Hyporesponsiveness to Clopidogrel Does Not Predict 1-Year Mortality

Written by ***Lori Alexander***

An analysis from the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents [ADAPT-DES; NCT00638794] trial showed that hyporesponsiveness to clopidogrel was not independently predictive of mortality at 1-year after percutaneous coronary intervention (PCI) with a drug-eluting stent (DES). Although hyporesponsiveness to clopidogrel was associated with increased risk of stent thrombosis and myocardial infarction (MI), it was also associated with a reduced risk of major bleeding, which has been strongly related to mortality, explained Gregg W. Stone, MD, Columbia University Medical Center, NewYork-Presbyterian Hospital, New York, New York, USA.

The trial enrolled 8583 patients at 11 sites in the United States and Germany between January 2008 and September 2010. All patients had PCI with implantation of ≥1 (noninvestigational) DES. Dr. Stone said the patients in the study represented a "real-world population," with about one-third having diabetes, one-quarter having a previous MI, and >50% having undergone a previous revascularization procedure.

The number of platelet reactivity units (PRU) and aspirin reactivity units (ARU) were assessed with the VerifyNow P2Y12 and Aspirin assays, respectively. Approximately 43% of patients were found to be hyporesponders to clopidogrel, defined as PRU >208. Hyporesponsiveness to aspirin, defined as a score of >550 ARU, was found in 5.6% of patients.

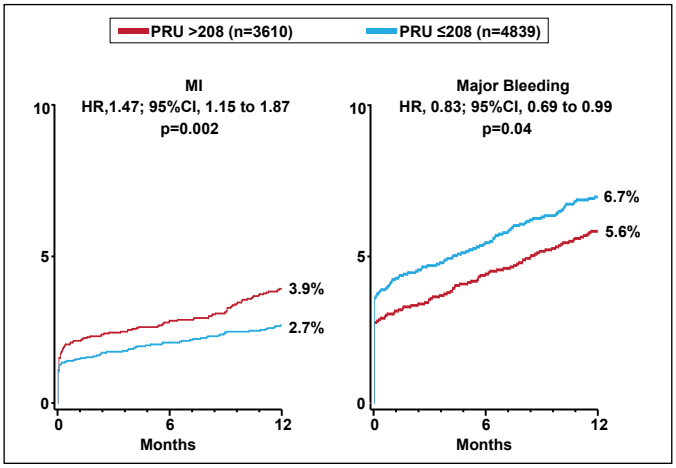
The first results of ADAPT-DES were presented last year when Dr. Stone reported that hyporesponsiveness to clopidogrel was significantly related to stent thrombosis within 30 days after PCI. The current analysis was designed to evaluate the impact of clopidogrel hyporesponsiveness on patient outcomes after 1 year of follow-up.

At 1 year, 74 stent thrombosis events had occurred in 70 patients (0.84%), MI had occurred in 224 patients (2.6%), major bleeding had occurred in 531 patients (6.2%), and 161 patients had died (1.9%). The rate of stent thrombosis was significantly higher for patients who were hyporesponsive to clopidogrel than for those with a PRU ≤208 (1.3% vs 0.5%; HR, 2.54; 95% CI, 1.55 to 4.16; p=0.0001). The rate of MI was also significantly higher for the group with hyporesponsiveness (3.9% vs 2.7%; HR, 1.47; 95% CI, 1.15 to 1.87; p=0.002).

In contrast, patients with hyporesponsiveness to clopidogrel had significantly lower rates of major bleeding (5.6% vs 6.7%; HR, 0.83; 95% CI, 0.69 to 0.99; p=0.04; Figure 1)

Hyporesponsiveness to aspirin predicted a slightly lower risk of bleeding but did not predict a difference in stent thrombosis, MI, or mortality. Dr. Stone noted that this finding raises the question of whether aspirin is of benefit for patients treated with a DES.

Figure 1. ADAPT-DES: MI and Major Bleeding According to Post-PCI PRU.



MI=myocardial infarction; PCI=percutaneous coronary intervention; PRU=platelet reactivity units; Reproduced with permission from GW Stone, MD.

Univariable analysis showed that hyporesponsiveness to clopidogrel was significantly associated with mortality, with a rate of 2.4% for patients with a PRU >208 compared with 1.5% for those patients with a PRU ≤208 (HR, 1.62; 95% CI, 1.18 to 2.22; p=0.002). However, he added that a number of factors associated with hyporesponsiveness are also associated with mortality (eg, age and diabetes). To address this issue, he and his coinvestigators performed a propensity adjustment for hyporesponsiveness to clopidogrel. A multivariable propensity score adjusted risk model demonstrated no independent association between hyporesponsiveness to clopidogrel and mortality (adjusted HR, 1.20; 95% CI, 0.85 to 1.70; p=0.30). Stent thrombosis, MI, and major bleeding remained significantly associated with hyporesponsiveness to clopidogrel in this analysis (p=0.001, p=0.01, and p=0.002, respectively).

Dr. Stone said that many more deaths were associated with major bleeding than with stent thrombosis and MI combined. He added that a complete effect in reversing hyporesponsiveness to clopidogrel would cause 4 bleeding events for every stent thrombosis prevented. He and his coinvestigators concluded that the findings

suggest that the use of potent antiplatelet agents to overcome hyporesponsiveness to clopidogrel is unlikely to improve survival unless the beneficial effects of reducing stent thrombosis and MI can be uncoupled from the likely increase in bleeding.

PARTNER B Shows Excellent Survival Rates in Inoperable TAVR Patients

Written by ***Rita Buckley***

Results from the Placement of Aortic Transcatheter Valve Trial [PARTNER B; NCT00530894] continue to support the role of transcatheter aortic valve replacement (TAVR) as the standard of care for symptomatic patients with aortic stenosis who are not surgical candidates, said E. Murat Tuzcu, MD, Cleveland Clinic, Cleveland, Ohio, USA. Dr. Tuzcu presented 3-year follow-up findings from the PARTNER B trial.

The objectives of the trial were to evaluate the clinical outcomes of TAVR compared with standard therapy at 3 years in patients with inoperable aortic stenosis (iAS), to assess valve hemodynamics and durability using echocardiography, and to perform subgroup analyses to better define the impact of comorbidities on outcomes.

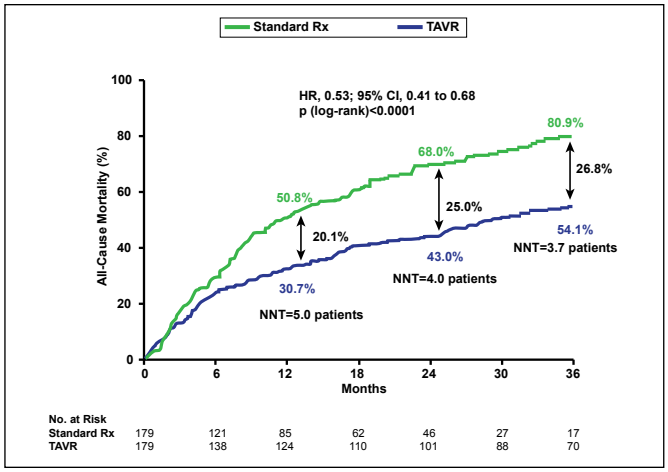
A total of 358 patients with iAS were randomized (1:1) to receive a transcather heart valve or standard medical therapy. The inclusion criteria were severe calcific aortic stenosis, defined as an echo-derived valve area of <0.8 cm^2 (effective orifice area index <0.5 cm^2/m^2), and mean gradient >40 mm Hg or jet velocity >4.0 m/s; NYHA Class ≥II; and inoperable, defined as risk of death or serious irreversible morbidity with surgical replacement >50% as assessed by a cardiologist and 2 surgeons.

Key endpoints for the 3-year analysis were all-cause and cardiac mortality; rehospitalization; adverse outcomes, including stroke, bleeding, renal failure, or myocardial infarction; NYHA functional class; days alive and out of hospital; echo-derived valve areas, transvalvular gradients, and post-TAVR aortic regurgitation; and mortality outcomes stratified by the Society of Thoracic Surgeons mortality risk score.

Baseline characteristics were similar between the 2 groups. The mean age was 83 years, and nearly half (46%) of the subjects were men. Patients in the standard-care group had significantly higher rates of chronic obstructive pulmonary disease compared with the TAVR group (52.5% vs 41.3%, respectively; p=0.04) and atrial fibrillation (48.8% vs 32.9%; p=0.04). The prevalence of porcelain aorta was 19.0% in the TAVR group versus 11.2% in the standard-care group (p=0.05).

The Kaplan-Meier estimated rates of all-cause mortality at 3 years were 80.9% in the standard-care arm versus 54.1% in the TAVR arm, an absolute reduction of 26.8% (HR, 0.53; 95% CI, 0.41 to 0.68; log-rank p<0.0001). The number needed to treat (NNT) was 3.7 patients (Figure 1). Rates for cardiovascular mortality were similarly reduced from 74.5% to 41.4%, a 33.1% reduction with an NNT of 3.0 patients. Serial landmark analyses performed at baseline, 12 months, and 24 months demonstrate a consistent, significant reduction in all-cause mortality for TAVR as compared with standard care.

Figure 1. Figure 1. All-Cause Mortality (ITT): Crossover Patients Censored at Crossover.



ITT=intention-to-treat; TAVR= transcatheter aortic valve replacement.
Reproduced with permission from EM Tuzcu, MD.

Based on the data, Dr. Tuzcu concluded that the benefits of TAVR as measured by all-cause mortality, cardiovascular mortality, repeat hospitalization, and functional status were sustained through 3 years of follow-up. Durability of the implanted valves was also demonstrated with no increase in transvalvular gradient or attrition of valve area. Detailed analysis of all randomized inoperable patients showed consistent results for all outcomes. He also noted that survival benefit of TAVR is dependent on the presence of comorbid illness and, without TAVR, mortality is similar irrespective of comorbid illness.

Three-year outcomes continue to support the role of TAVR as the standard of care for symptomatic patients with aortic stenosis who are not surgical candidates. "These data underscore the importance of patient selection before TAVR and the need for aggressive management of illnesses after TAVR," said Dr. Tuzcu.