THE BET PROTEIN INHIBITOR APABETALONE REDUCES CONGESTIVE HEART FAILURE INCIDENCE IN PATIENTS WITH ACUTE CORONARY SYNDROME AND DIABETES: RESULTS FROM THE BETONMACE TRIAL

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Background

Patients with diabetes and acute coronary syndrome (ACS) are at high risk for subsequent heart failure. Apabetalone is a selective inhibitor of bromodomain and extra-terminal (BET) proteins, epigenetic regulators of gene expression. Preclinical data suggest that apabetalone exerts favorable effects on pathways related to myocardial structure and function and therefore could impact subsequent heart failure events. The effect of apabetalone on heart failure events after an ACS is not currently known.

Methods

The phase 3 BETonMACE trial was a double-blind randomized, comparison of apabetalone versus placebo on the incidence of major adverse cardiovascular events (MACE) in 2,425 patients with a recent ACS and diabetes. The primary efficacy end point was the time to first occurrence of cardiovascular death or non-fatal myocardial infarction or stroke. This prespecified analysis investigated the impact of apabetalone on adjudicated hospitalizations for congestive heart failure.

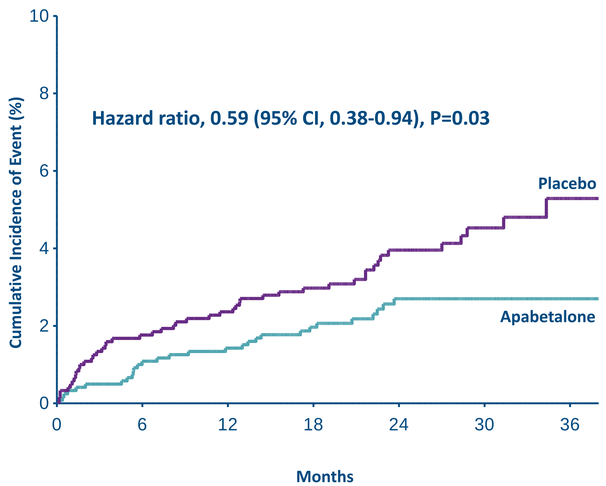
Results

Patients (age 62 years, 74.4% males, 90% high-intensity statin use, LDL-C 70.3 mg/dL, HDL-C 33.3 mg/dL and HbA1c 7.3%) were treated for an average 26 months. There were a total of 274 primary endpoints, 125 (10.9%) in the apabetalone group and 149 (12.4%) in the placebo group. Apabetalone did not reduce the primary end point of cardiovascular death or non fatal MI or stroke (HR 0.82, [95%CI 0.65-1.04], P=0.11). Apabetalone treated patients experienced a lower rate of first hospitalization for heart failure (2.4% vs. 4.0%, HR 0.59 [95%CI 0.38-0.94], P=0.03), total number of hospitalizations for heart failure (35 vs. 70, HR 0.47 [95%CI 0.27-0.83], P=0.01) and the combination of cardiovascular death or hospitalization for heart failure (5.7% vs. 7.8%, HR 0.72 [95%CI 0.53-0.98], P=0.04).

Table 1: Baseline Characteristics

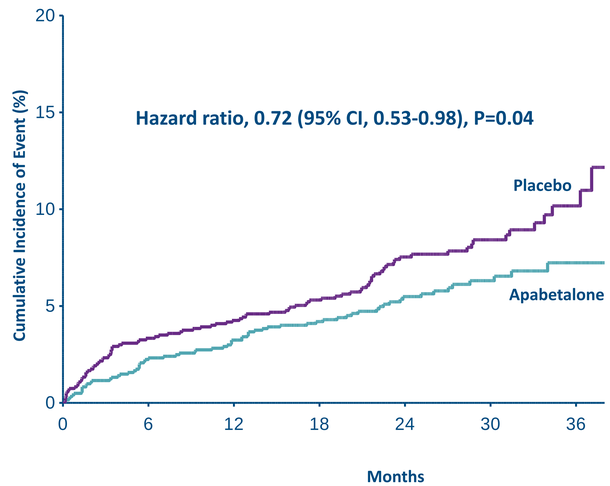
Parameter	Placebo (N=1206)	Apabetalone (N=1212)
Age (years)*	62 (56-68)	62 (55-68)
Males (%)	74.0	74.8
Caucasian (%)	87.6	87.7
Body mass index (kg/m^2)	30.3±5.0	30.2±4.8
Hypertension (%)	87.8	89.4
Dyslipidemia (%)	75.4	74.5
Current or ex-smoker (%)	10.4	12.1
Duration of diabetes (years)	8.7±7.7	84. ±7.6
Prior myocardial infarction (%)	14.7	14.4
Prior coronary revascularization (%)	21.2	21.4
History of heart failure (%)	14.8	15.1
Index ACS event		
STEMI (%)	38.6	38.4
Non-STEMI (%)	35.1	34.1
Unstable angina (%)	25.0	26.7
PCI for index ACS (%)	79.2	79.8
Time from index ACS to randomization (days)*	38 (25-62)	38 (25-63.5)

Figure 1: Hospitalization for Congestive Heart Failure



No. at Risk							
Placebo	1,206	1,153	1,138	984	676	414	124
Apabetalone	1,212	1,173	1,146	990	697	420	119

Figure 2: Hospitalization for Congestive Heart Failure or CV Death



No. at Risk							
Placebo	1,206	1,153	1,138	982	674	413	123
Apabetalone	1,212	1,172	1,146	987	697	420	116

Conclusions and Clinical Implications

Apabetalone treatment was associated with fewer hospitalizations for heart failure in patients with type 2 diabetes and recent ACS. When combined with CV death, similar trends were observed. Future studies are warranted to define the potential for BET inhibition with apabetalone in the prevention and treatment of heart failure in patients with diabetes and ACS.