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DOI: [10.1159/000138337](https://doi.org/10.1159/000138337)**Prasugrel in the Poststroke Cohort of the TRITON Trial: The Clear and Present Danger**

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The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) was an important phase 3, randomized study. The trial assessed head-to-head the efficacy and safety of the experimental thienopyridine prasugrel versus standard care with another P2Y₁₂ platelet inhibitor, clopi-

dogrel [1]. Patients with moderate- to high-risk acute coronary syndromes with the defined coronary anatomy and planned stent placement were randomized to prasugrel or clopidogrel for 6–15 months. The primary endpoint was the time to the first event of cardiovascular death, myocardial infarction or stroke, and occurred in 12.1% of patients treated with clopidogrel and 9.9% of patients randomized to prasugrel (for details, see table 1). This difference favoring prasugrel was predominantly attributed to the early decrease in ischemic episodes during the first 3 days after intervention [2]. Analysis of the individual components of the combined efficacy endpoint suggests that the difference between the two treatment arms was exclusively driven by the rates of non-fatal myocardial infarction (475 vs. 620 events) favoring prasugrel. In contrast, mortality was identical (prasugrel – 154; clopidogrel – 155), when for each cardiovascular death prevented by prasugrel versus clopidogrel (133/150), one additional fatal bleeding event (21/5) occurred in the prasugrel group [3]. There was no difference in stroke prevention (prasugrel – 61; clopidogrel – 60). The excess bleeding risk after prasugrel is not surprising because the antiplatelet potency of the prasugrel loading and maintenance dose chosen for TRITON was about 2.5 times more potent than the clopidogrel regimen [4].

Exploratory post hoc analyses of the TRITON data set revealed a lack of benefit, and even harm, for patients with previous ischemic stroke and transient ischemic attack (TIA) who received prasugrel compared to clopidogrel. Considering that hemorrhagic stroke was one of the exclusion criteria, there were 518 patients in TRITON with the history of ischemic stroke or TIA, which were equally distributed between the prasugrel (n = 262) and clopidogrel (n = 256) cohorts. The outcome and safety measured in patients with previous cerebrovascular ischemic events are summarized in table 2.

Table 1. Summary of the TRITON trial

Study design	Prospective, multicenter, randomized, double-blind, parallel-group
Study population	13,606 patients with moderate- to high-risk acute coronary syndromes including 3,534 patients with ST-elevated acute myocardial infarction, all with the defined coronary anatomy
Study drugs	Prasugrel 60 mg loading dose followed by 10 mg daily or clopidogrel 300 mg loading dose followed by 75 mg daily
Primary endpoint	First occurrence of myocardial infarction, stroke or death from cardiovascular causes
Key safety endpoint	Non-CABG TIMI major bleeding
Treatment duration	Treatment and follow-up period: 5–16 months
Summary of results	The rate of the primary efficacy endpoint was 12.1% with clopidogrel versus 9.9% with prasugrel; the rate of the prespecified safety endpoint was 1.8% with clopidogrel versus 2.4% with prasugrel
Final analysis	Results of TRITON suggest the benefit of prasugrel over clopidogrel for mostly early reduction of ischemic events at the cost of higher bleeding risks including life-threatening and fatal events; overall, mortality and strokes were evenly distributed between treatment arms

Table 2. Clinical outcomes and safety endpoints (%) in TRITON among patients with previous stroke or TIA

Thienopyridine	n	Efficacy endpoint	Safety endpoint	Combined endpoint
Prasugrel	262	19.1	5.0	23
Clopidogrel	256	14.4	2.9	16
Δ	518	24.6	42.0	30.4

n = Number of patients; efficacy endpoint = combination of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke; safety endpoint = non-CABG-related TIMI major bleeding; combined endpoint = sum of efficacy and safety endpoints; Δ = difference in the endpoints between treatment arms.

Analysis of the evidence presented in table 2 reveals the lack of efficacy and safety concerns for prasugrel when compared to clopidogrel in the subgroup of patients with the history of stroke or TIA. However, it must be pointed out that this subgroup of patients represents only a small fraction (3.8%) of the entire TRITON study population.

It is interesting to determine why patients with a history of stroke or TIA would experience more serious bleeding events overall. It is doubtful that many or most of these events were cerebral hemorrhages, since these occurred in only 36 patients overall (event rate of only 0.3% in each treatment group), and the total number of TIMI major bleeds in the stroke/TIA subgroup was only 20. Other large registries such as REACH have also shown that a history of stroke or TIA is associated with an increased risk of major systemic bleeding events [5].

Another subgroup of interest is the population who are elderly (>75 years), of low body weight (<60 kg) or with a history of stroke/TIA. This large subgroup (>1,300 patients) failed to show efficacy for prasugrel versus clopidogrel and had a trend for more TIMI major bleeding ($p = 0.10$). While it is true that subgroup analyses are prone to various systematic errors that often lead to false or misleading conclusions, they do provide potential insights when trying to understand differential effects of a treatment.

As further analyses are performed on the TRITON data set, it will be of great interest to see how measures of platelet function (or inhibition of platelet activity) correlate with both efficacy endpoints and major bleeding events. If such correlations are detected in TRITON, it might provide support for adopting a patient-specific approach for individualized dosing of some antiplatelet therapies. This triaging has the potential to significantly enhance both the efficacy and safety of such therapies. Such an approach might be of particular interest when using potent agents such as prasugrel, particularly when combined with aspirin in a high-risk population. Measurement of the antiplatelet effects of prasugrel in a high-risk population (such as those with a prior history of stroke/TIA) might also provide important insights into why such patients had a worsened efficacy/safety profile.

Despite the fact that TRITON was not a specific poststroke/TIA trial, only a small percentage of patients had a history of cerebrovascular disease and the clinical utility of prasugrel after very recent stroke is entirely unknown, the results of the study are very important for clinicians, which adds value to the increasing body of evidence suggesting that a more delicate strategy with modest platelet inhibition, especially in a chronic long-term setting, represents a substantial advantage over aggressive antiplatelet regimens in the majority of patients after stroke or TIA. Building the supportive evidence derived from MATCH [6] to CHARISMA [7], TRITON data confirm that the concept 'the more the better' is not suitable for the antiplatelet strategies in the majority of patients with vascular disease. With this respect, the results of the PROfESS trial [8], which are expected soon, will be critical for the comprehension of the better ways to prevent second strokes and maintain the optimal balance between efficacy and safety of platelet inhibitors to protect such high-risk patients from repeated vascular events.

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