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

Gregory G. Schwartz[1], Stephen J. Nicholls[2], Henry N. Ginsberg[3], Jan O. Johansson[4], Kamyar Kalantar-Zadeh[5], Ewelina Kulikowski[4], Peter P Toth[6], Norman Wong[4], Michael Sweeney[4], Kausik K Ray[7]

On behalf of the BETonMACE Investigators

[1]Division of Cardiology, University of Colorado School of Medicine, Aurora, CO USA; [2]Monash University Cardiovascular Research Center, Melbourne, Australia; [3]Vagelos College of Physicians and Surgeons, Columbia University, New York, NY USA; [4]Resverlogix Corp., Calgary, Alberta, Canada; [5]University of California Irvine School of Medicine, Orange, CA USA; [6]CGH Medical Center, Sterling, IL and Johns Hopkins University, Baltimore, MD USA; [7]Imperial College Center for Cardiovascular Disease Prevention, London UK

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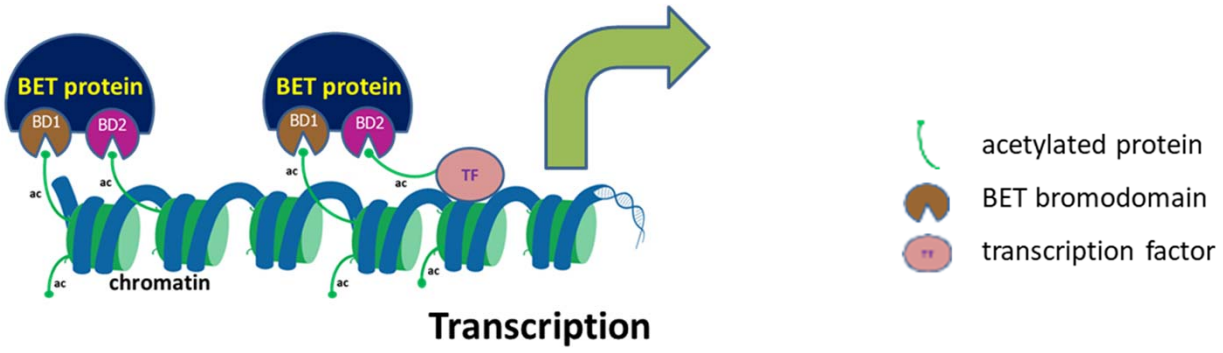
Background 1:
Epigenetic Regulation of Transcription by BET Proteins

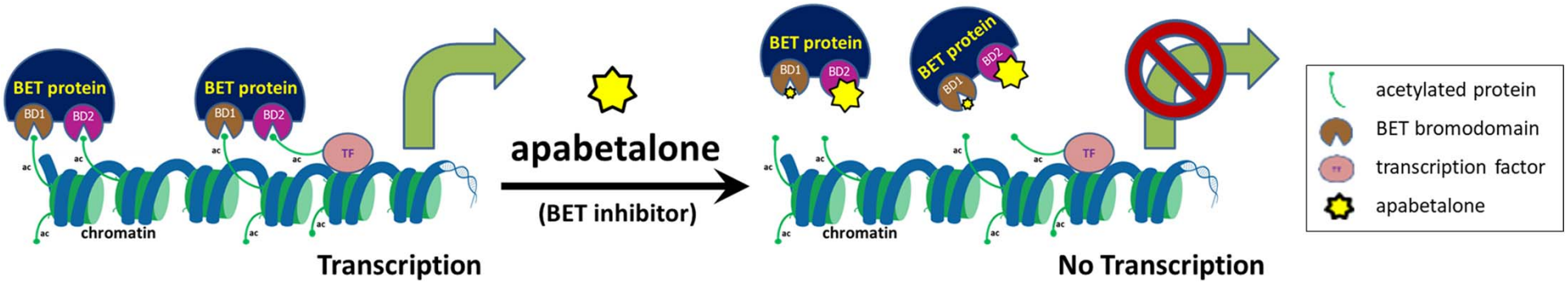
- Epigenetics refers to modifications to chromatin that regulate its activity
- Acetylated lysine residues on histone proteins are associated with active transcription regions of chromatin.
- **Bromodomain and Extraterminal (BET) proteins** bind to acetylated histones and recruit other transcription factors to bromodomains that drive gene expression.
- BET proteins may be pathologically activated under conditions of physiologic stress including diabetes and ischemic cardiovascular disease, promoting inflammation, coagulation, and vascular calcification.



Adapted from Ray KK et al., *Am Heart J* 2019; 217:72-83

Background 2:
BET Protein Inhibition with Apabetalone

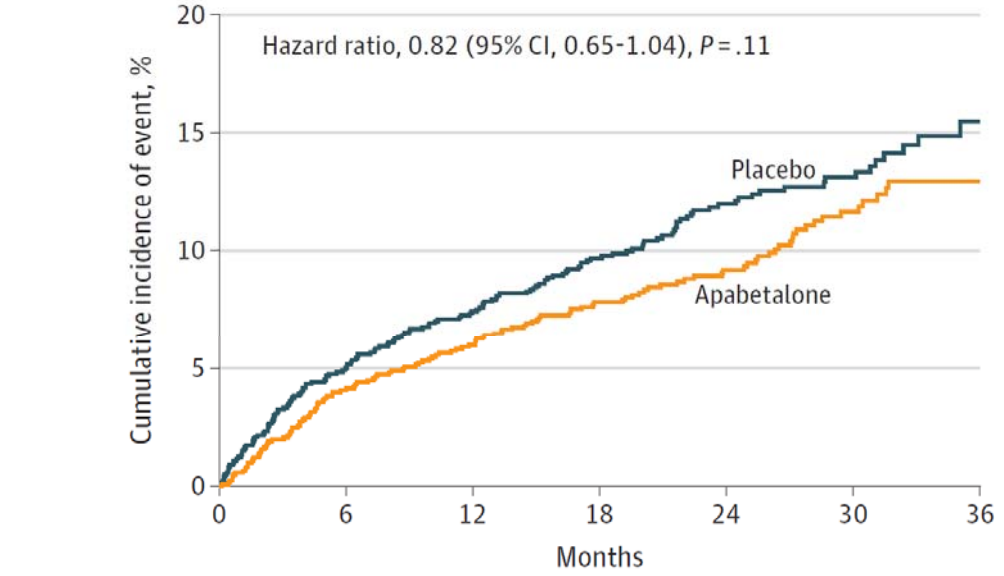
- **Apabetalone** is an orally active, small molecule BET protein inhibitor that binds to bromodomain BD2 to inhibit BET protein activity
- Apabetalone attenuated pathologic gene expression in preclinical models and in Phase 2 clinical studies.



Ray KK et al., *Am Heart J* 2019; 217:72-83

Background 3:
Design and Primary Results of the BETonMACE Trial

- Phase 3 cardiovascular outcomes trial
- **2425 patients with recent acute coronary syndrome, type 2 diabetes, and low HDL-C**
- Randomized treatment: **apabetalone 100 mg orally bid OR placebo**
- Median follow-up **26.5 months**
- **The primary endpoint** of major adverse cardiovascular events (MACE, comprising cardiovascular death, non-fatal MI or stroke) was numerically less frequent with apabetalone than placebo.



No. at risk							
Placebo	1206	1135	1102	937	641	383	108
Apabetalone	1212	1151	1114	950	672	397	107

Ray KK et al., *JAMA* 2020; 323:1565-73

Objective

- Despite current evidence-based treatments, patients receiving insulin for treatment of type 2 diabetes have a very high risk of MACE.[1,2]
- **The objective of this analysis** was to determine the relationship of insulin use to risk of MACE after ACS, and modification of that risk by apabetalone in the BETonMACE trial.

Methods

- Baseline characteristics were compared in patents treated versus not treated with insulin.
- Multivariable Cox regression analysis was performed to determine whether insulin treatment was an independent predictor of MACE.
- The incidence of MACE with apabetalone treatment hazard ratio (HR) was determined according to insulin treatment category.

Bundhun et al., *Cardiovasc Diabetol* 2015; 14:135; Mendez et al., *Postgrad Med* 2019; 131:376-382

Selected Baseline Characteristics

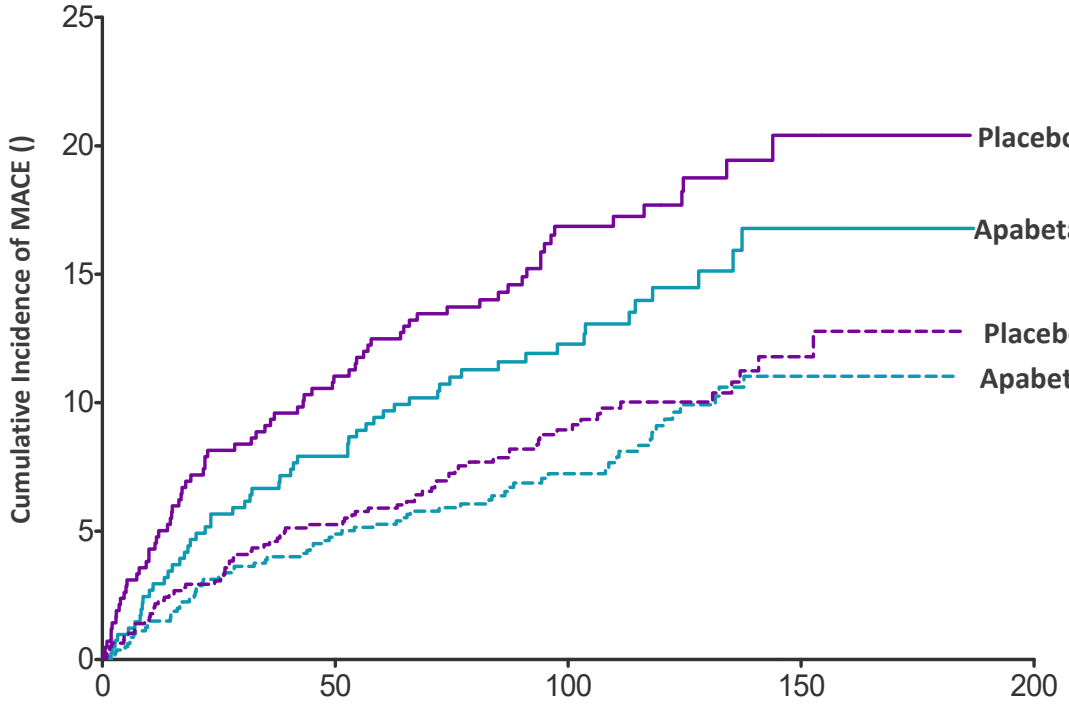
	All patients (N=2,418)	Insulin-treated (N=829)	Not insulin-treated (N=1,589)	Treated vs Not Treated P-value
Age, yrs, mean (SD)	61.3 (9.5)	61.0 (9.4)	61.4 (9.6)	0.36
Female, n (%)	**618 (25.6)**	**239 (28.8)**	**379 (23.9)**	**0.008**
Non-White Race, n (%)	**299 (12.4)**	**140 (16.9)**	**159 (10.0)**	**<0.0001**
Medical history				
Duration of diabetes, yrs (SD)	**8.5 (7.6)**	**12.6 (8.0)**	**6.4 (6.5)**	**<0.0001**
Prior MI, PCI, or CABG; n (%)	**865 (35.8)**	**331 (39.9)**	**534 (33.6)**	**0.002**
Heart failure; n (%)	**348 (14.4)**	**141 (25.0)**	**207 (13.0)**	**0.01**
Index ACS, n (%)				
STEMI	932 (52.7)	313 (37.8)	619 (39.0)	0.24
Non-STEMI	836 (47.3)	304 (36.7)	532 (33.5)	0.24
Unstable angina	625 (26.0)	200 (24.1)	425 (26.7)	0.19
Revascularization for index ACS	1,922 (79.5)	667 (80.5)	1,255 (79.0)	0.42
Cardiovascular and diabetes medications, n (%)				
High-intensity statin	**2,195 (90.2)**	**770 (92.9)**	**1,425 (89.7)**	**0.01**
ACE-inhibitor or ARB	2,229 (92.2)	770 (92.9)	1,459 (91.8)	0.40
Dual anti-platelet therapy	2,122 (87.8)	735 (88.7)	1,387 (87.3)	0.36
Metformin	**1,998 (82.6)**	**604 (72.9)**	**1,394 (87.7)**	**<0.0001**
Sulfonylurea	**707 (29.2)**	**177 (21.4)**	**530 (33.4)**	**<0.0001**
SGLT2 inhibitor	**298 (12.3)**	**137 (16.5)**	**161 (10.1)**	**<0.0001**
GLP-1 receptor agonist	**86 (3.6)**	**51 (6.2)**	**35 (2.2)**	**<0.0001**
Clinical chemistry, median (Q1–Q3)				
Estimated GFR (ml/min/1.73m^2)	98.3 (76.2 – 126.2)	95.7 (73.8 – 127.9)	99.7 (77.3 – 125.5)	0.23
Fasting glucose, mmol/L	**7.5 (6.1 – 9.7)**	**8.7 (6.8 – 11.4)**	**7.0 (5.9 – 9.0)**	**<0.0001**
Hemoglobin A1c,	**7.3 (6.4 – 8.7)**	**8.4 (7.5 – 9.6)**	**6.9 (6.2 – 7.8)**	**<0.0001**
LDL cholesterol, mmol/L	1.7 (1.3 – 2.2)	1.7 (1.3 – 2.2)	1.7 (1.3 – 2.2)	0.62

Insulin use is a predictor of MACE in unadjusted and adjusted Cox proportional hazards models

Model	Model Covariates	Placebo Insulin-Treated No. of Events/N (%)	Placebo Non-Insulin Treated No. of Events/N (%)	HR (95% CI) for Insulin Use	p-value
1	Unadjusted	73/420 (17.4)	76/786 (9.7)	1.89 [1.36 - 2.62]	0.0001
2	Age, sex, race, duration of diabetes, HbA1c, use of intensive statin, prior MI/PCI/CABG, and prior HF			1.86 [1.27 - 2.73]	0.0015
3	Model 2 plus adjustment for use of metformin, sulfonylurea, SGLT2i, and GLP-1RA			2.10 [1.42 – 3.10]	0.0002

Note: Hazard ratios are calculated by Cox proportional hazards model, stratified by country (countries with fewer than 100 patients combined) and baseline statin allocation

Cumulative Incidence of MACE by Insulin Treatment Category



HR = 0.80 (95% CI; 0.57 – 1.14)
p=0.23

HR = 0.85 (95% CI; 0.61 – 1.18)
p=0.42

Insulin x apabetalone: $p_{interaction}$= 0.78

No. at Risk					No. of Events	3-Yr Kaplan-Meier Event Rate	
Placebo +/+ Insulin	420	370	239	65	73	20.4	Δ = 3.6
Apabetalone +/+ Insulin	409	367	238	57	56	16.8	
Placebo -/- Insulin	786	736	462	106	76	12.8	Δ = 1.8
Apabetalone -/- Insulin	803	753	487	126	69	11.0	

Note: Hazard ratios are calculated by Cox proportional hazards model, stratified by country (countries with fewer than 100 patients combined) and baseline statin allocation

Limitations

1. Factors potentially associated with insulin use and prognostic for MACE, such as angiographic severity of coronary disease and left ventricular systolic function, were not captured in the trial database or considered in this analysis.

2. As a post hoc analysis of an overall neutral trial in numerically small subgroups, the effect of apabetalone according to insulin use should be interpreted cautiously and considered exploratory.

Conclusions

In patients with type 2 diabetes and recent ACS who receive intensive statin treatment, **insulin use:**

1. Is an independent predictor of higher risk for MACE

2. May identify patients who derive substantial absolute benefit from **apabetalone** treatment