Association of Serum Alkaline Phosphatase with CKD and Cognitive Function in Patients with Diabetes and Acute Coronary Syndrome

Mathias Haarhaus[1,2], Kausik K. Ray[3], Gregory G. Schwartz[4], Ewelina Kulikowski[5], Jan O. Johansson[6], Michael Sweeney[6], Aziz Khan[5], Christopher Halliday[5], Kenneth E. Lebioda[5], Norman C. Wong[5], Bengt Winblad[7], Henrik Zetterberg[8], Vincent Brandenburg[9], Srinivasan Beddhu[10], Marcello Tonelli[11], Carmine Zoccali[12], and Kamyar Kalantar-Zadeh[13,14]

[1]Division of Renal Medicine and Baxter Novum, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [2]Diaverum Sweden, Stockholm, Sweden; [3]Department of Primary Care and Public Health, School of Public Health, Imperial College London, London, United Kingdom; [4]School of Medicine, University of Colorado, Aurora, CO, United States; [5]Resverlogix Corp., Calgary, AB, Canada; [6]Resverlogix Inc., San Francisco, CA, United States; [7]Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Neurogeriatrics, Karolinska Institutet, Huddinge, Sweden; [8]Department of Psychiatry and Neurochemistry- Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [9]Department of Cardiology and Nephrology, Rhein-Maas-Klinikum, Würselen, Germany; [10]Division of Nephrology and Hypertension and Medical Service, Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, UT, United States; [11]Department of Medicine, University of Calgary, Calgary, AB, Canada; [12]CNR IFC, Clinical Epidemiology of Renal Diseases and Hypertension, Reggio Calabria, Italy; [13]Division of Nephrology and Hypertension, Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, School of Medicine, Orange, CA, United States; [14]Nephrology Section, Tibor Rubin Veterans Affairs Medical Center, Long Beach, CA, United States.

Background

Patients with diabetes and chronic kidney disease (CKD) have an increased risk for cardiovascular disease events and cognitive impairment. Alkaline phosphatase (ALP) is a risk marker and possible risk mediator for cardiovascular (CV) disease. Increased circulating levels of ALP associate with cognitive impairment, Alzheimer's disease and vascular dementia. Possible pathogenic mechanisms linking ALP to impaired cognition include disturbance of the blood brain barrier, impaired microcirculation, and dephosphorylation of tau. Apabetalone, a bromodomain and extraterminal (BET) inhibitor selective for bromodomain 2, lowers serum ALP and is being evaluated for prevention of CV disease events in the phase 3 BETonMACE trial. We examined baseline data from that trial to define the associations of ALP with CKD and cognitive function.

Methods

BETonMACE compares cardiovascular outcomes with apabetalone or placebo in 2,425 patients with diabetes and acute coronary syndrome. CKD was defined by eGFR <60 mL/min/1.73m^2. Cognition was assessed by the Montreal Cognitive Assessment tool (MoCA) in patients aged 70 and older at baseline (n=469) including in CKD patients (n=147).

Results

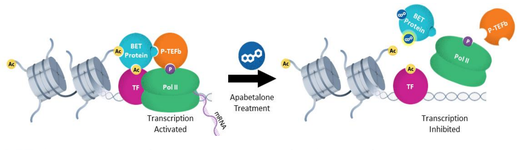
CKD was present in 11% (n=262) and was associated with age, female sex, longer history of diabetes, and higher ALP. Approximately half of the population showed MoCA score <26 suggesting early cognitive impairment. Lower MoCA score was associated with: a) higher ALP, and, b) with presence of CKD.

Summary

Elevated serum ALP is associated with poorer cognitive function and greater prevalence of CKD. Apabetalone, which lowers ALP, is being evaluated for effects on CV events, CKD, and cognitive function in the Phase 3 BETonMACE trial reporting 2019.

Apabetalone Mechanism of Action

BET proteins control gene transcription through interactions with transcription factors and recruitment of RNA polymerase II. Apabetalone binds to bromodomains in BET proteins, causing their release from chromatin and downregulation of BET sensitive gene expression.



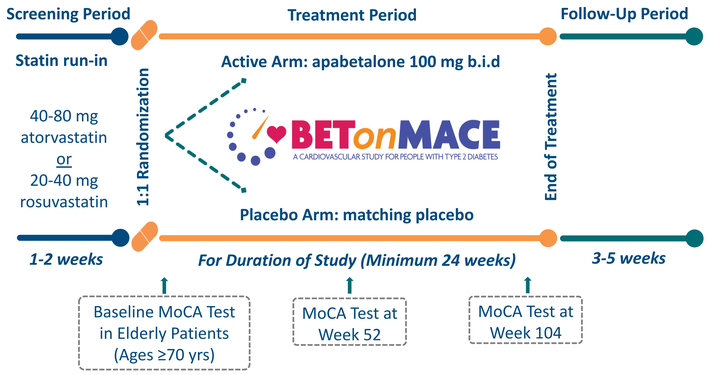
BET: bromodomain and extraterminal proteins
ac: acetylated lysine residue on DNA associated proteins
BD: bromodomain
TF: transcription factor

BETonMACE Baseline Characteristics

Clinical Characteristic	All Patients Randomized N	All Patients Randomized %	CKD (eGFR <60 mL/min/1.73m²) Subgroup N	CKD (eGFR <60 mL/min/1.73m²) Subgroup %	Non-CKD (eGFR ≥60 mL/min/1.73m²) Population N	Non-CKD (eGFR ≥60 mL/min/1.73m²) Population %	CKD Subgroup vs. Non-CKD Population p-value (Chi-Squared X² Test)
Age (yrs) (median) (min, max)	2,425	62 (31, 88)	262	71 (44, 88)	2,163	61 (31, 88)	***< 0.0001****
Sex (male)	1,806	74.5%	152	58.0%	1,654	76.5%	***< 0.0001***
Caucasian	2,115	87.2%	213	81.3%	1,902	87.9%	***0.002***
MoCA (≥70 yrs)	469	19.3%	147	56.1%	322	14.9%	***< 0.0001***
MoCA <26	246	52.5%	80	54.4%	166	51.6%	0.56
Index ACS Event:							
ACS / MI	1,787	73.7%	197	75.2%	1,590	73.5%	0.56
Unstable Angina	625	25.8%	63	24.0%	562	26.0%	0.50
History of PCI	1,930	79.6%	191	72.9%	1,739	80.4%	***0.004***
Medical History							
Diabetes History (median years) (IQR)		6.7 (2.2 – 13.0)		10.2 (3.8 – 18.0)		6.5 (2.1 – 12.4)	***< 0.0001 ****
BMI (kg/m²) (median) (IQR)		29.6 (26.7 – 33.2)		27.3 (24.5 – 30.1)		30.0 (27.0 – 33.6)	***< 0.0001 ****
Hypertension	2,144	88.4%	240	91.6%	1,904	88.0%	*0.09*
Tobacco Use	313	12.9%	17	6.5%	296	13.7%	***0.001***
Prior Stroke / TIA	184	7.6%	26	9.9%	158	7.3%	0.13
Cardiovascular Disease Medications:							
Atorvastatin	1,245	51.3%	141	53.8%	1,104	51.0%	0.40
Rosuvastatin	1,180	48.7%	121	46.2%	1,059	49.0%	
ACE Inhibitors	1,684	69.4%	162	61.8%	1,522	70.4%	***0.005***
ARBs	583	24.0%	82	31.3%	501	23.2%	***0.004***
Beta-Blockers	2,146	88.5%	232	88.5%	1,914	88.5%	0.98
Anti-Platelet Agents	2,392	98.6%	261	99.6%	2,131	98.5%	0.15
DAPT	2,086	86.0%	226	86.3%	1,860	86.0%	0.91
Diabetes Mellitus Medications:							
Insulin	769	31.7%	90	34.4%	679	31.4%	0.33
Diabetes Medications (Ex. Insulins):	2,072	85.4%	208	79.4%	1,864	86.2%	***0.003***
Metformin	1,866	76.9%	169	64.5%	1,697	78.5%	***< 0.0001***
Sulfonylureas	608	25.1%	73	27.9%	535	24.7%	0.27
DPP-4 Inhibitors	157	6.5%	30	11.5%	127	5.9%	***0.001***
SGLT2 Inhibitors	122	5.0%	7	2.7%	115	5.3%	*0.06*
GLP-1 Agonists	51	2.1%	2	0.8%	49	2.3%	0.11
Clinical Chemistry		**Median (IQR)**		**Median (IQR)**		**Median (IQR)**	
ALP† (U/L)	2,424	78 (64 – 94)	262	80 (64 – 97)	2,162	77 (64 – 94)	*0.07*
eGFR (mL/min/1.73m²)	2,413	99 (76 – 127)	262	49 (41 – 55)	2,151	104 (84 – 131)	***< 0.0001***
Albumin (g/dL)	2,413	4.30 (4.10 – 4.50)	262	4.20 (3.90 – 4.40)	2,151	4.30 (4.10 – 4.50)	***< 0.0001***
LDL-C (mg/dL)	2,395	65 (49 – 85)	262	65.5 (48 – 91)	2,133	65 (49 – 85)	0.62
HDL-C (mg/dL)	2,413	33 (30 – 37)	262	34 (30 – 37)	2,151	33 (30 – 37)	0.29
ApoA-1† (mg/dL)	483	118 (109 – 129)	50	119 (108 – 133)	433	118 (109 – 129)	0.95
hsCRP† (mg/dL)	493	2.81 (1.20 – 6.15)	53	3.45 (1.12 – 8.43)	440	2.74 (1.12 – 5.93)	0.23
Fibrinogen† (mg/dL)	471	385 (318 – 454)	51	396 (332 – 452)	420	384 (316 – 454)	0.32
HbA1c (%)	2,369	7.30 (6.40 – 8.70)	257	7.20 (6.40 – 8.50)	2,112	7.30 (6.40 – 8.70)	0.27
Platelets (10⁹/L)	2,295	249 (207 – 301)	251	241 (197 – 307)	2,044	250 (208 – 300)	0.34
NLR (ratio)	2,313	2.57 (1.99 – 3.36)	251	2.87 (2.20 – 3.90)	2,062	2.54 (1.95 – 3.31)	***< 0.0001***

Table Legend:
† results from visit 2 / week 0; all other values are from visit 1/screening
IQR: Interquartile Range
** Mann-Whitney U-Test (Wilcoxon Rank-Sum Test)*

BETonMACE Study Design

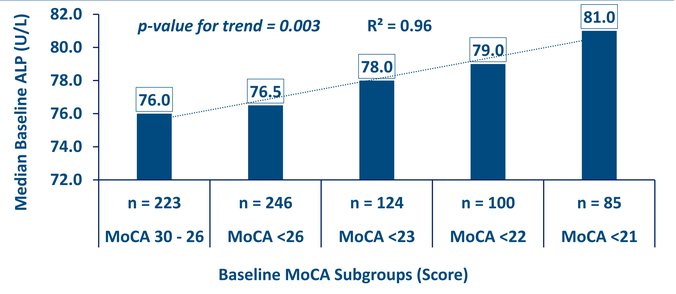


Inclusion criteria
- Type II Diabetes Mellitus (HbA1c > 6.5% or history of diabetes medications)
- CAD event 7 days - 90 days prior to screening including MI, unstable angina or percutaneous coronary intervention
- HDL < 45 mg/dL for males and < 45 mg/dL for females

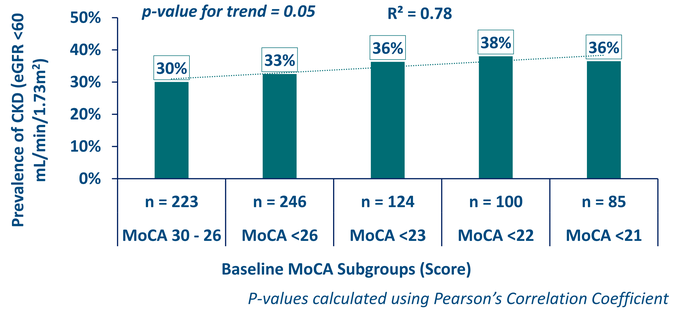
Primary Endpoint
- Time to first occurrence of adjudication-confirmed narrowly defined MACE (cardiovascular death, non-fatal MI and stroke)

The study is an event-based trial and continues until 250 MACE have occurred

Lower MoCA Scores Associates with Higher Serum ALP



Lower MoCA Scores Associates with Higher Prevalence of CKD



P-values calculated using Pearson's Correlation Coefficient

Summary and Conclusions

- Elevated circulating ALP is associated with poorer cognitive function.
- Patients with CKD exhibit higher serum ALP.
  - Apabetalone has been shown to lower serum ALP.
- Apabetalone is being evaluated for its effects on CV events, CKD, and cognitive function in the Phase 3 BETonMACE trial (reporting H2 2019).