THE EPIGENETIC BET-INHIBITOR APABETALONE REDUCES CARDIOVASCULAR EVENTS IN PATIENTS WITH TYPE 2 DIABETES, ACUTE CORONARY SYNDROME AND AN ELEVATED ANGULO NON-ALCOHOLIC FATTY LIVER DISEASE FIBROSIS SCORE - EXPLORATORY ANALYSIS OF THE BETONMACE TRIAL

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BACKGROUND

Non-alcoholic fatty-liver disease (NAFLD) is highly prevalent in patients (pts) with type 2 diabetes (T2DM) and associated with elevated cardiovascular (CV) risk. The pathogenesis of NAFLD may involve epigenetic dysregulation. Apabetalone (APB) is a novel bromodomain and extra-terminal (BET) protein inhibitor with potential effects to mitigate inflammatory, profibrotic, and prothrombotic processes that are associated with NAFLD and cardiovascular risk. The Angulo NAFLD fibrosis score (FS) is a biopsy-validated score that is associated with the degree of liver fibrosis in NAFLD.
In a *post hoc* analysis of the BETonMACE phase 3 trial in 2,425 pts with T2DM and acute coronary syndrome, we examined whether FS predicted CV risk and risk reduction with APB. We also evaluated the effect of APB on FS.

METHODS

FS was calculated using the Angulo NAFLD FS using 6 variables (age, BMI, hyperglycemia / diabetes, AST / ALT ratio, platelet count, and albumin). Patients were initially classified into three mutually exclusive categories according to their baseline Angulo FS <-1.455 (F0-F2), -1.455 to 0.675 (indeterminant), and >0.675 (F3-F4), where F0 through F4 connote fibrosis severity none, mild, moderate, severe, and cirrhosis, respectively. The exploratory *post hoc* composite of CV death, non-fatal myocardial infarction (MI), or stroke (MACE) and hospitalization for heart failure (HHF) in the placebo group was higher in indeterminant and F3-F4 categories compared to the F0-F2 category (17.2% vs 15.0% vs 9.7%). Therefore, for the present *post hoc* analysis, the former two categories were combined into an elevated NAFLD CVD risk group (FS+) that was compared with the F0-F2 group (lower NAFLD risk, $FS_{0\text{-}2}$).

RESULTS

- In the overall trial cohort, **APB treatment** was associated with **fewer primary endpoints of MACE (Hazard Ratio [HR] 0.82; 95% CI 0.65-1.04, p=0.11) (Figure 1),** and the exploratory *post hoc* **composite of MACE and HHF (Hazard Ratio [HR] 0.78; 95% CI 0.63-0.98, p=0.03) (Figure 2)**
- There were **618 patients** with a **low FS** (F0-F2) and **1,729 patients with higher FS** (patients in the indeterminate range or with F3-F4 fibrosis) **(FS+)**
- **FS+ pts** were **older (63 vs 56)**, had **longer duration of T2DM (9.0 vs 7.3 years)**, and **higher BMI (30.8 vs 28.6)** compared to F0-F2 pts **(Table 1)**
- Overall, **APB** was associated with **fewer MACE+HHF** compared to PBO in the FS+ pts **(HR 0.76; 95% CI 0.59-0.98, p=0.03)**, even when adjusted for age, duration of T2DM, and BMI **(HR 0.78; 95% CI 0.60-1.01, p=0.06) (Figure 3) (Table 2)**
- In the **FS+ group**, **APB reduced FS** over the duration of the trial compared to placebo **(p=0.02) (Figure 4)**

TABLE 1: Baseline Characteristics

	Full Study Cohort According to FS Category (n = 2,347)		
	FS+ Patients	**$F_{0\text{-}2}$ Patients**	**p-value**
Number of Participants	1,729	618	–
Fibrosis Score	**-0.17 (0.83)**	**-2.40 (0.97)**	**<0.0001**
Demographics			
Age, years	**63 (57 – 69)**	**57 (49 – 62)**	**<0.0001**
White, n (%)	**1,541 (89.1%)**	**513 (83.0%)**	**0.0001**
Body mass index, kg/m2	**30.8 (5.0)**	**28.6 (4.2)**	**<0.0001**
Hypertension history, n (%)	**1,566 (90.6%)**	**510 (82.5%)**	**<0.0001**
Smoking status, n (%)	**176 (10.2%)**	**89 (14.4%)**	**0.006**
Diabetes duration, years	**9.0 (7.8)**	**7.3 (6.9)**	**<0.0001**
Biochemical Parameters			
eGFR, mL/min/1.73 m^2	**95.8 (74.5 – 123.3)**	**106.4 (79.5 – 133.9)**	**<0.0001**
HbA1c, %	**7.3 (6.4 – 8.5)**	**7.6 (6.5 – 9.0)**	**0.0001**
Serum glucose, mg/dL	135.7 (110.8 – 175.5)	133.1 (109.3 – 172.9)	0.32
Total cholesterol, mg/dL	129.5 (109.8 – 157.0)	129.2 (112.5 – 153.8)	0.83
LDL cholesterol, mg/dL	65.2 (48.3 – 86.2)	65.0 (50.3 – 82.0)	0.97
HDL cholesterol, mg/dL	**33.6 (30.2 – 37.1)**	**32.9 (29.8 – 36.7)**	**0.008**
Triglycerides, mg/dL	147.5 (112.5 – 198.4)	150.1 (113.6 – 205.5)	0.25
Alkaline phosphatase, U/L	**76.0 (63.0 – 92.0)**	**82.0 (68.0 – 101.8)**	**<0.0001**
Alanine aminotransferase, U/L	**21.0 (16.0 – 29.0)**	**25.0 (18.0 – 34.0)**	**<0.0001**
Aspartate aminotransferase, U/L	19.0 (15.0 – 23.0)	18.0 (15.0 – 22.8)	0.07
AST / ALT, ratio	**0.86 (0.71 – 1.06)**	**0.73 (0.62 – 0.88)**	**<0.0001**
Albumin, g/L	**43.0 (41.0 – 44.0)**	**43.0 (41.0 – 45.0)**	**<0.0001**
Platelets, 10^9/L	**228.0 (194.0 – 262.0)**	**337.5 (295.0 – 385.0)**	**<0.0001**
Total bilirubin, umol/L	**9.4 (7.1 – 12.4)**	**8.3 (6.4 – 11.0)**	**<0.0001**
hsCRP, mg/L	2.7 (1.2 – 5.7) [n = 351]	3.7 (1.3 – 7.0) [n = 124]	0.16
NLR, ratio	2.5 (2.0 – 3.4)	2.6 (2.0 – 3.3)	0.21

Categorical variables are presented as n (%).
Continuous variables are presented as mean (SD) for normal data or median (quartile 1–quartile 3) for non-normal data.
P-values comparing groups at baseline were calculated using chi-square test for categorical variables, z-test for normal continuous variables, and Mann-Whitney Wilcoxon test for non-normal continuous variables

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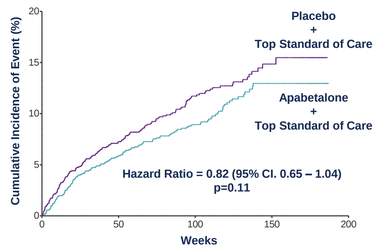
CONCLUSIONS

- This *post hoc* analysis of the BETonMACE trial identified pts with an elevated Angulo FS who appeared to be at a higher CV risk.
- Among these patients, APB treatment significantly reduced risk for MACE and HHF and attenuated the increase in hepatic FS over time.
- Further studies are needed to determine whether APB favorably modifies liver imaging or histology in conjunction with its effects on CV events.

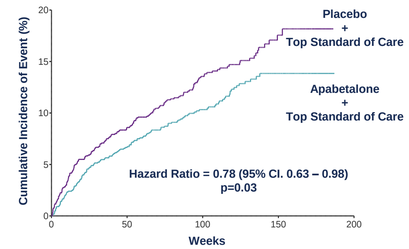
FIGURE 1



No. at Risk			No. of Events		
Placebo	1,206	1,105	724	183	149
APB	1,212	1,119	701	170	125

Kaplan-Meier estimate of time to first occurrence of MACE (CV death, MI, or stroke) in the BETonMACE trial

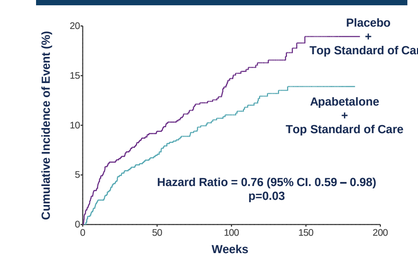
FIGURE 2



No. of Events				
1,206	1,091	688	168	173
1,212	1,109	710	181	139

Kaplan-Meier estimate of time to first occurrence of MACE (CV death, MI, or stroke) or HHF in the BETonMACE trial

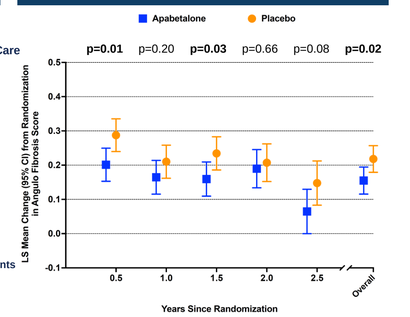
FIGURE 3



No. at Risk			No. of Events	
Placebo	877	787	488	121	135
APB	852	779	503	132	102

Kaplan-Meier estimate of time to first occurrence of MACE (CV death, MI, or stroke) or HHF in FS+ patients from the BETonMACE trial

FIGURE 4



Change in FS over time in FS+ patients according to assigned treatment group, analyzed using a repeated-measures mixed-effects model

TABLE 2

FS+ Patients According to Assigned Treatment Group (n = 1,729)

Kaplan-Meier Estimate of Time to First Occurrence	Hazard Ratio (HR) (95% CI)	p-value
Composite of MACE+HHF	**0.76 (95% CI 0.59 – 0.98)**	**0.03**
Adjusted for Age, T2DM Duration, and BMI	0.78 (95% CI 0.60 – 1.01)	0.06

DISCLOSURE INFORMATION

Dr. Toth is a speaker for Amarin, Amgen, Esperion, and Novo-Nordisk, and a consultant to Amarin, Amgen, Kowa, Merck, Resverlogix Corp., and Theravance.

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