NT-proBNP Levels in Diabetic Cardiomyopathy: Results from the ARISE-HF trial

APPLIED THERAPEUTICS

N. Ibrahim[1], J. Butler[2], WH. Wilson Tang[3], C. Lam[4], S. Del Prato[5], J. Ezekowitz[6], T. Marwick[7], R. Perfetti[8], J. Rosenstock[9], A. Urbinati[8], F. Zannad[10], J. Januzzi[11]

(1) Harvard T. H. Chan School of Public Health, Boston, United States of America (2) Baylor Scott & White Health, Dallas, United States of America (3) Cleveland Clinic, Cleveland, United States of America (4) Duke-NUS Graduate Medical School Singapore, Singapore, Singapore (5) University of Pisa, Pisa, Italy (6) University of Alberta, Edmonton, Canada (7) Baker Heart and Diabetes Institute, Melbourne, Australia (8) Applied Therapeutics, New York City, United States of America (9) Dallas Diabetes Research Center, Dallas, United States of America (10) University of Lorraine, Nancy, France (11) Massachusetts General Hospital - Harvard Medical School, Boston, United States of America

BACKGROUND

Diabetic Cardiomyopathy (DbCM) is a major cardiovascular complication in the absence of other risk factors such as coronary artery disease or uncontrolled blood pressure in individuals with diabetes. The ARISE-HF study is evaluating the safety and efficacy of a new highly selective aldose reductase inhibitor (AT-001) to improve or prevent the decline of cardiac functional capacity in individuals with DbCM.

PURPOSE

The main objective of this analysis is to assess plasma concentrations of N-terminal pro-B type natriuretic peptide (NT-proBNP) to characterize the cardiac status of individuals with DbCM enrolled into the ARISE-HF study.

METHODS

679 patients with DbCM defined by either structural/functional cardiac abnormalities or elevated natriuretic peptide or troponin concentrations along with impaired cardiac functional capacity were evaluated as a function of NT-proBNP at enrollment. Clinical and echocardiographic parameters correlating with NT-proBNP levels were determined using univariable and multivariable linear-regression analysis.

RESULTS

Median NT-proBNP in the overall study population was 71 ng/L (IQR 35-133). Main baseline characteristics were similar across baseline NT-proBNP concentrations, however participants with higher NT-proBNP levels had a greater left atrial volume (LAVI) (p<0.001) and higher right ventricular systolic pressure (p=0.04) on baseline echocardiogram. Higher NT-proBNP concentrations were associated with reduced physical activity reflected in lower Physical Activity Scale for the Elderly (PASE) Score (p<0.001) and a worse quality of life defined by a lower mKCCQ score (p=0.02). Individuals with higher plasma concentrations of NT-proBNP had lower cardiac functional capacity reflected in lower peak VO_2 and a higher anaerobic threshold represented by the minute ventilation/carbon dioxide production (VE/VCO2) (p=0.03) (Figure 1).

	Quartiles of NT-proBNP				
	Q1 N=169	Q2 N=169	Q3 N=169	Q4 N=172	P
Age (yrs)	64.3 (7.1)	67.8 (7.0)	68.2 (6.5)	69.8 (7.0)	<0.001
Male (n, %)	116 (68%)	84 (50%)	74 (44%)	64 (37%)	<0.001
BMI (kg/m^2)	30.9 (4.3)	30.8 (4.4)	30.3 (4.7)	30.2 (4.7)	0.41
SBP (mmHg)	130.7 (13.7)	129.8 (12.0)	129.5 (12.3)	129.7 (13.0)	0.73
Medical History					
Duration of T2DM (yrs)	13.5 (8.4)	13.5 (9.8)	14.6 (8.9)	14.4 (9.6)	0.52
Hypertension (n, %)	115 (68%)	110 (65%)	113 (67%)	125 (73%)	0.53
Dyslipidemia (n, %)	27 (16%)	26 (15%)	25 (15%)	29 (17%)	0.89
Concomitant medications (n, %)					
ACEI-ARBs	121 (71%)	100 (59%)	120 (71%)	114 (67%)	0.06
B-blockers	12 (7%)	23 (14%)	45 (27%)	57 (34%)	<0.001
SGLT2 inhibitors	50 (29%)	43 (25%)	43 (25%)	46 (27%)	0.89
GLP1-RA	54 (32%)	27 (16%)	28 (17%)	31 (18%)	<0.001
Laboratory test					
NTproBNP (ng/L)	18 (10-27)	54 (54-62)	94 (80-111)	200 (152-292)	<0.001
Hs-Tnt (ng/L)	6 (8-12)	9 (6-12)	8 (6-12)	9 (6-13)	0.45
HbA1c (%)	7.11 (0.77)	6.99 (0.83)	6.92 (0.75)	6.89 (0.79)	0.07
Hgb (g/dl)	14.2 (1.3)	13.8 (1.4)	13.5 (1.4)	13.2 (1.3)	<0.001
eGFR (ml/min/1.73m^2)	85.0 (15.7)	82.6 (15.0)	79.0 (16.7)	75.2 (16.2)	<0.001
Echocardiogram					
LVEF (%)	62.3 (5.1)	62.2 (5.7)	61.8 (5.2)	62.5 (5.9)	0.72
GLS (%)	-17.1 (2.9)	-17.5 (3.0)	-17.8 (2.8)	-17.7 (3.6)	0.25
LAVI (ml/m^2)	22.4 (7.3)	24.0 (7.1)	24.7 (7.3)	27.1 (7.5)	<0.001
LVMI (g/m^2)	75.9 (19.8)	79.0 (20.0)	75.7 (20.7)	80.2 (22.9)	0.08
E/e'	9.9 (5.0)	10.3 (3.8)	10.8 (4.4)	10.6 (4.5)	0.38
RVSP (mmHg)	21.8 (8.1)	22.8 (7.5)	24.1 (6.6)	24.6 (7.5)	0.04
mKCCQ questionnaire	92.3 (12.5)	91.2 (13.7)	89.5 (15.9)	88.0 (16.0)	0.02
PASE score	161.4 (94.9)	169.7 (98.8)	152.3 (79.8)	133.7 (79.2)	<0.001
CPET					
PeakVO$_2$ (ml/min/kg)	17.2 (3.9)	15.8 (3.6)	15.4 (3.9)	14.5 (3.4)	<0.001
VE/VCO$_2$	30.6 (4.8)	30.7 (5.1)	31.4 (5.6)	32.2 (6.0)	0.03

Results of the univariable and multivariable correlation of clinical and echocardiographic parameters with log-NT-proBNP are given in Figure 2. In a multivariable model age, sex, eGFR, Hgb, and LAVI were independent predictors for log-NT-proBNP levels.

Univariable correlation		
	Spearman's correlation coefficient	P-value
Age	0.271	<0.001
BMI	-0.062	0.11
SBP	-0.029	0.46
Male	-0.231	<0.001
Black or African American	-0.044	0.25
eGFR	-0.226	<0.001
Hgb	-0.297	<0.001
LAVI	0.272	<0.001
E/e'	0.094	0.02
GLS	-0.093	0.05
LVMI	0.074	0.06
RVSP	0.149	<0.001

Multivariable correlation		
	Standardized ß regression coefficient	p-value
Age	0.184	<0.001
Male	-0.225	<0.001
eGFR	-0.154	0.01
Hgb	-0.145	0.03
LAVI	0.165	<0.001
E/e'	-0.043	0.44
LVMI	0.103	0.08
GLS	-0.032	0.56
RVSP	0.031	0.58

CONCLUSIONS

- Elevated levels of NT-proBNP, even at values below the diagnostic threshold for overt HF, are associated with more severe echocardiographic changes and worse cardiac functional capacity in individuals with DbCM.
- The ARISE-HF study is evaluating the safety and efficacy of AT-001 to improve or prevent the decline of cardiac functional capacity in individuals with DbCM.