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High-sensitivity cardiac troponin T and N-terminal b-type natriuretic propeptide are associated with cardiac and all-cause mortality in older adults – A population-based ten-year follow-up study

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A R T I C L E I N F O

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A B S T R A C T

Background: Cardiac troponin T (cTnT) and N-terminal B-type natriuretic propeptide (proBNP) are mainly used as biomarkers to diagnose specific conditions of the heart, but they also have predictive ability. Our aim was to study their associations with cardiovascular and all-cause mortality in an older population in non-acute conditions.

Methods: A population-based study with a ten-year follow-up. The data comes from a community-based representative sample of an older population with 1260 participants (participation rate 82 %). Associations were analyzed using Cox proportional hazard models.

Results: Altogether, 467 (37%) subjects died during the 10-year follow-up period, and 149 of those of a cardiovascular disease. Both elevated cTnT and proBNP concentrations were statistically significantly associated with cardiovascular and all-cause mortality in older adults.

Conclusions: Our study shows that older population with higher cTnT and proBNP concentrations have an increased risk of cardiovascular and all-cause mortality. Acknowledging the elevated risk may aid in targeting follow-up, prevention, and treatment adequately and more individually.

1. Introduction

Cardiac troponins regulate the contraction of striated muscle in the heart. Cardiac troponin T (cTnT) along with cardiac troponin I are expressed specifically by the heart, and they are released from the myocardium when myocytes are damaged which may occur due to a variety of reasons including inflammation, necrosis, or trauma [1–7]. Troponin concentrations may be measured in the peripheral blood in ischemic conditions such as acute myocardial infarction and coronary artery disease [1,3] but also in non-ischemic acute and chronic heart diseases such as left ventricular hypertrophy and heart failure [3,6,8,9]. Also chronic kidney disease may increase their concentrations [2–7]. Elevated levels of cTnT are associated with cardiovascular and all-cause mortality in general and older populations with or without cardiac disease [3,5,6,8,10]. Cardiac troponin levels measured preoperatively or postoperatively can also be used to estimate an individual's perioperative risk when undergoing a noncardiac surgery [11,12].

Natriuretic peptides are secreted from cardiomyocytes in response to increased wall tension reflecting increased intravascular volume. They promote vasodilatation and regulate salt and water handling [13,14]. Natriuretic peptides, including N-terminal B-type natriuretic propeptide (proBNP), are used for diagnosing and monitoring of heart failure

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[15,16]. Their concentrations rise in left ventricular dysfunction but elevated concentrations may also be due to other conditions such as renal impairment or atrial fibrillation [16,17].

Studies have shown that the concentration of proBNP predicts cardiovascular events and mortality in the general population [18], and of future risks in patients with an existing condition such as the risk of mortality after acute myocardial infarction (AMI) [19], mortality in patients with acute heart failure [20] and even stroke risk after a transient ischemic attack [21]. There is also evidence of the prognostic value of proBNP for cardiovascular events in patients in long-term geriatric care [22] and also on general older population [23,24]. The prognostic value of proBNP for mortality after AMI persists even in the oldest patients [25].

The concentrations of both cTnT and proBNP increase with age also in a population with no cardiovascular diseases [24]. Our aim was to study the associations of these analytes with cardiovascular and all-cause mortality in older adults.

2. Methods

2.1. Ethics

The Lieto Elderly Study was conducted according to the guidelines of the Declaration of Helsinki. The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol (Diary number 112/1802/2015). Participants provided written informed consent for the study.

2.2. Study design and population

This study is part of a longitudinal epidemiological study carried out in the municipality of Lieto in Southwestern Finland [26]. All persons born in 1933 or earlier (n = 1596) were invited to participate in the baseline examination which was carried out between March 1998 and September 1999. Of those eligible, 63 died before they were examined, and 273 refused or did not respond, leaving 1260 (82 %) participants, 533 men and 727 women.

Cross-sectional data collected between March 1998 and September 1999 were used as baseline information. The data on the participants' previous diagnoses was collected from the municipalitýs electronic patient record system. All the study participants went through careful clinical examination, and blood samples were taken. The clinical examination included a comprehensive interview with history, lifestyle, and previous diagnoses, Rose questionnaire, numerous laboratory tests and an electrocardiogram test [26].

All individuals with a kidney disease (International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10] codes N00–N29) at baseline (n = 52) or with missing data (n = 10) were excluded from the study population, leaving 1198 participants.

Data for mortality was obtained for all study participants deceased between the baseline examination and the end of 2008 from the Statistics of Finland Causes of Death –registry identified with unique personal identification numbers. This provided a follow-up-period of 10 years. We studied both cardiovascular (ICD-10 codes I10-I15, I20-I25 and I30-I52) and all-cause mortality.

2.3. Laboratory measurements

Venous blood samples were obtained with minimal stasis between 8 and 10 a.m. after overnight fast at Lieto health centre. All participants were given verbal and written instructions before laboratory visit.

Blood samples were centrifuged, and aliquots of serum were stored at −70 °C. The analyses of cTnT and proBNP were performed on previously unthawed samples. Samples were analyzed at the Laboratory of Turku University Hospital.

The determination of cTnT and proBNP were performed on a Cobas® 8000 e801 analyser using electrochemiluminescence immunoassay (ECLIA) method (Roche Diagnostics, Mannheim, Germany; for cTnT the limit of detection (LoD) was 3 ng/L, the limit of quantification (LoQ) (10 % coefficient of variation (CV value)) 13 ng/L, and for proBNP LoD 5 ng/L, LoQ (20 % CV value) 50 ng/L). The mean CVs at the analyzing laboratory during the study period for two-level controls were 3.0 % and 3.8 % for cTnT, and 2.7 % and 2.8 % for proBNP.

2.4. Statistics

The comparisons of categorical baseline characteristics between groups were done with chi-square test. Mean ages between groups were compared using two-sample *t*-test. Mann-Whitney *U* test was used to compare the cTnT and proBNP concentrations between age groups and genders. The associations of the highest and lowest quartiles of the cTnT and proBNP concentrations with mortality were studied by gender and age groups. The follow-up period was calculated from the baseline measurements to the end of the 10-year follow-up period or to the death of the individual. Hazard ratios (HRs) and their 95 % confidence intervals (CIs) for cardiovascular and all-cause mortality were calculated using Cox proportional hazard models. In addition to unadjusted analyses, Cox regression analyses were adjusted for age, number of diagnoses, smoking, body mass index, Mini Mental State Examination score, diabetes and hypertension. P values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics

The study population was formed by 1198 individuals, 501 men and 697 women aged over 64 years. The mean age was 73.4 years (standard deviation 6.7). Of the participants, 676 had a cardiovascular disease, 430 of those had hypertension, and 254 had coronary artery disease. 174 participants had diabetes.

The median concentration of cTnT was 11.7 ng/L for men (interquartile range [IQR] 8.7–17.9) and 9.7 ng/L for women (IQR 6.9–14.6). The median concentration of proBNP was 117 ng/L for men (IQR 63–240) and 148 ng/L for women (IQR 84–300).

Additional characteristics of the study population are shown in Table 1.

3.2. Mortality

A total of 467 (37 %) subjects deceased during the 10-year follow-up period, and 149 of those of a cardiovascular disease. The total cardiovascular and all-cause mortality rates during the follow-up period are shown in Table 2 for different age groups and genders.

There were statistically significant age group and gender differences in both cTnT and proBNP concentrations. We divided the population into 64- to 74-year-olds, and over 75-year-olds because cTnT (median 8.9 ng/L vs 15.5 ng/L, $p < 0.001$) and proBNP (median 104 ng/L vs 230 ng/L, $p < .001$) increased significantly with age. Women had lower concentrations of cTnT ($p < .001$) and higher concentrations of proBNP ($p < .001$), and genders were analyzed separately.

Both elevated cTnT and proBNP concentrations were statistically significantly associated with cardiovascular and all-cause mortality during the 10-year follow-up period in each group without adjustments. cTnT was statistically significantly associated with cardiovascular and all-cause mortality in over 75-year-old men and women when adjusted for the statistically significant baseline factors, but in the younger age group statistical significance was not reached. ProBNP was significantly associated with cardiovascular mortality in both age groups in men and women also when adjusted for the baseline factors, and in over 75-year-

Table 1
Baseline characteristics of study participants (n = 1198).

	All participants *n* (%)	Deceased of any reason *n* (%)	Alive *n* (%)	p-value	Deceased of a cardiovascular disease *n* (%)	Others *n* (%)	p-value
Age, mean (standard deviation)	73.4 (6.7)	77.7 (7.4)	71.0 (4.9)	<0.001	77.7 (7.7)	72.9 (6.4)	<0.001
Female	697 (58)	237 (55)	460 (60)	0.059	75 (56)	622 (58)	0.657
Number of diagnoses				<0.001			<0.001
0–2	889 (74)	253 (58)	636 (83)		70 (53)	819 (77)	
3–4	256 (21)	134 (31)	122 (16)		44 (33)	212 (20)	
5 or more	53 (4)	47 (11)	6 (1)		19 (14)	34 (3)	
Smoking status				0.003			0.020
Non-smoker	783 (67)	259 (61)	524 (69)		74 (57)	709 (68)	
Ex-smoker	299 (25)	116 (28)	183 (24)		46 (35)	253 (24)	
Current smoker	95 (8)	47 (11)	48 (6)		10 (8)	85 (8)	
Mini Mental Stage Examination score				<0.001			<0.001
<26	242 (20)	167 (38)	75 (10)		49 (37)	193 (18)	
≥26	956 (80)	267 (62)	689 (90)		84 (63)	872 (82)	
Body mass index, kg/m^2				<0.001			0.017
<25	402 (34)	179 (41)	223 (29)		54 (41)	348 (33)	
25–29.9	519 (43)	162 (37)	357 (47)		42 (32)	477 (45)	
≥30	274 (23)	92 (21)	182 (24)		36 (27)	238 (22)	
Diabetes	174 (15)	86 (20)	88 (12)	<0.001	35 (26)	139 (13)	<0.001
Hypertension	430 (36)	182 (42)	248 (32)	0.001	67 (50)	363 (34)	<0.001

Table 2
Number and percentage of study participants who were alive or had deceased of any reason, and deceased of a cardiovascular disease at the end of the follow-up period of ten years in different age groups.

	n	Alive at the end of the follow-up period *n* (%)	Deceased of any reason *n* (%)	Deceased of a cardiovascular disease *n* (%)
Men				
64 to 69 years	215	167 (78)	48 (22)	17 (8)
70 to 74 years	150	103 (69)	47 (31)	17 (11)
75 to 79 years	87	35 (40)	52 (60)	13 (15)
Over 80 years	81	14 (17)	67 (83)	21 (26)
Total	533	319 (60)	214 (30)	68 (13)
Women				
64 to 69 years	235	200 (85)	35 (15)	9 (4)
70 to 74 years	194	148 (76)	46 (24)	16 (8)
75 to 79 years	132	88 (67)	44 (33)	13 (10)
Over 80 years	166	38 (23)	128 (77)	43 (26)
Total	727	474 (65)	253 (35)	81 (11)

old men and 64 to 74-year-old women for all-cause mortality (Tables 3 and 4).

4. Discussion

In our study, the cardiovascular and all-cause mortality were higher in participants with concentrations of cTnT or proBNP at the highest quartile compared with those in the lowest quartile, although statistical significance was not reached in all groups. Our results suggest that concentrations of both cTnT and proBNP reflect the cardiac health status, even in the absence of acute symptoms.

While cTnT is mostly applied in acute diagnostics, also earlier studies have found that it has predictive value [3,5,6,8,24]. Also, proBNP, a typical marker for heart failure, has been shown to predict mortality [18,19,25]. We studied if elevated concentrations of cTnT and proBNP are associated with cardiovascular and all-cause mortality in an older population when measured in a stable condition without acute symptoms.

Age obviously plays a major role in mortality of the older adults, which is why analyses in age groups and adjustments with age are important. In our study, the associations of higher cTnT and proBNP concentrations with both cardiovascular and all-cause mortality remained. The associations were mostly stronger in the older group of over 75-year-olds than in the younger age group. Overall, the associations were stronger for cardiovascular mortality.

Cardiac conditions, both diagnosed and possibly undiagnosed

Table 3
Hazard ratios (HRs) comparing the highest and lowest quartiles of cardiac troponin T (cTnT) and atrial natriuretic propeptide (proBNP) and their 95% confidence intervals (CI) for mortality of a cardiovascular disease for men and women in two age groups during the 10-year follow-up period.

		Upper limit of lowest quartile	Lower limit of highest quartile	HR unadjusted	95 % CI	p-value	HR *	95 % CI	p-value
cTnT	Men								
	64 to 74 years	7.8	13.3	7.21	1.61–32.23	0.010	3.54	0.66–19.05	0.141
	Over 75 years	13.5	29.6	6.93	2.14–22.47	0.001	4.74	1.08–20.78	0.039
	Women								
	64 to 74 years	6.0	10.6	7.35	1.65–32.85	0.009	2.99	0.55–16.25	0.206
	Over 75 years	9.7	21.2	7.65	3.04–19.22	<0.001	3.63	1.12–11.80	0.032
proBNP	Men								
	64 to 74 years	48	166	5.14	1.92–13.76	0.001	4.19	1.40–12.55	0.010
	Over 75 years	100	612	4.40	1.55–12.46	0.005	6.80	1.69–27.30	0.007
	Women								
	64 to 74 years	70	186	15.95	2.11–120.70	0.007	9.11	1.09–75.88	0.041
	Over 75 years	123	553	11.88	4.13–34.19	<0.001	8.66	2.60–28.83	<0.001

* Adjusted for age, number of diagnoses, smoking, body mass index, Mini Mental State Examination score, diabetes, and hypertension

Table 4
Hazard ratios (HRs) comparing the highest and lowest quartiles of cardiac troponin T (cTnT) and atrial natriuretic propeptide (proBNP) and their 95% confidence intervals (CI) for all-cause mortality for men and women in two age groups during the 10-year follow-up period.

		Upper limit of lowest quartile	Lower limit of highest quartile	HR unadjusted	95 % CI	p-value	HR *	95 % CI	p-value
cTnT	Men								
	64 to 74 years	7.8	13.3	2.17	1.16–4.09	0.016	1.47	0.69–3.12	0.321
	Over 75 years	13.5	29.6	4.57	2.57–8.12	<0.001	3.60	1.80–7.22	<0.001
	Women								
	64 to 74 years	6.0	10.6	3.80	1.93–7.50	<0.001	2.00	0.93–4.28	0.076
	Over 75 years	9.7	21.2	7.55	4.46–12.78	<0.001	3.94	2.00–7.76	<0.001
proBNP	Men								
	64 to 74 years	48	166	3.08	1.72–5.51	<0.001	2.39	1.25–4.57	0.009
	Over 75 years	100	612	2.00	1.20–3.35	<0.008	1.83	0.91–3.70	0.091
	Women								
	64 to 74 years	70	186	2.38	1.24–4.58	0.010	1.23	0.58–2.63	0.586
	Over 75 years	123	553	4.40	2.27–7.07	<0.001	1.98	1.09–3.65	0.025

* Adjusted for age, number of diagnoses, smoking, body mass index, Mini Mental State Examination score, diabetes, and hypertension

underlying cardiac conditions, are common in older population. This causes dispersion in the concentrations of cTnT and proBNP, especially in the oldest [24]. Both biomarkers are secreted or released by the myocardium[3,14], and their elevated concentrations indicate both an increased risk of cardiovascular mortality, but their predictive value can also be seen in their association with total mortality in our study, and in earlier studies[3,5,6,8,10,18,27]. Renal function is important in metabolism and removal of these biomarkers[14,28], and therefore underlying decreased kidney function may influence to this dispersion, although in this study the individuals with kidney diseases at baseline were excluded from the study. It is possible that also the increase in all-cause mortality is related to undiagnosed and untreated myocardial damage that might increase the likelihood of non-cardiovascular death.

Identification of increased risk may aid in assessing the health status of an older person, and planning their health interventions, although the right interventions must be considered on an individual basis. A persońs cTnT and proBNP concentrations must be interpreted in connection with the persons age, overall health status, and existing health conditions. Interventions directed at treating those with elevated cTnT or proBNP may reduce mortality from cardiovascular or other causes.

Our study had some limitations. The assay used for the measurement of cTnT detects different forms of cTnT in plasma, and we could not detect whether the participants' elevated cTnT was caused by intact and long forms of cTnT or smaller, truncated fragments that are detected in myocardial injury attributable to other causes than AMI or in renal dysfunction [29–31]. Also, we did not study macrotroponins, that could have resulted in increased concentrations of cTnT in some individuals. Concentration of cTnT and proBNP were measured only at one time-point at baseline.

The data came from a community-based representative sample of the Finnish older population, with a high participation rate (82 %) and a long follow-up period. The sample size was relatively large, even if the oldest age groups of men and women are smaller.

Even if baseline concentrations of cTnT and proBNP are higher in older population than in younger population[24], using age-adjusted reference values may be useful in screening and identifying a subgroup of older people with an elevated risk of both cardiovascular and all-cause mortality. The comparison of an individual's cTnT and proBNP concentrations with their prior concentrations can also aid in clinical evaluation.

5. Conclusions

Our study shows that older people with higher cTnT and proBNP concentrations have an increased risk of cardiovascular and all-cause mortality. Acknowledging the elevated risk may aid in targeting follow-up, prevention, and treatment adequately and more individually.

CRediT authorship contribution statement

Elisa Heikkilä: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Taina Katajamäki:** Methodology, Investigation. **Marika Salminen:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Kerttu Irjala:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Anna Viljanen:** Writing – review & editing, Investigation. **Marja-Kaisa Koivula:** Writing – review & editing. **Kari Pulkki:** Writing – review & editing, Supervision. **Matti Viitanen:** Writing – review & editing. **Tero Vahlberg:** Writing – review & editing, Methodology. **Laura Viikari:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement Section

Author Contributions

Corresponding author had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the study conception and design. Material preparation, data collection and analyses were performed by TK, EH, MS, KI and TV. The first draft of the manuscript was written by EH, and MS, KI, LV, KP, TK, AV, MV, MKK and TV commented on the **manuscript**. The authors read and approved the final manuscript.

Additional Contributions

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Data availability

Data will be made available on request.

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