Title

Reduction in the Risk of Major Adverse Cardiovascular Events With Apabetalone, a Bet Protein Inhibitor, in Patients With Recent Acute Coronary Syndrome and Type 2 Diabetes According to Insulin Treatment: Analysis of the Betonmace Trial

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Publication Date

2020

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Abstract

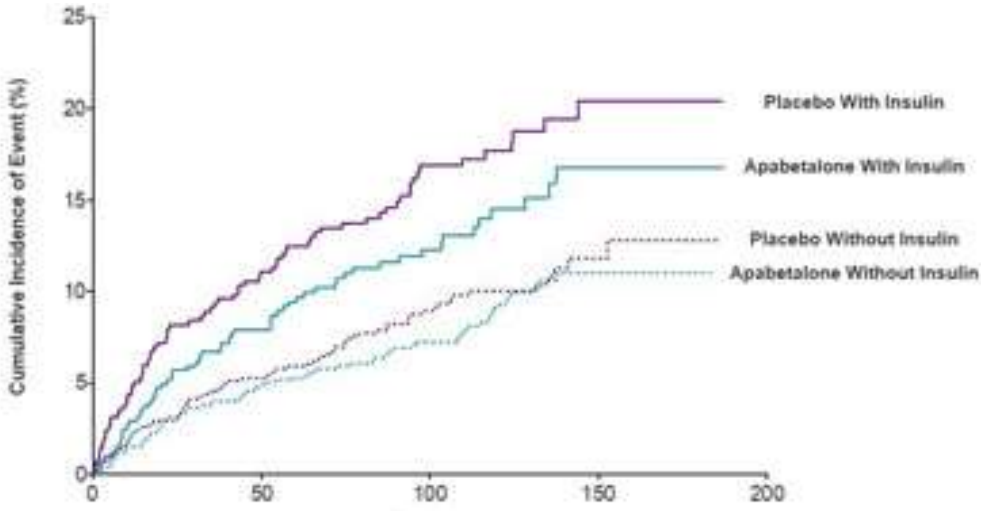
Introduction: Use of insulin has been associated with worse CV outcomes in patients (pts) with type 2 diabetes T2D. Apabetalone (APB) is a novel selective inhibitor of bromodomain and extra-terminal (BET) proteins, epigenetic regulators of gene expression. In the Phase 3 BETonMACE trial treatment with APB, compared with placebo, resulted in non-significantly fewer major adverse CV events (MACE: CV death, non-fatal MI or stroke) in 2425 pts with T2D and recent acute coronary syndrome (ACS).

Objective: In this analysis of BETonMACE we examined the relationship of insulin use to MACE risk and its modification by APB.

Methods: Baseline characteristics were compared in insulin-treated (INS) or not insulin-treated (no-INS) pts. The incidence of MACE and treatment hazard ratio (HR) were compared between these two subgroups.

Results: 829 (34.2%) pts received insulin at baseline, with or without other diabetes drugs. INS vs no-INS pts were more likely to be female (29 vs 24%), had longer duration of T2D (12.6 vs 6.4 yrs), higher HbA1c (8.4 vs 6.9%) and baseline glucose (156 vs 126 mg/dL), lower use of metformin (73 vs 87%) and sulfonylureas (21 vs 33 %), and higher use of SGLT2 inhibitors (16 vs 6%) and GLP1 receptor agonists (10 vs 2%). MACE in the placebo group was higher in INS than no-INS (17.4% vs 9.7%; HR 1.94; 95% CI 1.39-2.73; p=0.0001). Overall, APB was associated with fewer MACE (HR 0.82, 95% CI 0.65-1.04, p=0.11). The relative reduction in MACE with ABP was similar in INS (HR 0.78, 95% CI. 0.55-1.10, p=0.16) and no-INS (HR 0.87, 95% CI 0.63-1.21, p = 0.42, $p_{interaction}$=0.64). The absolute reduction in MACE with APB was numerically greater among INS than non-INS (3.69 vs 1.30%).

Conclusions: Pts with T2D and recent ACS treated with insulin are at high risk for MACE. High risk of MACE with insulin use is likely through association with other clinical characteristics prognostic for MACE. Insulin treatment may be a marker to identify pts with potential for large absolute reduction in MACE with APB.



No. at Risk					No. of Events
Apabetalone With Insulin	409	367	238	57	56
Apabetalone Without Insulin	803	753	487	126	69
Placebo With Insulin	420	370	239	65	73
Placebo Without Insulin	786	736	462	106	76

Acute coronary syndromes; Diabetes (Type II); Insulin; Drugs