Reduction in the risk of MACE with apabetalone in patients with recent acute coronary syndrome and diabetes according to NAFLD fibrosis score: exploratory analysis of the BETonMACE trial

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Background/Introduction: Both major adverse cardiovascular events (MACE) and non-alcoholic fatty-liver disease (NAFLD) are highly prevalent in patients with high BMI and long-standing type 2 diabetes (T2DM). NAFLD is characterized by an augmented hepatic inflammation and fat deposition and is strongly associated with metabolic syndrome. Patients with NAFLD are at an increased risk of cardiovascular (CV) events, and MACE is the leading cause of death for patients with NAFLD. Apabetalone (APB) is a novel selective inhibitor of bromodomain and extra-terminal (BET) proteins, epigenetic regulators of gene expression. In the Phase 3 BETonMACE trial treatment of 2,425 T2DM patients post ACS with APB, resulted in hazard ratios (HR) of 0.82 (p=0.11) for the primary endpoint of ischemic MACE (CV death, non-fatal MI or stroke) and 0.59 (p=0.03) for the secondary endpoint of heart failure hospitalization (HFH) vs placebo (PBO). Transient elevations of alanine aminotransferase greater than 5xULN occurred in 3.3% of APB treated patients.

Purpose: In this exploratory post hoc analysis of BETonMACE we evaluated risk modification for a composite of MACE+HFH by APB based on the Angulo NAFLD fibrosis score (FS) using 6 variables (age, BMI, hyperglycemia/diabetes, AST/ALT ratio, platelet count, and albumin). The NAFLD FS categorizes individuals into groups that correlate with differing levels of fibrosis in biopsy studies: (FS F0-F2, no significant fibrosis; FS ID, indeterminant; and FS F3-F4, significant fibrosis).

Methods: Baseline characteristics and blood measurements were used to determine NAFLD FS at baseline. The incidence of MACE+HHF was compared between treatment groups.

Results: Based on FS, there were 618 pts were classified as FS F0-F2 (n=328 APB, n=290 PBO), 1,440 pts were classified as FS ID (n=708 APB, n=732 PBO) and 289 pts were classified as FS F3-F4 (n=144 APB, n=145). MACE+HHF in the PBO group was higher in FS ID and FS F3-F4 compared to FS F0-F2 (17.2% vs 15.0% vs 9.7%) and therefore the former two groups were combined into an elevated risk FS+ group. FS+ pts were older (63 vs 56), had longer duration of T2DM (9.0 vs 7.3 yrs), and higher BMI (30.8 vs 28.6) compared to FS- pts. Overall, APB was associated with fewer MACE+HHF (HR 0.78, 95% CI 0.60–1.01, p=0.06) compared to PBO in the FS+ pts with adjustment for age, duration of T2DM and BMI.

Conclusions: Patients with T2DM and ACS may share common risk factors with patients with NAFLD. Apabetalone appears to exert a favorable effect on MACE in patients with risk factors for NAFLD. Whether apabetalone has a modulatory effect on the development and progression of NAFLD is an important question requiring further investigation.