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R2 Block 9

Citation: Montalescot, et al. (2013) Pretreatment with Prasugrel in Non-ST –Segment Elevation Acute Coronary Syndromes New England Journal of Medicine

Clinical Question: In patients who are having an NSTEMI, will administering prasugrel, a rapid onset P2Y12 platelet inhibitor, lower the morbidity and mortality in patients who will undergo PCI as compared to placebo.

Introduction: In theory clopidogrel (plavix) doesn't become clinically active until several hrs after administration. In patients that undergo PCI, two randomized studies suggested that pretreatment with plavix could reduce the rate of ischemic events at a cost of increasing the rate of major bleeding. The American College of Cardiology and American Heart Association give a class I recommendation for pretreatment in patients with an NSTEMI acute coronary syndrome. Could treatment with prasugrel add benefit due to its rapid onset of action? The current trial or the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention (ACCOAST) trial, compares systematic pretreatment with prasugrel at the time of diagnosis of NSTEMI vs placebo. Pretreatment was restricted to a maximum of 48 hrs prior to coronary angiography.

Methods:

Study: ACCOAST trial was a phase 3 randomized double-blind event driven study. Conducted at 171 centers in 19 countries. N of 4,046, randomized to the no-pretreatment vs pretreatment cohort. The pretreatment group received 30 mg loading dose of prasugrel before coronary angiography and an additional 30 mg of prasugrel at the time of PCI. Control group received placebo before coronary angiography and the approved 60mg-loading dose of prasugrel after angiography only in patient undergoing PCI. If the results of the angiography showed the patient needed a CABG or medical therapy the second loading dose was not received by the patients. The placebo or standard of care was defined as aspirin but not limited to just that medication.

Endpoints: Defined as first occurrence of death for CV causes, MI, stroke, urgent revascularization or the need for rescue therapy with glycoprotein IIb/IIIa inhibitors through 7 days after randomization. Major and minor bleeding per the TIMI (thrombolysis in myocardial infarction) criteria was also evaluated.

Stat Analysis: Primary efficacy analyses for efficacy and safety end point were performed through day 7 and through day 30 after randomization. Rates expressed as Kaplan-Meier estimates: hazard-ratio estimates and 95% confidence intervals obtained from a Cox proportional-hazards model, 2-sided P values calculated.

Results/Conclusion: From Dec 2009 through Nov 2012 4,033 patients were split, 2,037 into the pretreatment with prasugrel and 1,996 with no pretreatment with prasugrel. PCI performed in 68.7% of patients at a median time of 4.3 hrs after the initial loading dose. Through day 7, the strategy of chosen CABG was 6.2% and medical management 25.1%. It was found that there was no significant between-group difference in any of the components of the primary endpoint, in total mortality, rate of stent thrombosis, or in prespecified composite secondary end points at day 7 or 30. Pretreatment with prasugrel was not associated with significant decrease in the rate of ischemic events while awaiting angiography. In the cohort who underwent PCI there was no difference between the two groups in respect to the primary end point. There was no benefit of pretreatment in the subgroups of the global population or PCI cohort. However, per the TIMI criteria, through day 7 the loading dose of prasugrel was associated with a significantly higher bleeding in the pretreatment vs control group. Increase by a factor of 6 in life threatening bleeding not related to CABG and increase by a factor of 3 in all major bleeding. No change in excess or fatal bleeding or ICH with pretreatment.

Discussion:

While pretreatment with ASA and P2Y12 antagonist has been class I recommendation and common practice in treatment in patients with NSTEMI acute coronary syndrome, we found that pretreatment with prasugrel did not reduce the rate of ischemic events in the overall population or cohort who underwent PCI, CABG group or medical treatment group. There was significantly more major and life-threatening bleeding not related to CABG in the pretreatment group when compared to the control. The rates of stent thrombosis and death were equally low in both groups. The benefit of adding plavix to aspirin was shown in the CURE trial in which conservative medical management strategy was evaluated. However, this subsequent trial showed that adding a stronger anti-platelet agent like prasugrel did not reduce the incidence of thrombotic

complications in either the overall population or among patients undergoing PCI. Hence if we extrapolate this data to the use of prasugrel in the ED for NSTEMI, this did not reduce the rate of major ischemic events up to day 30 but increased the rate of major bleeding complications. In a recent meta-analysis of more than 37,000 patients who underwent PCI and were pretreated with plavix, there was no survival benefit when compared to placebo alone (ASA). In reality, all the data suggests that there is no increase in survival or improvement of ischemic endpoints when using P2Y12 antagonists of any type as a pretreatment strategy. However, I would defer to the cardiologist for their opinion.
