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Supplemental methods

Study participants

The present analyses comprise 496 out of 544 patients recruited between 2008 and 2015 who had an echocardiographic examination at study baseline. The remaining 48 patients had no baseline echocardiographic studies for technical reasons (unavailability of the operator who performed the echocardiographic examinations). These 48 patients did not differ in age, gender, eGFR, blood pressure and CV event rate from those 496 patients who had a baseline echocardiographic examination.

Baseline examination

A standardized questionnaire was used to record prevalent diabetes mellitus, current drug intake, cardiovascular (CV) comorbidity (defined as a history of myocardial infarction, coronary artery angioplasty / stenting / bypass surgery, major stroke, carotid endarterectomy / stenting, non-traumatic lower extremity amputation, or lower limb artery bypass surgery / angioplasty / stenting), family history of premature CV events and a history of smoking. In addition, comorbidity was assessed by means of chart review.

Patients were categorized as active smokers if they were current smokers or had stopped smoking <1 month before entry into the study. Patients with self-reported or physician-reported diabetes mellitus, with a fasting blood glucose level of >126 mg/dl or with current use of hypoglycemic medication, were categorized as diabetic.

Weight and height was measured in all patients. Body mass index (BMI) was calculated as weight (kg) / (height (m))², and body surface area (BSA) was estimated as ([height (cm) x weight (kg)] / 3600) $^{0.5}$) (1).

Echocardiography measurements

Left-ventricular mass (LVM) and left-atrial volume (LAV) was determined by using the formula suggested by ASE guidelines (2):

$LVM = 0.8 \times \{1.04[(LVD + PWT + SWT)^3 - (LVD)^3]\} + 0.6$ g,

where LVD is the LV diameter at end diastole and PWT / SWT are posterior and septal wall thickness at end diastole.

$LAV = 8/3\ \pi\ [(A1) \times (A2) / L]$,

where A1 is the LA area in an apical four-chamber view, A2 the LA area in an apical two-chamber view, and L the shorter LA length measured from the back wall to line across the hinge points.

Dividing LVM and LAV by BSA yielded the LVM index (LVMI) and LAV index (LAVI), respectively, which account for variations in body size.

Supplemental Results

During 4.5±2.0 years of follow-up, 104 patients suffered HF/ACM (in detail: 50 patients with HF decompensation, 54 patients with death of any cause without preceding HF decompensation), while 127 (26%) suffered the second primary end-point AE/ACM (in detail: 7 patients with fatal or non-fatal acute myocardial infarction, 22 patients with percutaneous coronary intervention, 3 patients with coronary artery bypass grafting, 22 patients with fatal or non-fatal stroke, 3 patients with carotid stenting / surgery, 20 patients with lower limb artery bypass surgery / angioplasty / stenting, one patient with amputation above the ankle, 26 patients with other fatal cardiovascular events, 23 patients with death of non-cardiovascular cause; in case of multiple events, only the first event is listed).

References

1. Mosteller, RD: Simplified calculation of body-surface area. *N Engl J Med,* 317**:** 1098, 1987.

2. Lang, RM, Bierig, M, Devereux, RB, Flachskampf, FA, Foster, E, Pellikka, PA, Picard, MH, Roman, MJ, Seward, J, Shanewise, JS, Solomon, SD, Spencer, KT, Sutton, MS & Stewart, WJ: Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr,* 18**:** 1440-63, 2005.

Supplemental table S1. Baseline characteristics of study participants, divided by tertiles of NT-proBNP

	Total cohort (n=496)	NT-proBNP 1st tertile (n=166)	NT-proBNP 2nd tertile (n=165)	NT-proBNP 3rd tertile (n=165)	p-value
Age (years)	65.0 ± 12.4	57.4 ± 12.7	67.1 ± 10.4	70.6 ± 10.2	**<0.001**
Gender (female)	205 (41 %)	58 (35 %)	86 (52 %)	61 (37 %)	**0.002**
Prevalent CVD	160 (32 %)	31 (19 %)	45 (27 %)	84 (51 %)	**<0.001**
BMI (kg/m²)	30.4 ± 5.5	30.7 ± 5.5	30.3 ± 6.0	30.1 ± 5.0	0.60
Diabetes mellitus	188 (38 %)	51 (31 %)	58 (35 %)	79 (48 %)	**0.004**
Current nicotine	54 (11 %)	24 (14 %)	12 (7 %)	18 (11 %)	0.11
Cholesterol (mg/dl)	192 ± 43	196 ± 41	195 ± 45	186 ± 42	0.06
NT-proBNP (pg/ml)	211 (90 - 602)	63 (39 - 90)	211 (156 - 276)	1040 (603 - 2051)	**<0.001**
CRP (mg/l)	2.7 (1.2 - 5.0)	2.7 (1.2 - 4.3)	2.2 (0.9 - 4.7)	3.5 (1.5 - 7.2)	**0.003**
Phosphorus (mg/dl)	3.37 ± 0.68	3.17 ± 0.56	3.33 ± 0.58	3.61 ± 0.81	**<0.001**
Parathyroid hormone (pg/ml)	52 (37 - 82)	43 (33 - 58)	49 (37 - 65)	82 (48 - 131)	**<0.001**
eGFR (ml/min/1.73m²)	46 ± 16	56 ± 14	47 ± 14	36 ± 13	**<0.001**
CKD stage					**<0.001**
G2	103 (21 %)	61 (37 %)	35 (21 %)	7 (4 %)	
G3a	169 (34 %)	75 (45 %)	60 (36 %)	34 (21 %)	
G3b	137 (28 %)	24 (14 %)	48 (29 %)	65 (39 %)	
G4	87 (18 %)	6 (4 %)	22 (13 %)	59 (36 %)	
Albuminuria (mg/g creatinine)	32 (7 - 201)	18 (5 - 118)	21 (7 - 115)	87 (24 - 402)	**<0.001**
Systolic BP (mmHg)	152 ± 24	148 ± 19	153 ± 23	157 ± 28	**0.002**
Diastolic BP (mmHg)	86 ± 13	87 ± 11	87 ± 14	83 ± 14	**0.002**
ACE-inhibitors	171 (34 %)	59 (36 %)	53 (32 %)	59 (36 %)	0.74
Angiotensin receptor blockers	251 (51 %)	83 (50 %)	94 (57 %)	74 (45 %)	0.09
Aldosteron receptor blocker	111 (22 %)	27 (16 %)	45 (27 %)	39 (24 %)	0.05
Beta blockers	341 (69 %)	78 (47 %)	120 (73 %)	143 (87 %)	**<0.001**
Loop diuretics	216 (44 %)	36 (22 %)	63 (38 %)	117 (71 %)	**<0.001**
Thiazide / thiazide-like diuretics	254 (51 %)	85 (51 %)	86 (52 %)	83 (50 %)	0.95
Statins	254 (51 %)	74 (45 %)	88 (53 %)	92 (56 %)	0.10
LVMI (g/m²)	92.8 ± 28.0	82.8 ± 21.0	88.2 ± 24.4	107.9 ± 31.3	**<0.001**
E / e’	8.9 ± 3.3	7.3 ± 2.2	8.7 ± 2.9	10.7 ± 3.8	**<0.001**
LAVI (ml/m²)	37.9 ± 12.9	30.6 ± 8.3	36.9 ± 11.0	46.3 ± 13.5	**<0.001**
Impaired systolic LV function	65 (13 %)	4 (2 %)	14 (8 %)	47 (28 %)	**<0.001**

Data are presented as mean ± SD or median (interquartile range) for continuous variables, numbers of patients (percentage) for categorical variables; CVD: cardiovascular disease; BMI: body mass index; CRP: c-reactive protein; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; BP: blood pressure, LVMI:

left-ventricular mass index; LAVI: left-atrial volume index; systolic LV function: systolic left-ventricular function; p-values correspond to the comparison of patients characteristics according to NT-proBNP levels (univariable analysis of variance or Kruskal-Wallis test for continuous variables and chi-square tests or Fisher's exact test for categorical variables).

Supplemental table S2. Partial Spearman correlation coefficients (adjustment for eGFR)

	NT-proBNP (pg/ml)		LVMI (g/m²)		LAVI (ml/m²)		E/e'	
	rho	p-value	rho	p-value	rho	p-value	rho	p-value
NT-proBNP (pg/ml)	-	-	0.28	<0.001	0.54	<0.001	0.40	<0.001
LVMI (g/m²)	0.28	<0.001	-	-	0.32	<0.001	0.20	<0.001
LAVI (ml/m²)	0.54	<0.001	0.32	<0.001	-	-	0.32	<0.001
E/e'	0.40	<0.001	0.20	<0.001	0.32	<0.001	-	-

LVMI: left-ventricular mass index; LAVI: left-atrial volume index; eGFR: estimated glomerular filtration rate

Supplemental table S3. Cox models

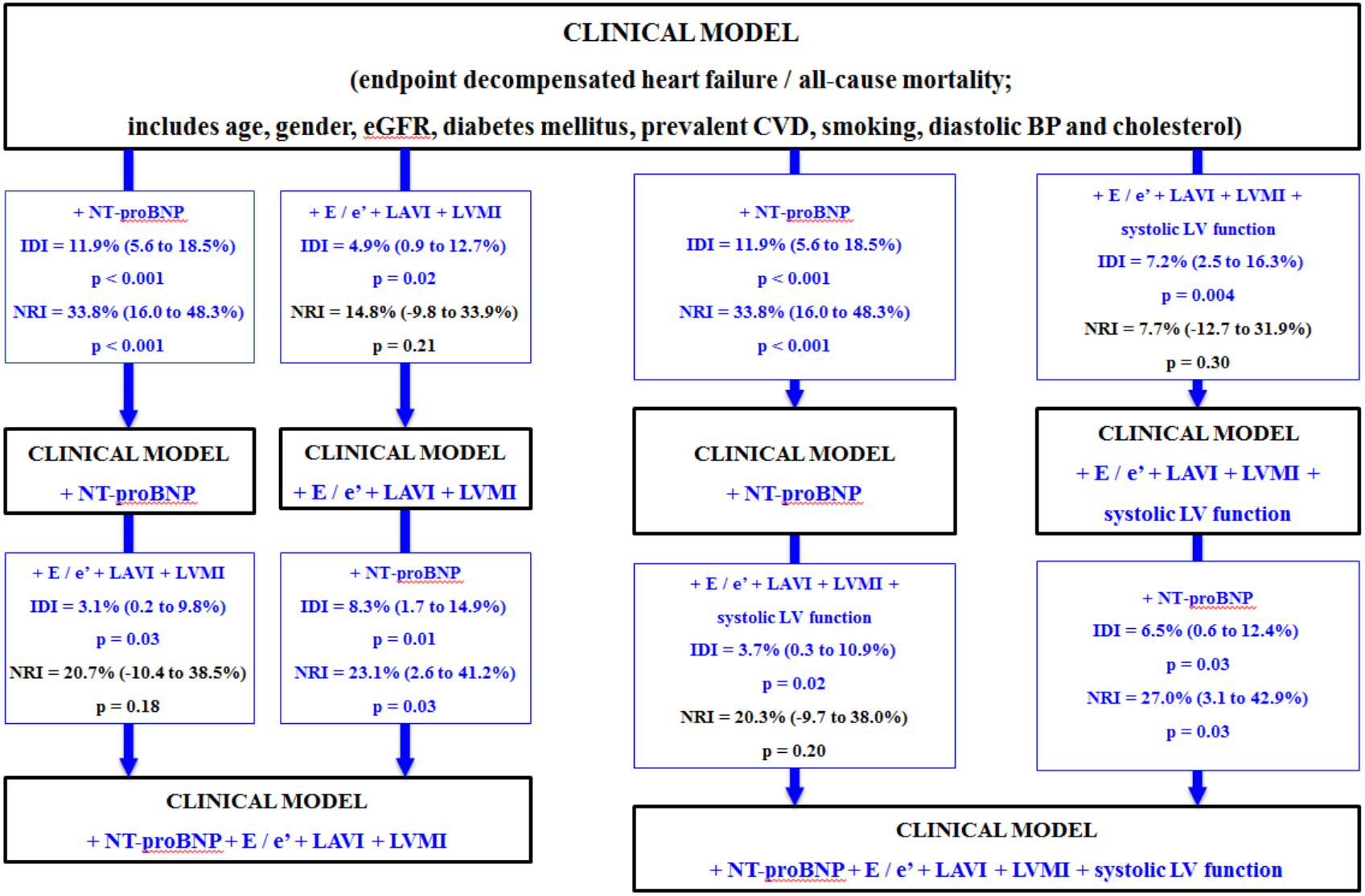
		HF/ACM		AE/ACM	
		HR (CI 95 %)	**p-value**	**HR (CI 95 %)**	**p-value**
Continuous predictors					
Log NT-proBNP		3.74 (2.15-6.52)	**<0.001**	2.28 (1.38-3.76)	**0.001**
LVMI		1.01 (1.00-1.02)	0.08	1.01 (1.00-1.02)	0.17
LAVI		1.00 (0.98-1.02)	0.74	1.00 (0.98-1.02)	0.98
E/e‘		0.96 (0.89-1.03)	0.25	1.06 (1.00-1.14)	0.07
Categorized predictors					
NT-proBNP			**0.002**		**0.04**
	2nd tertile*	1.69 (0.60-4.74)	0.32	1.05 (0.50-2.22)	0.89
	3rd tertile*	4.26 (1.54-11.76)	**0.005**	2.06 (0.97-4.36)	0.06
LVMI			0.86		0.52
	2nd tertile*	1.12 (0.58-2.17)	0.73	0.88 (0.49-1.58)	0.67
	3rd tertile*	1.20 (0.62-2.31)	0.59	1.19 (0.67-2.13)	0.55
LAVI			0.17		0.22
	2nd tertile*	0.92 (0.43-2.00)	0.84	0.75 (0.40-1.41)	0.38
	3rd tertile*	1.59 (0.76-3.31)	0.22	1.20 (0.65-2.22)	0.56
E/e’			0.54		0.45
	2nd tertile*	0.90 (0.43-1.91)	0.79	1.25 (0.65-2.40)	0.50
	3rd tertile*	1.28 (0.65-2.53)	0.48	1.47 (0.80-2.72)	0.21
Systolic LV function	impaired (vs. normal)	2.32 (1.29-4.17)	**0.005**	1.50 (0.87-2.58)	0.15

HR: hazard ratio; CI: confidence interval; LVMI: left-ventricular mass index; LAVI: left-atrial volume index; LV function: left-ventricular function; eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease; BP: blood pressure

Model is adjusted on age, gender, eGFR, diabetes mellitus, prevalent CVD, smoking, diastolic BP, cholesterol total, NT-proBNP and all echographic parameters (LVMI, LAVI, E/e’, Systolic LV function).

*reference is the 1st tertile

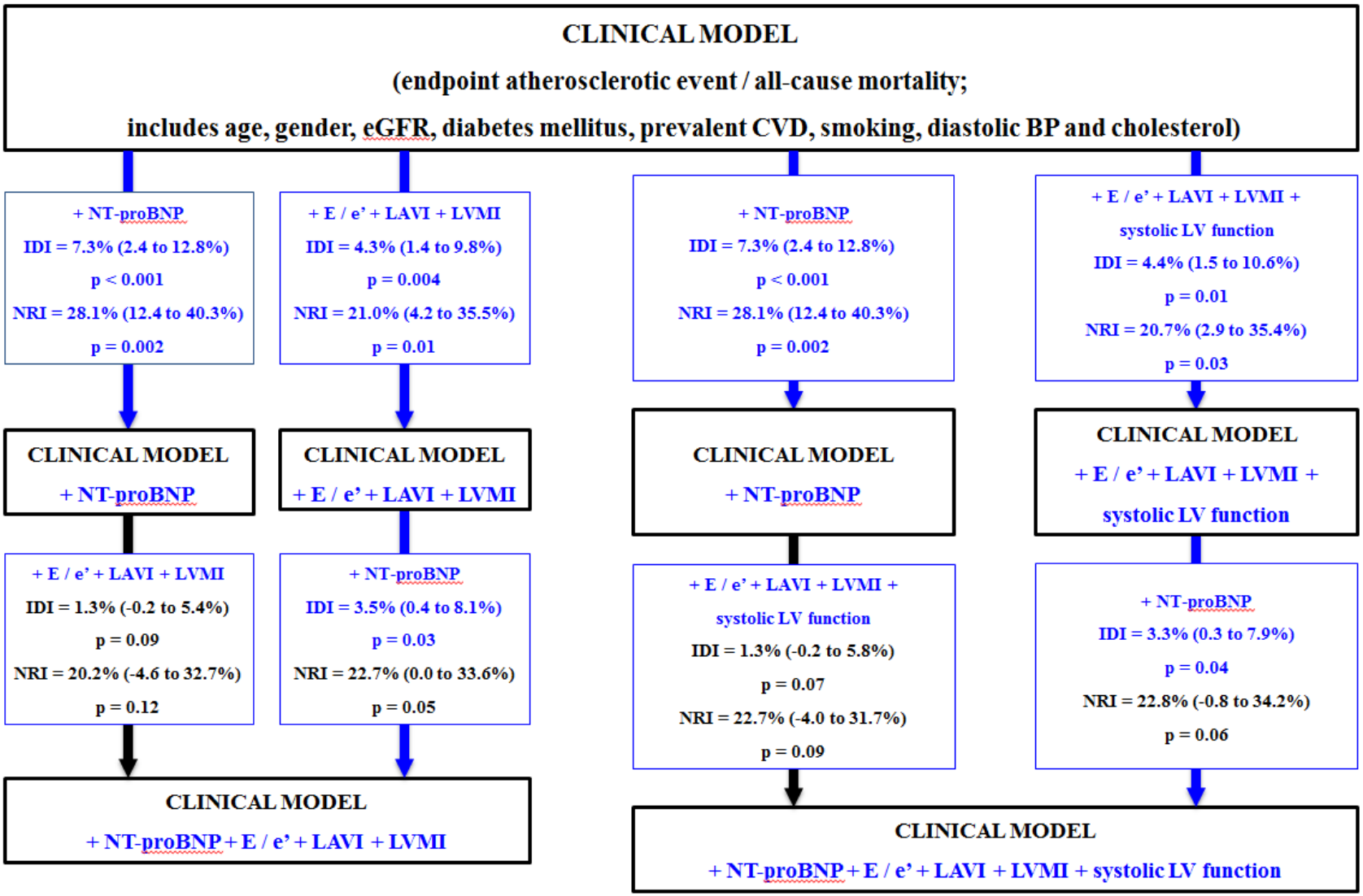
Supplemental figure S1. Clinical model (endpoint heart failure / all-cause mortality)



Discriminative value (IDI: integrated discrimination improvement; NRI: net reclassification improvement) of NT-proBNP and echocardiographic variable on top of clinical variables for the prediction of endpoint heart failure / all-cause mortality.

eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease; BP: blood pressure; LV: left ventricular; LAVI: left-atrial volume index; LVMI: left-ventricular mass index

Supplemental figure S2. Clinical model (endpoint atherosclerotic event / all-cause mortality)



Discriminative value (IDI: integrated discrimination improvement; NRI: net reclassification improvement) of NT-proBNP and echocardiographic variable on top of clinical variables for the prediction of endpoint atherosclerotic events / all-cause mortality.

eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease; BP: blood pressure; LV: left ventricular; LAVI: left-atrial volume index; LVMI: left-ventricular mass index.