Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndrome (ACS)- Summary

Background

Clinical guidelines recommend dual platelet therapy in patients with acute coronary syndrome (ACS) including those undergoing percutaneous coronary intervention (PCS). Traditionally this therapy includes the use of aspirin and clopidogrel. However despite the established clinical benefit of this approach many patients continue to have recurrent atherothrombotic events while receiving dual antiplatelet therapy.

Prasugrel is a novel antiplatelet agent that is a third-generation thienopyridine. Both clopidogrel and prasugrel are prodrugs that require hepatic metabolism to form the active metabolite that binds irreversibly to the P2Y(12) adenosine diphosphate (ADP) receptor. This allows for the inhibition of platelet aggregation for the lifetime of the platelet. However platelet inhibition by prasugrel is more immediate and intense when compared to clopidogrel. The TRITON-TIMI 38 trial was a comparison of prasugrel with clopidogrel in patients that with moderate-to-high-risk ACS that were scheduled to undergo PCI. The trial tested the hypothesis that more intense platelet inhibition leads to lower ischemic events (1).

Study Design

A total of 13,608 subjects were enrolled in the TRITON-TIMI 38 trial. Patients were randomly assigned to receive prasugrel (60mg loading dose and 10mg maintenance dose) or clopidogrel (300mg loading and 75 mg maintenance), for a total of 6-15 months. Patients were randomly assigned to the clopidogrel or prasugrel group in two strata: 1074 patients with moderate-to-high risk unstable angina (UA) or non-ST-elevation MI (NSTEMI) and 3534 patients with ST-elevation MI (STEMI). The study drug was administered within 1 hour after PCI in 74% of patients, 25% of patients received the drug before the first coronary guidewire was placed, and 1% of patients received the drug more than 1 hour after PCI. The patients were also required to use aspirin at a daily dose of 75-162mg. Study visits were conducted at hospital discharge, 30 days, 90 days and at 3 month intervals for a total of 6-15 months. The primary efficacy end point measure included death from cardiovascular causes, nonfatal myocardial infarction (MI) or nonfatal stroke. A key safety endpoint was major TIMI major bleeding that was not related to coronary-artery bypass grafting (CABG), non CABG-related TIMI life-threatening bleeding and TIMI major or minor bleeding.

Results

Patients that received prasugrel had a significant decrease in the primary endpoint —rate of death from cardiovascular causes including nonfatal myocardial infarction or nonfatal stroke. The primary endpoint rates were 12.1% for clopidogrel versus 9.9% for prasugrel ($P<0.001$). Additionally prasugrel caused a significant decrease in MI followed by death from cardiovascular causes as well as reduced stent thrombosis by 52%. These results were promising and confirmed the hypothesis that more intense platelet inhibition leads to lower ischemic events. However, the relative rate of TIMI major hemorrhage was increased by 32% with prasugrel. The major concern in this study was the extent of

TIMI major bleeding that was not related to CABG. Life threatening bleeding occurred at 1.4% in the prasugrel group versus 0.9% in the clopidogrel group (P=0.01). In some cases the bleeding was fatal 0.4% prasugrel versus 0.1% clopidogrel (P=0.002).

As a result of the discordance between the efficacy and safety results the investigators conducted a series of post hoc analyses to identify the subgroups of patients who did not have a favorable net clinical benefit with prasugrel. There were three specific groups identified:
Group 1: Patients with a previous stroke of transient ischemic attack (TIA)
Group 2: Patients ≥75 years of age
Group 3: Patients weighing <60 kg

Patients from group 1 had a net harm from prasugrel therapy (hazard ratio, 1.54; 95% CI, 1.02 to 2.32; P=0.04). These patients had numerically worse clinical outcomes as measured by the primary endpoint and had more frequent bleeding (including intracranial hemorrhage) than patients without a history of cerebrovascular events. The rates of intracranial hemorrhage were 2.3% in the prasugrel patients and 0% in clopidogrel group (P=0.02). Therefore prasugrel should not be used at the dose studied in this trial for this group of patients. Intensive inhibition of platelet aggregation in this group carries high risks.

Patients from group 2 (hazard ratio, 0.99; 95% CI, 0.81 to 1.21; P=0.92) and 3 (hazard ratio, 1.03; 95% CI, 0.69 to 1.53; P=0.89) had no net clinical benefit when compared clopidogrel. These patients were also at increased risk of bleeding. Although there was bleeding in both the prasugrel and clopidogrel groups. Patients in the prasugrel group had a higher incremental risk of bleeding than the clopidogrel group and this eliminated any net overall benefit of prasugrel in this subgroup. These results are consistent with previous data on antithrombotic therapy in these groups. Advanced age as well as low body weight results in an increased risk of bleeding.

In patients without any of these 3 risk factors there was a greater efficacy with prasugrel (hazard ratio, 0.74; 95% CI, 0.66 to 0.84; P<0.001). Patients without these risk factors also had no significant difference in the rate of major bleeding and had a substantially favorable net clinical benefit with prasugrel.

Dr Bhatt comments on the trial in the accompanying editorial. According to Dr Bhatt serious bleeding is a high price of to pay for the reduction of ischemic events seen in these patients (2). In fact for each death from cardiovascular events prevented by prasugrel there was approximately one episode of fatal bleeding. Bhatt also noted that although the total risk of fatal bleeding was low, it occurred in a clinical trial setting that had specific inclusion criteria. This raises the concern that the bleeding rate in a real clinical situation may be higher.

Conclusion
Prasugrel may benefit patients with ACS who are undergoing PCI and are at a high risk for ischemic events but a low risk for bleeding (2), as long as these patients do not have a

previous history of cerebrovascular events. Patients who have a lower risk of ischemic events and a high risk of bleeding may have better outcomes with clopidogrel. Similarly elderly or low body weight patients may have a high risk of bleeding and less benefit with prasgurel. Patients with a history of stroke or TIA should not be administered prasugrel at the doses studies in the TRITON-TIMI 38 study. Patients without a history of cerebrovascular events seem to benefit from prasugrel. When clinicians consider the choice of antiplatelet regiments for the treatment of patients with ACS they need to weigh the risks and benefits of intensive inhibition of platelet aggregation.

References

1. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel vs clopigogrel in patients with acute coronary syndromes. N Eng J Med 2007;357:2001-2015.

2. Bhatt DL. Intensifying platelet inhibition—navigating between Scylla and Charybdis. N Eng J Med 2007;357:2078-2081.