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Question: In Patients with ACS is there anything that we can give in the ER that is better than our current therapies?

Introduction: Current Guidelines state in patients in ACS with or without ST segment elevation current clinical practice guidelines recommend dual antiplatelet treatment with aspirin and clopidogrel. The efficacy of clopidogrel is compounded by the variable transformation of the drug into its active metabolite with variable platelet inhibition. Prasugrel, another type of drug, results in a lower risk of MI and stent thrombosis but is associated with higher major risk of bleeding in ACS patients who undergo PCI. Ticagrelor or Brilinta as it is known, is a reversible and faster acting ADP receptor inhibitor and hence theoretically superior to Plavix. The following is known as the PLATO trial (Study of Platelet Inhibition and Patient Outcomes) to determine whether Brilinta is indeed superior to Clopidorgrel (Plavix) in ACS patients.

Methods: PLATO was a multicenter double blind trial. Eligibility criteria included those with ACS with or without ST segment elevation and at least 2 of the three criteria met: ST segment changes on EKG, positive biomarker; or one of several risk factors age>60, previous MI or CABG, TIA, Carotid stenosis of >50%, pervious stroke, DM, PVD, CKD. For patients with ST segment elevation 2 inclusion criteria had to be met, persistent ST segment elevation in 2 contiguous leads, new LBBB, and intention to perform primary PCI. Patients were randomly assigned to receive Plavix or Brilinta administered in a double blind, double dummy fashion. Brilinta was given in a loading dose of 180 mg followed by 90 mg BID, Plavix was a 300 mg loading dose followed by 75 mg daily. Patients undergoing PCI after randomization received an additional dose of drug at the time of PCI, either 300 mg of Plavix or 90 mg of Brilinta in a blind fashion. In patients undergoing a CABG, study drug was withheld in the Plavix group for 5 days and the Brilinta group for 24-72 hrs. Outpatient visits were scheduled at 1, 3, 6, 9 and 12 months. Death from vascular causes was defined as death from cardiovascular causes or cerebrovascular causes and any death without another known cause. Myocardial infarction was defined in accordance with the universal definition. Evaluation for stent thrombosis was performed according to the Academic Research Consortium criteria. Stroke was defined as focal loss of neurologic function caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death. They defined major life-threatening bleeding as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the hemoglobin level of 5.0 g per deciliter or more, or the need for transfusion of at least 4 units of red cells.

Results: 18,624 patients from 862 centers in 43 countries from October 2006 to July 2008 were recruited. The primary end point occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% of patients vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). This pattern was also reflected in a reduction in the rate of death from any cause with ticagrelor (4.5%, vs. 5.9% with clopidogrel; P<0.001). The rate of stroke did not differ significantly between the two treatment groups, although there were more hemorrhagic strokes with ticagrelor than with clopidogrel (23 [0.2%] vs. 13 [0.1%], nominal P=0.10). Concerning our first secondary objective of ascertaining the effect in patients for whom invasive treatment was planned, the rate of the primary end point was also lower with ticagrelor (8.9%, vs. 10.6% with clopidogrel; P=0.003). Among patients who received a stent during the study, the rate of definite stent thrombosis was lower in the ticagrelor group than in the clopidogrel group (1.3% vs. 1.9%, P=0.009). Side effect profile of both drugs also showed no significant difference in the rates of major bleeding 11.6% vs 11.2%. TIMI scores also showed no significant differences in bleeding between Brilinta and Plavix. During CABG, there were no significant differences in the rates of major bleeding or transfusions as

well. There was a higher rate of non-CABG major bleeding with more episodes of intracranial bleeding in the Brilinta arm 0.3% vs 0.2%, P=.06.

Limitations: The pharmaceutical manufacturer AstraZeneca sponsored this study and oversaw the conduct of the trial. This inherently gives a bias in the way people view this landmark cardiology study as well. The average time of ACS to medicine administration was approx 10 hr after their chest pain. Hence the applicability to ER is limited. If we look at costs for the two medications, the generic version of Plavix is $1 a day as compared to $7.68 for Brilinta.

Discussion: PLATO shows that treatments with Brilinta as compared to Plavix in patients with ACS significantly reduced rates of death, MI, or stroke. The drug achieved this without a significant increase in the overall rate of major bleeding. The incremental reduction in the risk of coronary thrombotic events (i.e., myocardial infarction and stent thrombosis) through more-intense P2Y12 inhibition with ticagrelor is consistent with similar effects of prasugrel. Furthermore, the benefits with ticagrelor were seen regardless of whether invasive or noninvasive management was planned; this issue has not been investigated with other P2Y12 inhibitors. Treatment with ticagrelor was also associated with an absolute reduction of 1.4 percentage points and a relative reduction of 22% in the rate of death from any cause at 1 year. The improved survival rate with ticagrelor might be due to the decrease in the risk of thrombotic events without a concomitant increase in the risk of major bleeding, as seen with other antithrombotic treatments in patients with an acute coronary syndrome. There were also no increases in CABG major bleeding events if surgery was planned and the drug was withheld for a shorter period of time due to its half-life. While in conclusion we can say with patients with ACS with our without ST segment elevation, Brilinta as compared to Plavix significantly reduced the rate of death from vascular causes, MI, or stroke, how can we extend this to treatment in the ER? First off each hospital is dependent on their protocols and we as ER docs don't necessarily give this medication without approval from the cardiologist. Furthermore, the average time given after the onset of ACS is 10 hr and we usually see patients that come in earlier so the applicability maybe limited. However the above data does suggest in patient with unstable angina or NSTEMI giving Brilinta and ASA would be beneficial. I believe that as more time goes by the use of Brilinta will be more prevalent in our patient populations and recognizing its use as an anticoagulant will be beneficial in the ER.