INTRODUCTION
Potent and consistent P2Y12 receptor inhibition is associated with reduced risk of atherothrombotic events in patients presenting with acute coronary syndromes (ACS), but with inevitable increased risk of bleeding as demonstrated in TRITON1 and PLATO2 trials – a finding that is especially pertinent to the treatment of medically managed NSTE ACS patients, who typical have a greater burden of comorbidities that predispose to bleeding.

Given the significant proportion of non-ST elevation myocardial infarction (NSTE) ACS patients managed medically worldwide and the need to mitigate both ischemic and bleeding risks in this vulnerable, high-risk population, novel clinical trials are needed.

TRIOLOGY TRIAL
The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial was published in the New England Journal of Medicine in October 2012.3 The study was sponsored by Eli Lilly and Company, Indianapolis, IN, and Daiichi Sankyo Co, Ltd, Tokyo, Japan.

TRILOGY ACS is randomized, double-blind, double-dummy, active control, event-driven trial, that was conducted to evaluate whether aspirin plus prasugrel is superior to aspirin plus clopidogrel for long-term therapy in patients with unstable angina (UA) or NSTEMI who are treated medically without revascularization.

The study enrolled 9326 patients with ACS and a final medical management without revascularization within 10 days after the index event. A total of 7243 patients were younger than 75 years of age (77.7%), where as 2083 patients were 75 years of age or older (22.3%). Angiography was not required for enrollment, but if such a procedure was planned, it had to be performed before randomization. Major exclusion criteria included a history of transient ischemic attack or stroke, PCI or CABG within the previous 30 days, renal failure requiring dialysis, and concomitant treatment with an oral anticoagulant.

Study treatment was administered on a background of daily low-dose aspirin (between 75 and 100 mg). Subjects not on a stable regimen of clopidogrel (stable regimen of clopidogrel was defined as having received a ≥ 300-mg loading dose (LD) within 72 h of the index event followed by 75 mg daily OR having received 75 mg daily for ≥ 5 days before the index event and daily thereafter) and randomized within 72 h of the index event initiated study treatment with a LD; otherwise, the first study drug dose administered was either a maintenance dose (MD) of clopidogrel (75 mg) or prasugrel (5 or 10 mg). Prasugrel LD was 30-mg and MD was 10-mg, subjects aged ≥ 75 years or b 60 kg in weight received 5-mg prasugrel MD.

The median duration of exposure to a study drug was 14.8 months (inter-quartile range, 8.2 to 23.6). The median duration of follow-up for all patients in the trial was 17.1 months (interquartile range, 10.4 to 24.4).

RESULTS
Regarding efficacy, at 30 months, there was no significant between group difference in the rate of the primary end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal...
stroke) among the primary cohort of patients under the age of 75 years. At a median follow-up of 17 months, the primary end point occurred in 13.9% of the prasugrel group and 16.0% of the clopidogrel group (hazard ratio in the prasugrel group, 0.91; 95% confidence interval [CI], 0.79 to 1.05; \( p = 0.21 \)).

Among patients under the age of 75 years, the Kaplan–Meier curves for the primary end point overlapped until approximately 12 months, after which the curves diverged. Similar observations were made for each of the secondary end points (death from cardiovascular causes, all myocardial infarctions, and strokes). The difference in treatment effect between the first 12 months and subsequent months was tested in a post hoc analysis using a time-dependent Cox proportional-hazards model; in this analysis, the time period and the interaction between the time period and treatment were time dependent factors. The frequency of the primary end point through 12 months was similar among study groups, with a weak trend toward a reduced risk in the prasugrel group after 12 months (\( p = 0.07 \) for interaction). So as superiority was not established in this cohort (age < 75), the prespecified testing strategy did not direct further superiority testing, but efficacy and safety results for the overall cohort (all ages) were presented in the result of the study for completeness, with no difference between the two groups.

Regarding safety, at 30 months, the key bleeding end points of non–CABG-related severe or life-threatening events (according to GUSTO criteria)\(^4\) and major bleeding (according to TIMI criteria)\(^5\) occurred with similar frequency among patients under the age of 75 years in the two study groups. TIMI life-threatening, fatal, or intracranial bleeding occurred infrequently, and rates were balanced in the two study groups, both in patients under the age of 75 years and in the overall population. Among the younger patients, rates of non–CABG-related severe or life-threatening or moderate bleeding (GUSTO criteria) and major or minor bleeding (TIMI criteria) were higher in the prasugrel group, and the authors considered this observation as an evidence for more intense platelet inhibition with prasugrel. The frequency of new, nonbenign neoplasms in the overall treated population did not differ significantly between the prasugrel group and the clopidogrel group (1.9% vs. 1.8%, \( p = 0.79 \)).

**WHAT HAVE WE LEARNED FROM TRIOLOGY?**

TRILOGY ACS trial was addressing an important cohort which is always missing from large randomized trials focusing in ACS; those are the patients who present with UA or NSTEMI and the plan of management is medical treatment without revascularization, as those patients present high risk group that needs specific management plan, and close follow up.

Unlike the results of TRITON trial (ACS patients undergoing PCI who received prasugrel had fewer ischemic events compared with patients receiving clopidogrel, including fewer spontaneous MI occurring \( > 30 \) days after randomization),\(^1,6\) in TRILOGY ACS there was no reduction in the rate of major cardiovascular events in patients younger than 75 years old with UA or NSTEMI who did not undergo revascularization and were kept on prolonged treatment with prasugrel, as compared with those who were kept on clopidogrel.

In TRITON trial the risk of bleeding events was higher in patients receiving prasugrel compared with clopidogrel. However in TRILOGY, there was no difference between both groups regarding major, severe bleeding and the frequency of new nonbenign neoplasms.

Finally an important observation was noticed from the results of the trial; an unexpected time-dependent divergence of treatment effect was observed after 12 months of therapy. When evaluated before and after 12 months, the interaction of the treatment effect of prasugrel for the time to the first event was weak, but the late separation of the event curves was consistent for primary and component end points, an observation that was also apparent in the analysis of multiple recurrent ischemic events. The reasons for this finding remain uncertain, since there have been few studies focusing on high-risk patients who did not undergo revascularization. Consequently, it is possible that a median follow-up period of 17 months was not long enough to explore the divergence of ischemic events in patients receiving medical therapy alone.

Still there are some inquiries that are not answered by the study: 1) Prasugrel LD in TRILOGY ACS trial was 30 mg, does a higher LD of prasugrel (60 mg as used in TRITON trial)\(^1\) would be more beneficial in patients with planned medical treatment without revascularization. 2) The only evidence of intense platelet inhibition was the higher rate of moderate bleeding in the prasugrel group, would platelet inhibition tests for all patients be more helpful to identify the effect of the drug compared to clopidogrel. 3) Patients on anticoagulation or those on regular dialysis were not included in the study,
is it safe to use prasugrel instead of clopidogrel for those patients (for long term treatment) regarding the incidence of major or life threatening bleeding.

REFERENCES

[1] Morrow DA, Wiviott SD, White HD, Nicolau JC, Bramucci E, Murphy SA, Bonaca MP, Ruff CT, Scirica BM, McCabe CH, Antman EM, Braunwald E. Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction. *Circulation*. 2009;119(21):2758–2764.

[2] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045–1057.

[3] Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruislylo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng CD, Merkely B, Gasparovic V, Corbalan R, Cinteza M, McLendon RC, Winters KJ, Brown EB, Lokhnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM, TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*. 2012;367(14):1297–1309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22920930. Accessed October 28, 2012.

[4] Anon. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329(10):673–682.

[5] Bovill EG, Terrin ML, Stump DC, Berke AD, Frederick M, Collen D, Fett F, Gore JM, Hillis LD, Lambrew CT, Leiboff R, Mann KG, Marks JE, Pratt CM, Sharkey SW, Sopko G, Tracy RP, Chesebro JH. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the TIMI, Phase II Trial. *Ann Intern Med*. 1991;115(4):256–265.

[6] Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001–2015.