

Effects of Alogliptin and Placebo on N-Terminal-pro-Brain Natriuretic Peptide in Patients with Type 2 Diabetes and Recent Acute Coronary Syndromes

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INTRODUCTION

In patients with type 2 diabetes (T2D) and recent acute coronary syndrome (ACS), EXAMINE showed that cardiovascular (CV) event rates, mortality and hospitalized heart failure (HHF) with the DPP-4 inhibitor alogliptin were not increased compared with placebo, including in patients with history of HF and elevated levels of brain natriuretic peptide (BNP).
 Although it has been reported that BNP is a substrate to DPP-4, there is no evidence that this might be also the case for N-terminal pro-BNP (NT-pro-BNP).

HYPOTHESIS

In an on-treatment biomarker study, we investigated the effects of alogliptin on NT-pro-BNP, a HF biomarker likely less affected by DPP4 inhibition.

METHODS

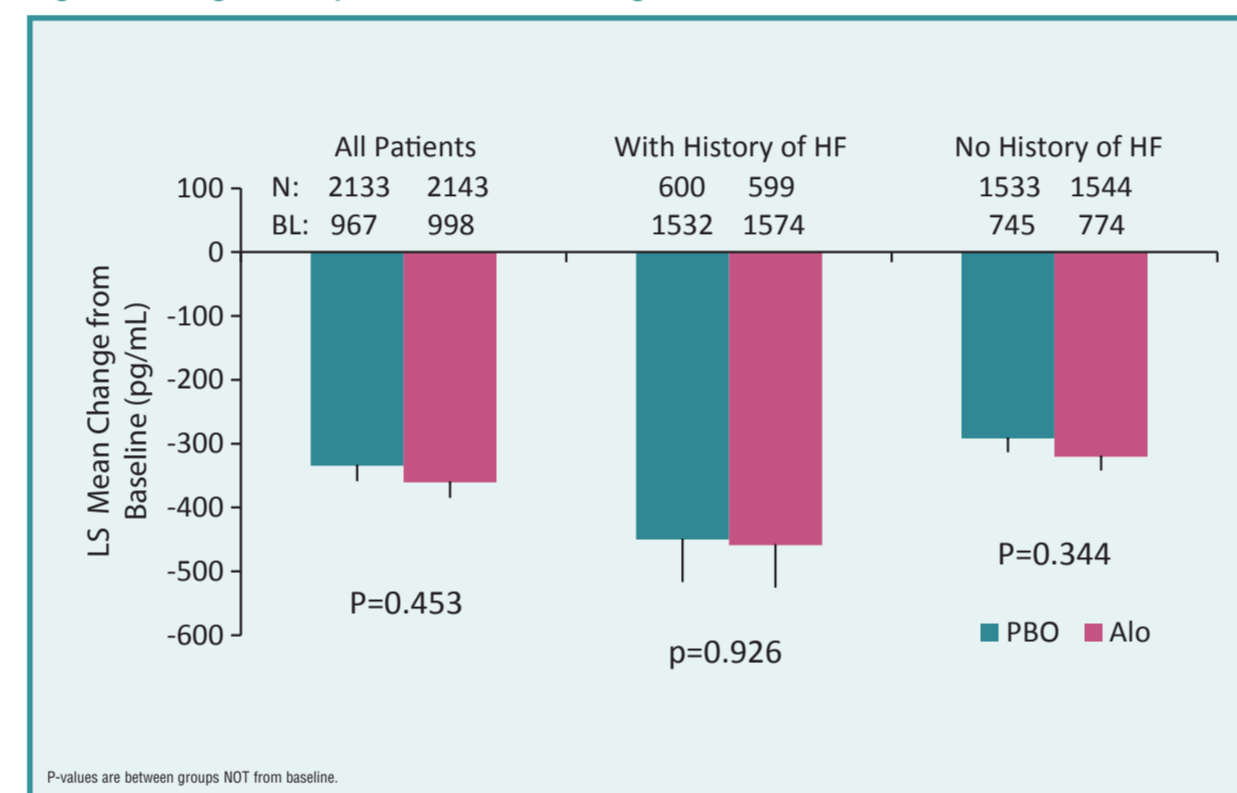
Patients with T2D who had an ACS within the previous 15-90 days were randomly assigned to alogliptin or placebo added to existing anti-hyperglycemic and cardiovascular therapies. Patients with compensated HF were included (28% at baseline). Among patients, NT-pro-BNP was measured in all 5380 randomized patients at baseline and 6 months post-randomization, using ELISA (Roche Diagnostics (Indianapolis, IN) NT-pro-BNP on the Cobas 6000 analyzer). Changes from baseline were assessed with an ANCOVA model controlling for treatment, geographic region, kidney function, and baseline NT-pro-BNP.

RESULTS

Table 1. Baseline Patient Characteristics by History of Heart Failure Prior to Randomisation

Characteristic	History of Heart Failure Prior to Randomisation		No History of Heart Failure Prior to Randomisation	
	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Median age – years	63	62	60	60
Age ≥ 65 years – no. (%)	337 (43.7)	305 (40.0)	636 (33.0)	629 (32.8)
Male sex – no. (%)	467 (60.6)	464 (60.9)	1361 (70.5)	1359 (70.9)
Duration of Diabetes, years – median (range)	7.9 (0.0, 39.2)	6.8 (0.0, 48.5)	6.8 (0.0, 44.3)	7.3 (0.0, 49.9)
Baseline Glycated hemoglobin – mean (SD)	8.12 (1.12)	8.15 (1.12)	7.99 (1.07)	7.99 (1.10)
Median body weight – kg (range)	82.3 (17.4, 151.5)	82.3 (39.0, 196.3)	79.2 (36.0, 185.0)	79.2 (35.5, 189.6)
BMI – median (range)*	29.7 (17.4, 51.2)	29.5 (15.9, 60.6)	28.5 (15.7, 55.9)	28.5 (15.6, 68.3)
White	634 (82.2)	604 (79.3)	1332 (69.0)	1339 (69.8)
Black	39 (5.1)	40 (5.2)	62 (3.2)	75 (3.9)
Asian	83 (10.8)	107 (14.0)	464 (24.0)	435 (22.7)
Cardiovascular Risk Factors and History – no. (%)				
Current smoker	72 (9.3)	105 (13.8)	279 (14.5)	278 (14.5)
Hypertension	704 (91.3)	694 (91.1)	1525 (79.0)	1546 (80.6)
Myocardial infarction**	689 (89.4)	691 (90.7)	1700 (88.1)	1654 (86.3)
Percutaneous coronary intervention**	389 (50.5)	391 (51.3)	1300 (67.4)	1292 (67.4)
Coronary artery bypass grafting**	125 (16.2)	124 (16.3)	222 (11.5)	217 (11.3)
Stroke	29 (3.8)	24 (3.1)	46 (2.4)	46 (2.4)
Peripheral arterial disease	117 (15.2)	124 (16.3)	145 (7.5)	128 (6.7)
Median renal function (eGFR)†	66.40	64.96	72.65	73.17
eGFR > 60 ml/min/1.73m ² – no./total no. (%)	482 (62.5)	454 (59.6)	1447 (75.0)	1432 (74.7)
eGFR < 60 ml/min/1.73m ² – no./total no. (%)	289 (37.5)	308 (40.4)	483 (25.0)	485 (25.3)
Index Inclusion ACS – no. (%)				
Myocardial infarction	536 (69.5)	555 (72.8)	1548 (80.2)	1513 (78.9)
Unstable angina	234 (30.4)	203 (26.6)	375 (19.4)	402 (21.0)
Time Post-Index ACS to Randomization, Days				
Median	47.0	48.0	42.0	44.0
Interquartile range	32.0, 69.0	31.0, 69.0	29.0, 62.0	29.0, 62.0
CHF NYHA – no. (%)				
NYHA I	174 (22.6)	157 (20.6)	NA	NA
NYHA II	424 (55.0)	441 (57.9)	NA	NA
NYHA III	148 (19.2)	136 (17.8)	NA	NA
NYHA IV	10 (1.3)	10 (1.3)	NA	NA
Baseline NT-pro-BNP (pg/ml)				
Median	699	630	381	342
Interquartile range	210,1724	232,1652	145,905	133,835
Baseline Concomitant Cardiovascular Medications				
ACE inhibitor and/or ARB	668 (86.6%)	651 (85.4%)	1533 (79.4%)	1559 (81.3%)
ACE inhibitor	525 (68.1%)	479 (62.9%)	1156 (59.9%)	1163 (60.7%)
ARB	166 (21.5%)	185 (24.3%)	408 (21.1%)	431 (22.5%)
Beta Blockers	648 (84.0%)	629 (82.5%)	1560 (80.8%)	1574 (82.1%)
Diuretics (all)	466 (60.4%)	467 (61.3%)	539 (27.9%)	542 (28.3%)
Thiazide diuretics	138 (17.9%)	152 (19.9%)	263 (13.7%)	263 (13.7%)
Loop diuretics	254 (32.9%)	250 (32.8%)	228 (11.8%)	208 (10.9%)
MRAs	207 (26.8%)	179 (23.5%)	145 (7.5%)	149 (7.8%)

Figure 1. Changes in NT-pro-BNP values following 6 months of treatment in EXAMINE

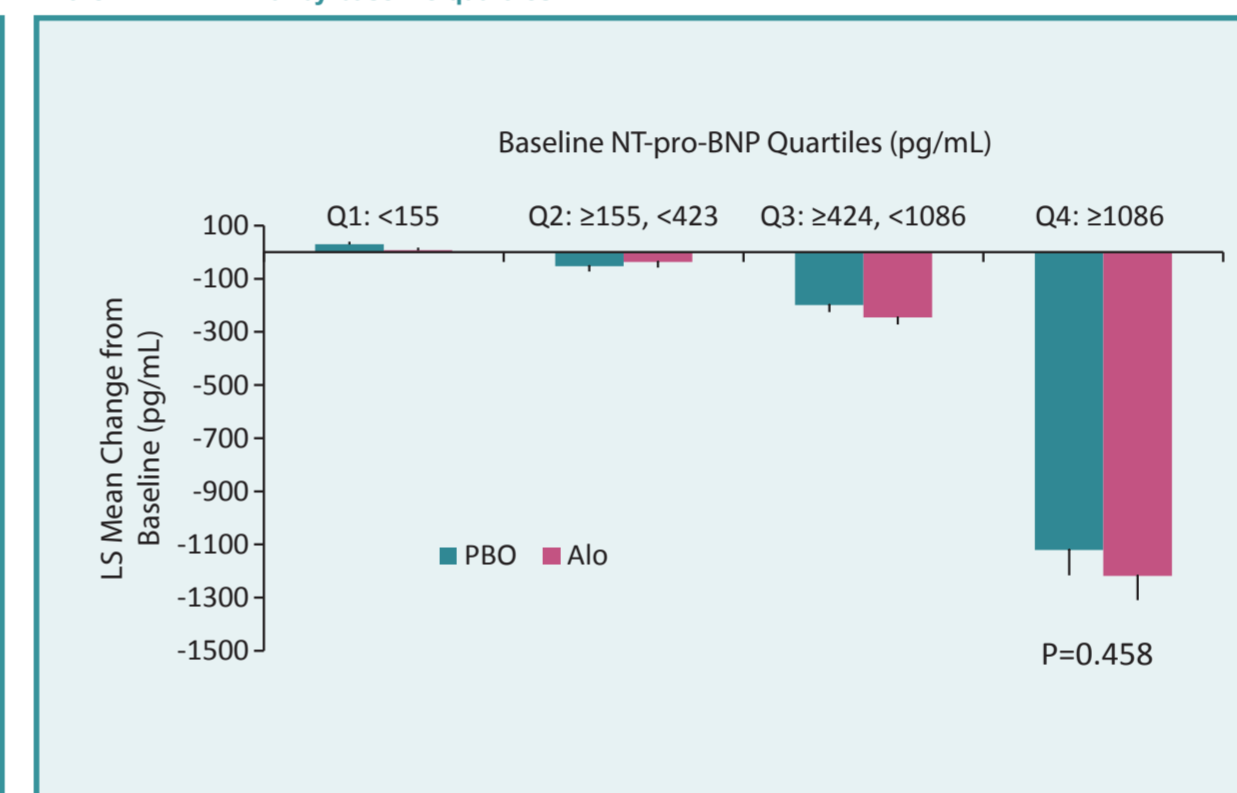


- NT-pro-BNP
 - Was highest at baseline in patients with history of HF
 - Decreased as expected 6 months post-ACS while under the treatment of site investigator-cardiologists
 - Decreased equally in the alogliptin and the placebo groups

Table 2. Primary MACE by Quartile of Baseline NT-pro-BNP

	Q1: <155		Q2: ≥155, <423		Q3: ≥424, <1086		Q4: ≥1086	
	Alo	PBO	Alo	PBO	Alo	PBO	Alo	PBO
Primary MACE n (%)	31 (4.8)	35 (5.3)	54 (8.2)	52 (8.1)	80 (12.4)	74 (11.2)	134 (19.9)	146 (23.2)
CV death	1 (0.2)	4 (0.6)	10 (1.5)	5 (0.8)	22 (3.4)	25 (3.8)	51 (7.6)	73 (11.6)
Non-Fatal MI	25 (3.9)	26 (4.0)	41 (6.2)	40 (6.2)	48 (7.5)	42 (6.4)	72 (10.7)	60 (9.5)
Non-Fatal Stroke	5 (0.8)	5 (0.8)	3 (0.5)	7 (1.1)	10 (1.6)	7 (1.1)	11 (1.6)	13 (2.1)
Hazard Ratio (alo/pbo)	0.927		1.058		1.123		0.819	
2-sided 95% CI	(0.573, 1.501)		(0.725, 1.545)		(0.819, 1.540)		(0.649, 1.034)	
2-sided P-value	0.758		0.770		0.472		0.093	

Figure 2. Changes from Baseline in NT-pro-BNP levels on alogliptin and placebo following 6 months in the EXAMINE Trial by baseline quartiles

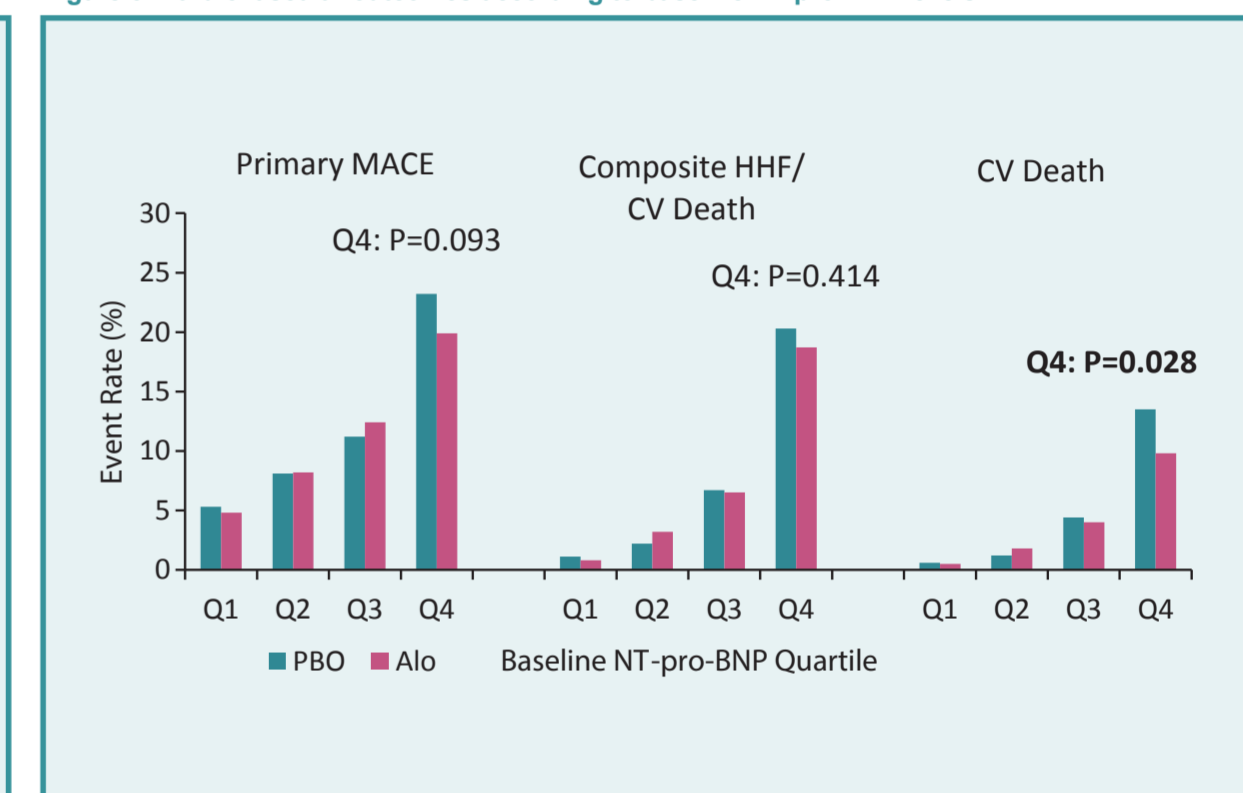


- NT-pro-BNP decreased equally in patients treated with alogliptin and patients treated with placebo, in all subgroups of baseline NT-pro-BNP

Table 3. Composite of HHF and CV Death by Quartile of Baseline NT-pro-BNP

	Q1: <155		Q2: ≥155, <423		Q3: ≥424, <1086		Q4: ≥1086	
	Alo	PBO	Alo	PBO	Alo	PBO	Alo	PBO
Composite Endpoint	5 (0.8%)	7 (1.1%)	21 (3.2%)	14 (2.2%)	42 (6.5%)	44 (6.7%)	126 (18.7%)	128 (20.3%)
CV death	3 (0.5%)	4 (0.6%)	12 (1.8%)	7 (1.1%)	24 (3.7%)	27 (4.1%)	52 (7.7%)	70 (11.1%)
HHF	2 (0.3%)	3 (0.5%)	9 (1.4%)	7 (1.1%)	18 (2.8%)	17 (2.6%)	74 (11.0%)	58 (9.2%)
Hazard Ratio (alo/pbo)	0.733		1.468		1.015		0.902	
2-sided 95% CI	(0.235, 2.284)		(0.762, 2.829)		(0.663, 1.553)		(0.704, 1.156)	
2-sided P-value	0.592		0.251		0.946		0.414	

Figure 3. Cardiovascular outcomes according to baseline NT-pro-BNP levels in EXAMINE



- Baseline NT-pro-BNP levels were predictive of CV outcomes in both treatment groups
- Alogliptin had no significant effect on the rate of MACE (primary outcome), or on the composite of hospitalisations for heart failure + Cardiovascular death (secondary outcome); it was associated with a significantly lower CV death rate in the highest risk group (highest NT-pro-BNP quartile)

Table 4. CV Death by Quartile of Baseline NT-pro-BNP

	Q1: <155		Q2: ≥155, <423		Q3: ≥424, <1086		Q4: ≥1086	
	Alo	PBO	Alo	PBO	Alo	PBO	Alo	PBO
CV death n (%)	3 (0.5)	4 (0.6)	12 (1.8)	8 (1.2)	26 (4.0)	29 (4.4)	66 (9.8)	85 (13.5)
Hazard Ratio (alo/pbo)	0.777		1.498		0.927		0.699	
2-sided 95% CI	(0.179, 3.377)		(0.622, 3.606)		(0.545, 1.577)		(0.508, 0.962)	
2-sided P-value	0.736		0.368		0.779		0.028	

CONCLUSIONS

- NT-pro-BNP decreased equally with alogliptin and placebo in a post-ACS T2D population following 6 months of therapy.
- NT-pro-BNP was not increased by alogliptin – even in patients with a prior history of HF and/or with high baseline NT-pro-BNP levels – supporting the notion that this DPP-4 inhibitor does not increase LV filling pressures consistent with the lack of increases in heart failure outcomes.

REFERENCES

White WB, Cannon CP, Heller SR, et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327-35.