggregation is more rapid, intense and consistent than clopidogrel's, both at standard and higher dosages. This difference in effect is due to the greater efficacy of prasugrel in generating its active metabolite, which in vitro shows the same potency as clopidogrel.

The randomized, controlled, double blind study enrolled 13,608 patients with NSTEMI (within 72 hrs from first symptoms) or STEMI (within 12 hrs from first symptoms if treated with primary PCI or within 14 days if treated with drugs). The inclusion criteria were the standard diagnostic ones for NSTEMI and STEMI, with the addition, for NSTEMI patients, of a TIMI Risk Score ≥ 3 . The main exclusion criteria included treatment with thienopyridines within the last 5 days before enrollment, and treatment with fibrinolytics (within the last 24 hrs for fibrinolytic-specific and 48 hrs for those non-specific).

A particular feature of the study was that the randomization and the subsequent administration of the loading dose of the drug were carried out only after CORO and the decision to perform PCI (up to 1 hour after the intervention). In patients whose coronary anatomy was known and were scheduled for PCI, the loading dose could be given 24 hours prior to the procedure. Prasugrel was given as a loading dose of 60 mg followed by 10 mg/day as maintenance, while clopidogrel was given in doses of 300 mg and 75 mg, respectively.

The primary end point was a composite of the rate of cardiovascular death, non fatal myocardial infarction and non fatal stroke. Primary safety end points were TIMI major bleeding, TIMI major and minor bleeding and life-threatening bleeding. The sample needed was calculated at 13,000 (9,500 NSTEMI and 3,500 STEMI).

The study enrolled 13,608 patients (10,074 NSTEMI and 3,534 STEMI) with a mean therapy duration of 14.5 months. Ninety-nine percent of patients underwent PCI, 94% received at least one stent and 47% a drug-eluting stent (DES).

Table 1 shows the results in term of efficacy of the study.

Table 1

	Prasugrel (%)	Clopidogrel (%)	HR	95% CI
Primary end point	9.9	12.1	0.81	0.73 - 0.90
Cardiovascular death	2.1	2.4	0.89	0.70 - 1.12
Non fatal MI	7.3	9.5	0.76	0.67 - 0.85
Non fatal stroke	1.0	1.0	1.02	0.71 - 1.45
Urgent revascularization	2.5	3.7	0.66	0.54 – 0.81
Stent thrombosis	1.1	2.4	0.48	0.36 – 0.64

There was a statistically significant decrease in the primary clinical end point in the prasugrel group, due mainly to the reduction in non fatal myocardial infarction; urgent target vessel revascularization (uTVR) was also reduced with prasugrel, while the incidence of stent thrombosis was practically cut in half.

The study safety main end points are shown in table 2.

Table 2

Haemorrhages	Prasugrel (%)	Clopidogrel (%)	HR	95 % CI
TIMI major haemorrhages non CABG related*	2.4	1.8	1.32	1.03-1.68
Life-threatening haemorrhages	1.4	0.9	1.52	1.08-2.13
Fatal haemorrhages	0.4	0.1	4.19	1.58-11.11
TIMI major haemorrhages CABG related	13.4	3.2	4.73	1.90-11.82

* safety primary end point

It is obvious that prasugrel's greater efficacy as compared to clopidogrel in regard to IPA is clearly related to a greater incidence of major bleedings, most marked in the fatal ones and those related to CABG procedures. This result had not been anticipated, given the outcomes of the phase 2 JUMBO-TIMI 26, where the comparison was between 3 different prasugrel doses and the standard clopidogrel dosage; the primary clinical end point – significant bleeding non CABG related (TIMI major + minor) at 30 days – was not significantly different in prasugrel versus clopidogrel (1.7% vs 1.2%).

As in many other studies, the investigators had taken in consideration the net clinical benefit, that is, the combination of the primary efficacy (but with total instead of just cardiovascular mortality) and

safety end points (TIMI major bleedings non CABG related). Treatment with prasugrel had a worse outcome than with clopidogrel in only one patient subgroup: in patients with previous cerebro-vascular accident (CVA), the net clinical benefit had a HR of 1.54 (95% CI 1.02-2.32). Two other patient subgroups did not show a net clinical benefit with prasugrel: patients ≥ 75 years (HR 0.99, 95% CI 0.81-1.21) and those weighing < 60 kg (HR 1.03, 95% CI 0.69-1.53). Patients without these three risk factors had a clear net clinical benefit from prasugrel (HR 0.80, 95% CI 0.71-0.89), particularly those with diabetes (12.2 vs 17%, HR 0.70), who also did not show a significant increase in major bleedings. The efficacy primary end point was already evident at 30 days (HR 0.77, 95% CI 0.67-0.88); the NNT (number needed to treat = the number of patients needed to treat for 15 months to avoid one efficacy primary end point) was 46 and the NNH (number needed to harm = number of patients needed to treat to cause a TIMI major bleeding) was 167. Nevertheless, the increase in major haemorrhages must be carefully evaluated in clinical settings, given the association between bleeding events and unfavourable outcomes, including death and the negative prognostic factors inherent to transfusion. Prasugrel's favourable results are probably due the higher and more consistent levels of its active metabolite, as compared to clopidogrel, to a greater inhibition of platelet aggregation, a lower inter-patient variability and a lower percentage of patients, who were poor responders or even resistant to the drug. However, it must be said that the comparison between prasugrel and clopidogrel, both administered after the coronarography and before PCI in the TRITON study, was not fair toward clopidogrel, whose IPA action takes 6 hours to equal the prasugrel effect at 30 minutes. On the other hand, if we consider the events occurring after the 3rd day, when both drugs have reached their steady state, the difference in term of efficacy persists for prasugrel, leading to the hypothesis of a clinical benefit due to greater IPA in the long run.

Another controversial point relates to the clopidogrel loading dose: even if the recommended dose is 300 mg, it is well known that many cardiologists utilize 600 mg to reach the optimal IPA faster. However, in the PRINCIPLE-TIMI 44 study, prasugrel demonstrated greater efficacy in inhibiting platelet aggregation, both in the short and in the long run, when compared to a clopidogrel dose twice the normal (600 mg loading dose and 150 mg maintenance). Table 3 shows the results of the PRINCIPLE study.

Table 3

	IPA with 20 μ mol ADP (%)	
time	prasugrel	clopidogrel
6 hours	74.8 \pm 13 *	31.8 \pm 21.2
maintenance	61.3 \pm 17.8 *	46.1 \pm 21.3

* $p < 0.0001$

In conclusion, the TRITON-TIMI 38 has confirmed the hypothesis that greater levels of IPA are associated to a greater reduction in ischaemic clinical events in NSTEMI patients undergoing PCI. This favourable effect, however, is associated with an increase in TIMI major haemorrhages; on the other hand, the net clinical benefit, which takes into account both the efficacy and the risk total profile, weighs in favor of prasugrel. Therefore, this last seems to be indicated in patients who have an elevated probability of ischaemic events, but lower in terms of bleeding, whereas the patients with a lower risk for ischaemic events but higher for bleeding complications can continue to benefit from clopidogrel.

References

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