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

P. P. Toth[1], G. G. Schwartz[2], S. J. Nicholls[3], C. Halliday[4], H. N. Ginsberg[5], J. O. Johansson[4], K. Kalantar-Zadeh[6], E. Kulikowski[4], K. Lebioda[4], N. Wong[4], M. Sweeney[4], and K. K. Ray[7]

[1]CGH Medical Center, Sterling, United States of America; [2]University of Colorado, School of Medicine Division of Cardiology, Aurora, United States of America; [3]Monash Centre of Cardiovascular Research & Education in Therapeutics, Melbourne, Australia; [4]Resverlogix Corp., Calgary, Canada; [5]Columbia University, Irving Institute for Clinical and Translational Research, New York, United States of America; [6]University of California at Irvine, Division of Nephrology and Hypertension, Irvine, United States of America; [7]Imperial College London, Imperial Centre for Cardiovascular Disease Prevention, London, United Kingdom of Great Britain & Northern Ireland

Background

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 augmented hepatic inflammation and fat deposition and is strongly associated with insulin resistance. 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 subsequent to an acute coronary syndrome (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+HFH 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+HFH 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%), thus 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+HFH (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.

Table 1. Baseline Patient Characteristics

Characteristic	FS+ Patients (N=1,729)		
	Apabetalone (N=852)	Placebo (N=877)	P-value vs. Placebo
Age (years)*	63 (57 – 69)	64 (58 – 70)	0.12
Males, n (%)	636 (74.6%)	645 (73.5%)	0.64
Caucasian, n (%)	754 (88.5%)	787 (89.7%)	0.45
Body mass index (kg/m^2)†	30.7 (4.9)	30.9 (5.1)	0.57
Hypertension, n (%)	784 (92.0%)	782 (89.2%)	0.052
Current or ex-smoker, n (%)	92 (10.8%)	84 (9.6%)	0.45
Duration of diabetes (years)†	8.8 (7.9)	9.1 (7.8)	0.45
Index ACS event			
STEMI, n (%)	289 (48.7%)	308 (49.8%)	0.77
Non-STEMI, n (%)	304 (51.3%)	311 (50.2%)	0.77
Unstable angina, n (%)	251 (29.6%)	247 (28.4%)	0.63
Time from index ACS to randomization (days)*	40 (26 – 65)	41 (27 – 63)	0.67

P-values comparing groups at baseline were calculated using chi-square tests for categorical variables and Wilcoxon tests (*) or z-tests (†) for continuous variables

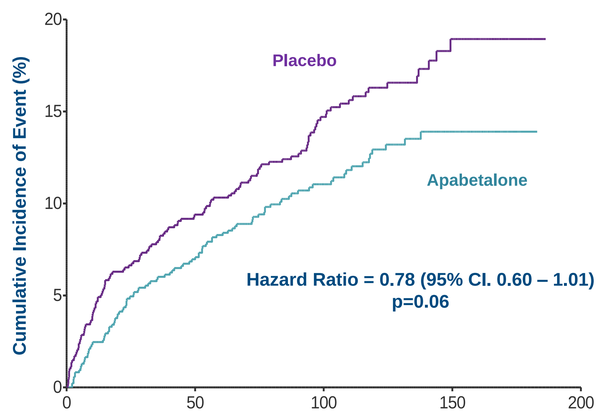
Table 2. Medication Use at Baseline

Medication	FS+ Patients (N=1,729)		
	Apabetalone (N=852)	Placebo (N=877)	P-value vs. Placebo
Cardiovascular Medications			
Atorvastatin, n (%)	447 (52.5%)	453 (51.7%)	0.77
Rosuvastatin, n (%)	405 (47.5%)	424 (48.3%)	0.77
High-intensity statin, n (%)	771 (90.5%)	802 (91.4%)	0.54
Ezetimibe, n (%)	20 (2.3%)	24 (2.7%)	0.72
ACE inhibitor/ARBs, n (%)	793 (93.1%)	812 (92.6%)	0.76
Beta-blockers, n (%)	775 (91.0%)	804 (91.7%)	0.66
Anti-platelet agents, n (%)	840 (98.6%)	868 (99.0%)	0.61
Diabetes Medications			
Metformin, n (%)	694 (81.5%)	715 (81.5%)	0.98
Insulin, n (%)	307 (36.0%)	339 (38.7%)	0.28
Sulfonylureas, n (%)	273 (32.0%)	255 (29.1%)	0.20
DPP4 inhibitors, n (%)	129 (15.1%)	120 (13.7%)	0.43
SGLT2 inhibitors, n (%)	104 (12.2%)	102 (11.6%)	0.77
GLP1 receptor agonists, n (%)	25 (2.9%)	33 (3.8%)	0.41

Table 3. Baseline Biochemical Parameters

Biochemical Parameter	FS+ Patients (N=1,729)		
	Apabetalone (N=852)	Placebo (N=877)	P-value vs. Placebo
Fibrosis Score, points†	-0.19 (0.84)	-0.16 (0.82)	0.57
HbA1c, % *	7.3 (6.4 – 8.5)	7.2 (6.4 – 8.5)	0.49
Serum glucose, mg/dL *	136.9 (111.5 – 176.9)	133.5 (109.9 – 173.5)	0.20
Total cholesterol, mg/dL *	127.4 (109.4 – 155.5)	130.7 (110.6 – 157.8)	0.20
LDL cholesterol, mg/dL *	65.0 (48.3 – 86.2)	65.4 (48.0 – 86.5)	0.47
HDL cholesterol, mg/dL *	33.6 (29.8 – 37.1)	33.6 (30.2 – 37.1)	0.71
Triglycerides, mg/dL *	145.3 (111.6 – 195.7)	150.6 (114.3 – 200.4)	0.13
Alkaline phosphatase, U/L *	77.0 (63.0 – 93.0)	76.0 (62.0 – 91.0)	0.22
Alanine aminotransferase, U/L *	21.0 (16.0 – 29.0)	22.0 (16.0 – 29.0)	0.32
Systolic BP (mmHg) *	130 (120 – 140)	130 (120 – 140)	0.70
Diastolic BP (mmHg) *	78 (70 – 82)	78 (70 – 82)	0.89
Total bilirubin, umol/L *	9.3 (7.0 – 12.3)	9.5 (7.1 – 12.4)	0.34
hsCRP, mg/L *	3.0 (1.3 – 5.7) [n=174]	2.3 (1.1 – 5.6) [n=177]	0.38
NLR, ratio *	2.6 (2.0 – 3.4)	2.5 (1.9 – 3.3)	0.79

Kaplan-Meier Estimate of Time to First Occurrence of the Composite End Point of CV Death, Myocardial Infarction, Stroke, or Hospitalization for Heart Failure in FS+ Patients



No. at Risk					No. of Events
Placebo	877	787	488	121	135
Apabetalone	852	779	503	132	102

Conclusions

Patients with T2DM and ACS may share common risk factors with patients with NAFLD and are often treatment resistant. Apabetalone showed a trend for lowering MACE in post-ACS patients with NAFLD (HR=0.78, 95% CI 0.60-1.01, p=0.06).