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Apabetalone, a selective BET protein inhibitor, reduces ischemic cardiovascular events and hospitalization for heart failure in patients with acute coronary syndrome and type 2 diabetes

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Background: Despite established treatments, patients with type 2 diabetes mellitus (T2DM) and acute coronary syndrome (ACS) are at higher risk of ischemic cardiovascular (CV) events and hospitalization for heart failure (HHF) compared to those without T2DM. LDL-C lowering or use of GLP-1 agonists predominantly affects ischemic CV events, with little effect on HHF. Conversely, treatment with SGLT-2 inhibitors reduces HHF, with less effect on ischemic CV events. Preclinical studies indicate that bromodomain and extra-terminal (BET) proteins coordinate gene transcription for pathways that promote atherothrombotic events as well as heart failure. We assessed the clinical effect of apabetalone (APB), a novel BET protein inhibitor, on a composite of non-fatal ischemic CV events, HHF, and CV death in a post hoc analysis of the BETonMACE trial

Methods: BETonMACE was a double-blind, placebo-controlled phase 3 study in patients with T2DM and recent acute coronary syndrome receiving standard of care risk factor management. In 13 countries, 2425 patients were enrolled. We conducted a time-to-event analysis for first adjudicated

CV death or non-fatal MI, stroke, or HHF using a log-rank test and Cox proportional hazards model.

Results: At baseline median age was 62 years, 25.6% were female, 87.6% white, and use of high intensity statin, ACE inhibitors/ angiotensin II blockers, dual antiplatelet therapy and beta blocker were 90, 88, 92 and 91% respectively. A total of 312 subjects had an endpoint event, with 139 (11.5%) patients in the ABP group and 173 (14.3%) among PBO (HR 0.78, 95% CI 0.63–0.98, p=0.03, Figure). At 26 months, the absolute risk reduction was 3.2% and number needed to treat was 31. Numerically favorable HRs were observed for each component endpoint except for stroke (Table).

Conclusion: This present analysis suggests that BET inhibition with APB may be a novel pathway through which to reduce both HHF and ischemic CV events in high risk patients with T2DM thus impacting broader clinical outcomes with potentially large benefits for patients and healthcare systems.

Event (n)	HR	95% CI
Nonfatal MI (171)	0.80	0.59, 1.08
Nonfatal stroke (34)	1.01	0.52, 1.98
Hosp heart failure (77)	0.59	0.39, 0.94
CV death (99)	0.81	0.54, 1.19
Composite (312)	0.78	0.63, 0.98

