Title

BET PROTEIN INHIBITION AND COGNITION: A PRE-SPECIFIED SUBSTUDY OF THE BETONMACE PHASE 3 TRIAL EVALUATING APABETALONE IN PATIENTS WITH DIABETES AND ACUTE CORONARY SYNDROME

Journal

Journal of the American College of Cardiology, 73(9)

ISSN

0735-1097

Authors

Ray, Kausik K
Nicholls, Stephen
Sweeney, Michael
et al.

Publication Date

2019-03-01

DOI

10.1016/s0735-1097(19)32470-2

ACC.19

1864
JACC March 12, 2019
Volume 73, Issue 9

Prevention

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Poster Contributions
Poster Hall, Hall F
Monday, March 18, 2019, 9:45 a.m.-10:30 a.m.

Session Title: Prevention: Clinical 5
Abstract Category: 32. Prevention: Clinical
Presentation Number: 1331-413

Authors: *Kausik K. Ray, Stephen Nicholls, Michael Sweeney, Jan Johansson, Norman Wong, Ewelina Kulikowski, Kenneth Lebioda, Peter Toth, Henry Ginsberg, Kamyar Kalantar-Zadeh, Mathias L. Haarhaus, Bengt Winblad, Jeffrey L. Cummings, Gregory Schwartz, Resverlogix Corp., Calgary, Canada, Imperial College London, London, United Kingdom*

Background: Type 2 diabetes (T2D) and cardiovascular disease (CVD) are associated with impaired cognition. Epigenetic dysregulation by bromodomain and extraterminal domain (BET) proteins is implicated in CVD, as well as T2D and dementia. Apabetalone (ABL) is a selective BET inhibitor which in phase 2 trials was associated with a significant 55% reduction in major adverse CV events. Effects of ABL on cognition are unknown.

Methods: The ongoing phase 3 cardiovascular outcomes trial BETonMACE compares ABL (100 mg orally twice daily) with placebo in 2425 patients with recent acute coronary syndrome (ACS), T2D, and low HDL cholesterol, enrolled at 195 sites in 13 countries. The primary outcome is time to first occurrence of CV death, myocardial infarction, or stroke. Cognition, a pre-specified secondary outcome, is assessed at baseline and annually in patients 70 years and older by the Montreal Cognition Assessment (MoCA). MoCA covers several cognitive domains including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. A score of $\leq$25 of 30(31) indicates cognitive impairment. MoCA score change from preliminary blinded data shows a standard deviation of 3.2 points and a sample size of 54 subjects per arm to provide a 90% power to detect a mean between-group difference of 2 points at $p<0.05$.

Results: Baseline MoCA (versions 7.1, 7.2, and 7.3) was performed in 19% of BETonMACE participants (n=460, mean age 74). Compared with the entire BETonMACE cohort, the MoCA subset is older, comprises more women (35 vs. 25%), has lower eGFR (70 vs. 99 ml/min), and higher neutrophil/lymphocyte ratio (2.80 vs. 2.33) (all $p<0.0001$). At baseline 53% (n=243) show a MoCA score $\leq$25, indicating cognitive impairment. Demographics and basic serum chemistry in the MoCA score $\leq$25 population does not differ significantly from the whole MoCA population.

Conclusion: Cognitive impairment, as assessed by MoCA, is common among elderly patients with diabetes and ACS. BETonMACE will determine whether the first-in-class BET-inhibitor ABL affects the time course of cognitive function in these patients, as well as macrovascular CV events.