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Journal

CIRCULATION, 140(25)

ISSN

0009-7322

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Publication Date

2019

Resuscitation Science Symposium 2019

Circulation, Volume 140(25), 17 December 2019, p e965-e1011

DOI: 10.1161/CIR.0000000000000742

20884

Effect of *BET* Protein Inhibition With *Apabetalone* on Cardiovascular Outcomes in Patients With Acute Coronary Syndrome and Diabetes - Results of the BETonMACE Trial

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Background: Bromodomain and extra-terminal (BET) proteins are epigenetic transcription modulators of inflammation, thrombogenesis, and lipoprotein metabolism that contribute to atherothrombosis. BET inhibitors are small molecule epigenetic regulators of chromatin structure and gene expression with therapeutic potential in atherosclerosis. Apabetalone is the first in class BET inhibitor that selectively targets bromodomain 2 (BD2), resulting in favourable effects on transcription of a variety of atherothrombotic mediators. A pooled analysis of phase 2 trials showed that apabetalone reduced the incidence of death or non-fatal cardiovascular (CV) outcomes compared with placebo, with more prominent benefits in patients with conditions associated with BET system activation such as type 2 diabetes mellitus (T2DM), high C-reactive protein or low HDL-cholesterol. The BETonMACE trial tested the hypothesis that addition of treatment with apabetalone to standard of care therapies improves CV outcomes in patients with T2DM and low HDL-C after an acute coronary syndrome (ACS).

Methods: BETonMACE (NCT02586155) is an international, multi-center, randomized, double-blind, placebo-controlled trial in patients with recent ACS, T2DM and low HDL-C conducted at 195 sites in 13 countries. Patients with ACS in the preceding 7-90 days, T2DM, and HDL-C <=40 mg/dl for men, <=45 mg/dl for women, were assigned in double-blind fashion to receive apabetalone 100 mg orally twice daily or matching placebo (1:1) on top of guideline recommended standard of care including intensive or maximum-tolerated treatment with atorvastatin or rosuvastatin. The primary outcome was time to the first occurrence of CV death, non-fatal myocardial infarction (MI), or stroke. The study continued until 250 primary endpoints had accrued. Apabetalone and placebo groups were compared using a two-sided stratified log-rank test; assuming a 2-sided type 1 error rate of 5% and cumulative incidence of the primary endpoint of 10.5% in the placebo arm at 18 months, a sample size of 2400 patients followed for a median of 18 months provides 80% power to detect a 30% relative risk reduction with apabetalone. **Results**: Enrollment began in November 2015 and ended in July

2018 with 2425 participants randomized. MI was the index ACS event in 74% (STEMI 53%, NSTEMI 47%) with unstable angina constituting 26%. Characteristics of participants included median age 62 years, 25% female sex, majority white race (87%), and coronary revascularization for the index ACS (80%). Use of high intensity statin treatment was 91% at study entry with median LDL-C 65 mg/dl, HDL-C 33 mg/dl, and HbA1c 7.3%. Median follow up was 26 months.

Conclusion: The BETonMACE trial will be the first study to report whether epigenetic modulation with a selective BET protein inhibitor is a safe and effective approach to reduce cardiovascular risk.

Key Words: BET inhibition; Epigenetics; Cardiovascular outcomes