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ORIGINAL ARTICLE

Higher BNP/NT-pro BNP levels stratify prognosis equally well in patients with and without heart failure: a meta-analysis

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Abstract

Aims The initial and dynamic levels of B-type natriuretic peptide (BNP) and N-terminal-prohormone BNP (NT-proBNP) are routinely used in clinical practice to identify patients with acute and chronic heart failure. In addition, BNP/NT-proBNP levels might be useful for risk stratification in patients with and without heart failure. We performed a meta-analysis to investigate, whether the value of BNP/NT-proBNP as predictors of long-term prognosis differentiates in cohorts with and without heart failure.

Methods and results We systematically searched established scientific databases for studies evaluating the prognostic value of BNP or NT-proBNP. Random effect models were constructed. Data from 66 studies with overall 83 846 patients (38 studies with 46 099 patients with heart failure and 28 studies with 37 747 patients without heart failure) were included. In the analysis of the log-transformed BNP/NT-proBNP levels, an increase in natriuretic peptides by one standard deviation was associated with a 1.7-fold higher MACE rate (hazard ratio [95% confidence interval]: 1.74[1.58–1.91], $P < 0.0001$). The effect sizes were comparable, with a substantial overlap in the confidence intervals, when comparing studies involving patients with and without heart failure (1.75[1.54–2.0], $P < 0.0001$ vs. 1.74[1.47–2.06], $P < 0.0001$). Similar results were observed when stratifying by quartiles of BNP/NT-proBNP. In studies using pre-defined cut-off-values for BNP/NT-proBNP, elevated levels were associated with the long-term prognosis, independent of the specific cut-off value used.

Conclusions BNP/NT-proBNP levels are predictors for adverse long-term outcome in patients with and without known heart failure. Further research is necessary to establish appropriate thresholds, especially in non-heart failure cohorts.

Keywords BNP; NT-proBNP; Prognosis; General population cohorts

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Introduction

Natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal-prohormone BNP [NT-proBNP]) are cardiac hormones secreted in the atria and ventricles. They play important roles in electrolyte and water homeostasis, lipolysis and blood pressure regulation. Both are synthesized in response to mechanic stress and neurohormonal stimulation (i.e. the release of noradrenalin and angiotensin II).[1,2] The initial and dynamic levels of BNP and NT-proBNP are routinely used in clinical practice to identify patients with acute and chronic heart failure and to stratify them according to risk.[3] In addition to its value in patients with heart failure, BNP/NT-proBNP may also serve as a predictor of the manifestation of cardiovascular disease in primary prevention cohorts independent of whether traditional cardiovascular risk factors are present.[4,5] In addition, in a large registry, BNP/NT-proBNP levels were effectively used to stratify patients with coronary artery disease but without heart failure according to survival.[6] Considering those observations, BNP/NT-proBNP levels are gaining interest as predictors of major adverse cardiac events (MACEs) and all-cause mortality and can potentially be used for cardiovascular risk stratification.

The standardized cut-off levels for BNP and NT-proBNP that are currently used in clinical practice are based on the stratification of patients with heart failure. In patients without heart failure, however, relatively lower values are observed. This leads to the assumption that the prognosis for patients with BNP/NT-proBNP levels at the upper limit of the normal range might be worse than the prognosis for patients with BNP/NT-proBNP levels lower in the range, even if both are determined to be within the normal boundaries. However, a specific cut-off level of BNP/NT-proBNP for the prediction of prognosis in patients without heart failure has not yet been determined. Therefore, we performed a meta-analysis of existing studies investigating the value of BNP/NT-proBNP as a predictor of long-term prognosis in patients with heart failure and the general population.

Methods

We performed a systematic review and meta-analysis of existing studies to evaluate the predictive ability of BNP/NT-proBNP for the long-term prognosis in patients with and without heart failure. The systematic review and meta-analysis of studies were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7] and in accordance with the 'Meta-analysis Of Observational Studies in Epidemiology (MOOSE)' recommendations[8] and the Cochrane Handbook for Systematic Reviews of Interventions.[9] The study was registered in INPLASY with the ID 202240175.

Data sources, searches, and selection

The database searches were performed by two authors (S. H. and I. D.) in PubMed, the Cochrane Library, SCOPUS, and Web of Science. We used the following key search terms: 'BNP' or 'NT-proBNP' and 'prognosis'. Manuscripts with prospective data assessments published prior to 24 April 2020 were included in our search. We made our search specific and sensitive using Medical Subject Heading terms and free text. The search was restricted to full-text articles with human subjects that were published in English. All duplicates were identified and removed manually. We screened 8401 articles by reading the abstracts. Two authors (S. H. and I. D.) independently reviewed the titles and abstracts of the studies. Studies that remained after the initial screening were subjected to full-text assessments to identify the studies that met the inclusion criteria. This process was supervised by A. A. M., and a consensus was negotiated in cases of disagreement.

Data inclusion criteria

We included prospective studies evaluating the prediction of all-cause mortality or MACEs based on BNP or NT-pro BNP levels. Only studies with a follow-up duration $>$90 days were included. There were no restrictions on comorbidities. Only studies in adults were included (inclusion criteria: age $>$18 years). We included studies analysing clinical as well as population based cohorts.

Data exclusion criteria

Studies evaluating the occurrence of events other than MACEs or all-cause mortality (e.g. atrial fibrillation) were excluded. Records were screened and studies were excluded with undesired topic, if no or only the abstract was available, if the full text article was not available in English language. Secondly, only full text articles were assessed for eligibility. Retrospective, meta-analysis, systematic reviews and undesired study designs were excluded. We excluded, studies not subdividing heart failure and non-heart failure individuals. However, analysing increase or decrease of BNP/NT-proBNP levels or lack of comparability were excluded. Studies including individuals $<$18 years of age were excluded.

Outcomes and measures of association

The primary endpoint was defined as all-cause mortality or major cardiac events (MACE). MACE was defined differently in the included studies, however only studies including at least one of the following definitions were added: cardiovascular or all-cause mortality, myocardial infarction, stroke, or heart failure hospitalization. Details on the definition of MACE in the included studies are depicted in *Table 1*. Outcome measure was defined as hazard ratios and corresponding confidence intervals.

Exposure

To ensure comparability, we analysed studies by dividing and analysing them based on the increments and BNP/NT-proBNP thresholds. We separated by (i) log-transformed BNP/NT-pro BNP levels and increment of 1 SD increase; (ii) increment of 1 SD; (iii) those that separated the BNP/NT-proBNP levels into quartiles; and (iv) using pre-defined cut-off levels. While some studies subdivided BNP/NT-proBNP levels into quartiles before analysing them, some studies predefined specific cut-off levels for analysing increased risk.

Included studies were not specific heart failure cohorts. Studies including cohorts with only a minority of heart failure patients in the included individuals like the one of Peet *et al*.

Table 1 Key study characteristics of included studies

Author	Year	Sample size, n	Mean/ median age	Men, %	NT-pro BNP	BNP	LV-EF, %	Follow-up (years)	Primary endpoints	Reference
Alehagen *et al.*	2011	470	73	51.5	235.9 pg/mL			13	All-cause mortality	10
Baggish *et al.*	2010	720	74.77	51.34	5707.74 pg/mL			1	All-cause mortality	29
Beleigoli *et al.*	2013	1470	69.1 ± 7.2	39		82 (44–148) pg/mL		9	All-cause mortality	15
Berin *et al.*	2014	279	62.5 ± 13	80	3527 ± 7830 pg/mL		26 ± 7	2.8	All-cause mortality	5
Bosselmann *et al.*	2013	424	72 (34–92)	71			30 (13–45)	4.5	All-cause mortality	30
Bruch *et al.*	2008	341	57 ± 12	79	2155 ± 4455 pg/mL		36	1.7	Cardiac events, rehospitalization due to heart failure (HF)	31
Chuang *et al.*	2014	106	71 ± 13	51	10 997 (5283–25 443) pg/mL		42	2.1	All-cause mortality, cardiac mortality, HF mortality, myocardial infarction, absence of precipitating factors, sudden unexpected death	32
Coats *et al.*	2013	847	53 ± 15	67	659.65 pg/mL		59 ± 11	3.5	All-cause mortality, heart transplantation (HTX)	33
Corte *et al.*	2010	90	59 ± 12	52		38.14 pg/mL		1.2	All-cause mortality, HTX	34
D'Amato *et al.*	2013	183	50 ± 17	64	615 (310–1025) pg/mL			3.9	Cardiovascular death, HTX, CRTD implantation	35
Dallmeier *et al.*	2015	1422	75.5 ± 6.5	56.5	153.0 (82.0–318.0) pg/mL			4.0	All-cause mortality	36
Daniels *et al.*	2008	957	77 (60–97)	39	121.13 pg/mL			6.8	All-cause mortality, cardiovascular mortality	37
Dini *et al.*	2009	155	69 ± 11	80	745 (442–1672) pg/mL		35 ± 7	2	Cardiac death, hospitalization due to HF, any episode of HF requiring change of medication	38
Dini *et al.*	2008	142	71 ± 11	78	3283 ± 585 pg/mL		28 ± 7	1.7	All-cause mortality	39
Dini, Fontanive *et al.*	2008	369	68.24	76,24	2115.07 pg/mL		30	2.4	Cardiac mortality, cardiac events: HF-related hospital admission	40
Eurlings *et al.*	2014	309	72.0 ± 12.0	57,3	7897 (4345–14 030) pg/mL		35.9 ± 14.3	2	All-cause mortality, HF readministration or mortality	41
Franke *et al.*	2011	504	58 (48.8–67.7)	79,4			29.81	1.7	All-cause mortality, hospitalization due to cardiac reason, HTX	24
Fu *et al.*	2015	306	85.0 (80.0–89.0)	81	1743.4 (513.5–4796.3) pg/mL		57.0 (49.5–61.0)	1.3	All-cause mortality	42
Geerse *et al.*	2013	206	65.3 ± 14.1	51,9	868.53 pg/mL			2.3	All-cause mortality	43
Hamaya *et al.*	2019	429	68.0 ± 9.5	78.3	85 (45–176) pg/mL		66 (61–70)	1.5	All-cause mortality, myocardial infarction, hospitalization for HF, targeted vessel remote vascularization	25
Hinderliter *et al.*	2008	211	57 ± 12	69	1675 ± 2657 pg/mL		32 ± 11	4	All-cause mortality	44
Hwang *et al.*	2013	117	57 (45–64)	55.6		95 (46–204.5) pg/mL	60.9 ± 8.1	4.5	Cardiac death, cardiac hospitalization	45
Ishigami *et al.*	2014	457	63.9 (55.4–71.4)	61.5		217 (109–471) pg/mL	67 (61–72)	1.6	All-cause mortality plus severe events	46
Kang *et al.*	2015	1670	70	48.9	4508 (8–35 000) pg/mL			1	All-cause mortality	47
Kara *et al.*	2015	3589	59.3 ± 7.7	47.5	68 (38–124) pg/mL	17.7 (9–32.1) pg/mL		8.9	Coronary events, stroke, cardiovascular (CV) death	4
Kim *et al.*	2011	555	62 ± 12	52	365 (99–1071) pg/mL		54	2	Cardiovascular death, rehospitalization due to HF	48
Kistorp *et al.*	2005	764	67.9 ± 10	42.3				5	Major cardiovascular events (MACE) including non-fatal myocardial infarction, fatal coronary heart disease, unstable angina pectoris, HF, stroke, transient ischaemic attack	16

(*Continues*)

Table 1 (continued)

Author	Year	Sample size, n	Mean/ median age	Men, %	NT-pro BNP	BNP	LV-EF, %	Follow-up (years)	Primary endpoints	Reference
Klingenberg *et al.*	2018	1892	63.73 ± 12.32	68.6	900 pg/mL			1	All-cause mortality	[49]
Kociol *et al.*	2011	7039	80 (74–86)	43.7		832 (451–1660) pg/mL	40 (28–58)	1	All-cause mortality	[50]
Komajda *et al.*	2011	2563	71 ± 7	49	320 (126–928) pg/mL		59 ± 0.09	3	All-cause mortality	[51]
Kotecha *et al.*	2019	522	66 (58–73)	67.2		40 (15–90) pg/mL	64 (53–71)	5	All-cause mortality	[52]
Kozdag *et al.*	2010	334	62 ± 13	65.2		642.5 (199–1377) pg/mL	25 ± 10	1.4	MACE, including sudden death, HTX, death to HF, receipt of a shock due to ventricular fibrillation in patients with cardioverter defibrillator	[53]
Kubánek *et al.*	2009	354	72 (64–78)	75	1683 (617–4364) pg/mL		31 (25–37)	0.5	All-cause mortality	[14]
Leistner *et al.*	2013	4775	55.8 ± 13.8; (18–95)	58.1	122.2 ± 303.8 pg/mL			5	All-cause mortality, myocardial infarction, manifestation of coronary artery disease [CAD (revascularization, CABG, and PCI)]	[17]
León de la Fuente *et al.*	2011	982				8.1 (35.8–179.7) pg/mL		2	All-cause mortality	[54]
Lindholm *et al.*	2017	13 164	65.0 (59.0–71.0)	81.7	172 (83–373) pg/mL			3.7	CV death, myocardial infarction, stroke	[55]
Lurati Buse *et al.*	2014	1559	67 ± 10	73.8	433 (277–794) pg/mL		60 (49–65)	1	All-cause mortality, MACE (myocardial infarction, cardiac arrest, CAD, HF, hospitalization due to HF)	[56]
McKie *et al.*	2006	1991	62 ± 10	47.8	134.4 ± 230.4 pg/mL			5.6	All-cause mortality	[18]
McKie *et al.*	2011	1769	62 ± 10	47	76.97 pg/mL			9	All-cause mortality, revascularization	[57]
Metra *et al.*	2007	107	66.4	28	4421 (1621–8536) pg/mL		24.1	0.5	All-cause mortality	[58]
Minami *et al.*	2016	4501	73	58		654.9 (636.1–674.2) pg/mL		1.4	All-cause mortality	[26]
Mizutani *et al.*	2017	1094	85 (82–88)	29.2		186 (93–378) pg/mL	62.0 (52.0–68.0)	2	All-cause mortality	[59]
Morrow *et al.*	2006	4497	62.5	75.6		11.5 (5–45) pg/mL		2	All-cause mortality, HF	[60]
Nishii *et al.*	2008	83	56 ± 20	71		210 ± 148 pg/mL	31 ± 8	1.5	All-cause mortality, readmission for HF	[61]
Omland *et al.*	2007	3761	63	81	139.3 (71.3–272.1) pg/mL			4.8	Cardiovascular mortality	[62]
Pareek *et al.*	2017	1324	67.11	68	90.24 pg/mL		61 ± 8	8.6	Myocardial infarction, stable or unstable HF, cardiovascular death, stroke	[63]
Parissis *et al.*	2009	300	65 ± 12	83		561.4 pg/mL	40	1	MACE including death or hospitalization due to CV causes	[64]
Park *et al.*	2014	1608	68	50	4638 pg/mL			1	All-cause mortality	[65]
Pfister *et al.*	2008	290	64 (54–72)	80	1001 (355–2409) pg/mL		40 (30–48)	1.4	All-cause mortality, hospitalization due to acute HF, urgent HTX	[66]
Pimenta *et al.*	2010	83	56 (47–70)	61.6		130.3 (65.2–363.0) pg/mL		0.5	All-cause mortality	[11]
Ruwald *et al.*	2014	337	62.09	66	270.62 pg/mL			6.7	All-cause mortality	[67]
Song *et al.*	2010	210	61 ± 11	70	733 ± 504 pg/mL		34.6 ± 14.4	1	Composite endpoint of hospitalization due to HF or other cardiac-related problems	[27]

(*Continues*)

Table 1 (continued)

Author	Year	Sample size, n	Mean/ median age	Men, %	NT-pro BNP	BNP	LV-EF, %	Follow-up (years)	Primary endpoints	Reference
Tang *et al.*	2013	3635	63 ± 11	65		83 (34–200) pg/mL		3	MACE including death, non-fatal myocardial infarction, non-fatal cerebrovascular accident	68
Tarnow *et al.*	2004	198	41 ± 10	61.1	110 (5–79 640) pg/mL			9.3	All-cause mortality	69
Tello-Montoliu *et al.*	2007	358	67.4 ± 12.4	64.2	498 (137.2–1857.5) pg/mL			0.5	All-cause mortality, revascularization, HF mortality	13
van Peet *et al.*	2013	282	85	39	495 (198–1314) pg/mL			5	Cardiovascular mortality	70
Vickery *et al.*	2008	213	68 (58–75)	68.1	752.67 pg/mL	48.54 pg/mL		4.4	All-cause mortality	71
Vorovich *et al.*	2014	1512	56 ± 15	66		173 (47–579) pg/mL	33 ± 17	4	All-cause mortality, HTX, ventricular assist device system (VAD) implantation	72
Vrtovec *et al.*	2003	241	67 ± 14	59			27 ± 9	0.5	All-cause mortality	12
Wang *et al.*	2004	3346	58.5	46.7	8.23 pg/mL			5.2	All-cause mortality, cardiovascular events	19
Wannamethee *et al.*	2014	3870	68.61 ± 5.51	100	97.51 (46–189) pg/mL			11	Incident HF, HF death	73
Whalley *et al.*	2008	228	70.3 ± 7.3	45	439.76 pg/mL		57.7 ± 12.8	1.5	CV death and/or hospitalization	28
Winkler *et al.*	2008	1255	65	55	3361 pg/mL			4	All-cause mortality	74
Yin *et al.*	2007	152	56 ± 14	77	2419.6 pg/mL		26 ± 5	0.5	Cardiac death, HTX, hospitalization due to HF	75
Zethelius *et al.*	2008	1135	71 ± 0.6	100	232 ± 397 pg/mL			10	All-cause mortality	20
Zhu *et al.*	2016	1499	61.4 ± 11.4	42	41.6 (19.8–81.9) pg/mL			4.8	All-cause mortality	76

were assigned to 'non-heart failure'. Likewise, in general population cohorts also individuals with existing heart failure may be included. However, as subjects with present heart failure represent only a minority of these cohorts, only account for these studies were categorized as non-heart failure cohorts.

Data extraction

Data were extracted independently by S. H. and I. D. using a pre-specified collection form. The following data were collected: year of publication, overall sample size, mean age, percentage of male patients, existing heart failure, percentage of patients with chronic kidney disease (if available), clinical cohort or general population, follow-up in years, median or mean BNP/NT-proBNP levels at baseline, left ventricular ejection fraction (LV-EF), hazard ratios (HR) and their associated confidence intervals (CI), and the increments or cut-off values used in the regression analysis. We extracted the values for the primary endpoint, the overall cohort, and fully adjusted multivariable models, as defined by the respective studies. If multivariable models were not available, univariate model results were included. Whenever BNP or NT-proBNP was reported in pmol/L, we converted the values to pg/mL to allow comparisons.

Data analysis

The mean/median age, percentage of patients who were male, mean/median BNP/NT-proBNP levels, LV-EF and percentage of patients with chronic kidney disease are presented for all participants in each study. To ensure comparability, we analysed studies by dividing those that separated the BNP/NT-proBNP levels into quartiles using pre-defined cut-off levels and those that calculated hazard ratios via log-transformed BNP/NT-proBNP levels or per 1 SD increase and analysing them. Data are expressed as hazard ratios and 95% confidence intervals for dichotomous outcomes. The definition of the outcomes used was that reported in the individual studies. Heterogeneity was assessed using the I^2 statistic. A value $>75\%$ indicated considerable heterogeneity.[9] All hazard ratios and corresponding confidence intervals are displayed in the form of forest plots. All analyses were performed using Review Manager 5.4 (The Cochrane Collaboration).

Results

Trial recruitment and patient characteristics

The initial search resulted in 8401 citations. A total of 7686 studies were excluded after the titles and abstracts were

read. The full text of the remaining 715 articles were read, and 647 records were excluded based on study design, lack of the outcomes of interest, and short follow-up durations (<90 days). The PRISMA chart showing the study selection and exclusion process is shown in *Figure 1*. Overall, 66 studies with a total of 83 846 patients were included. The mean/median age in the included studies ranged from 41 to 85 years. The mean/median BNP/NT-proBNP levels ranged from 11.5 to 832 pg/mL for BNP and 8.23 to 10 997 pg/mL for NT-proBNP. As expected, in studies including general population cohorts and individuals without known heart failure, the BNP/NT-proBNP levels were lower than in studies including heart failure patients. The mean/median LV-EF ranged from 24 to 67%. Twenty-one studies used log-transformed BNP/NT-proBNP levels, eight studies defined the BNP/NT-proBNP level increase per SD, and 25 used predetermined cut-off values. Twelve studies stratified BNP/NT-pro BNP levels into quartiles before analysing the predictive ability. Two studies stratified BNP/NT-pro BNP levels into tertiles and one study stratified them into quintiles; these studies were excluded because of the lack of comparability.

BNP/NT-pro BNP as a predictor of long-term prognosis

All included studies were performed prospectively. The longest follow-up duration was 13 years,[10] and the shortest was 6 months.[11–14]

In the 21 studies using log-transformed BNP/NT-pro BNP levels, an increased risk of 74% for the primary endpoint was observed in patients with elevated levels (HR [95% CI]: 1.74 [1.58, 1.91]) (*Figure 2A*).

Eight of the included studies defined the hazard ratio per 1 SD increase and showed a 45% higher risk of the primary endpoint in patients with elevated levels of BNP/NT-proBNP (1.45 [1.24–1.70]) (*Figure 3*). Six studies used community-based cohorts,[15–20] limiting the analysis of studies that only included patients with known heart failure (n = 2).

Comparable effect sizes and overlapping confidence intervals were observed in studies comparing the fourth quartile of BNP/NT-proBNP levels to the first as a reference (2.77 [1.80–4.25]) (*Figure 4*).

We performed subgroup analysis for studies using log transformed BNP/NT-pro BNP as well as for studies using BNP/NT-pro BNP in quartiles. We observed similar effect sizes without significant differences in the subgroups of heart failure and non-heart failure individuals (P for subgroup differences in log transformed = 0.85; P for subgroup differences in quartiles = 0.20) (*Figures 2B* and *4*). We did not perform subgroup analysis for studies presenting BNP/NT-pro BNP per 1 SD increase because only two of those studies included heart failure individuals. Subgroup analysis did not seem to be appropriate due to lack of comparability.

As duration of follow-up varied among the included studies, we performed a subgroup analysis in the group of log-transformed BNP/NT-pro BNP values and observed similar effect sizes after separating the studies according to duration of follow-up (till <1 year, till 1–5 years, and longer than >5 years for the analysis of log-transformed BNP/NT-proBNP values and observed similar effect sizes independent of duration of follow-up (HF [95% CI)]: 1.87 [0.94, 3.71]; 1.86 [1.56, 2.22]; 1.64 [1.37, 1.95]). The test for subgroup differences among the subgroups was not significant (P = 0.59).

Almost all studies include male and female participants, except for the study of Wannamethee *et al*. 2014, and Zethelius *et al*. 2008, which included only male participants. Considering this, we evaluated the effect when removing these two studies from the analysis and reported similar effect sizes. Removing the study of Zethelius *et al*. we documented a hazard ratio of 1.43 [1.22–1.67] compared with including the study of Zethelius *et al*. 1.45 [1.24–1.7]. Likewise, similar effect sizes were observed when removing the study of Wannamethee *et al*. (2.49 [1.64–3.78] compared with including the study of Wannamethee (2.77 [1.8–4.25]).

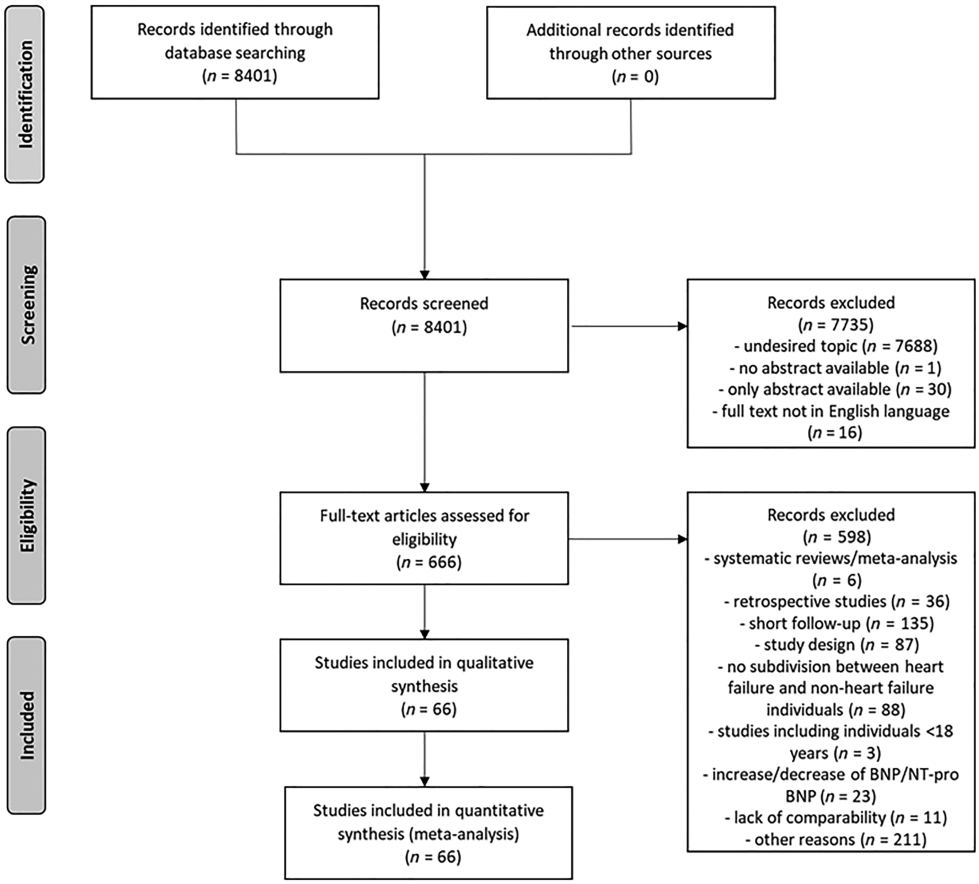
Assuming that clinical cohorts are already on higher risk of all-cause mortality we performed another subgroup analysis. We separated the studies to their setting clinical vs population based cohorts and observed relevant differences. As expected, we observed higher effect sizes in the subgroup of clinical cohorts (clinical cohorts: 2.32 [1.94, 2.79], population based cohorts: 1.46 [1.28, 1.65] Supporting Information, *Figure S2*).

When comparing studies that used cut-off values for BNP/NT-proBNP, the predictive value remained consistent (2.68 [1.69–4.24]) (Supporting Information, *Figure S1*). Independent of whether the pre-determined BNP/NT-proBNP cut-off levels were in the normal range or drastically higher, the effect sizes were similar (*Figure 5*). This supports the assumption that BNP/NT-proBNP levels have predictive prognostic value in general population cohorts, independent of whether the cut-off value used is inside the normal range or above the cut-off values routinely used for the diagnosis of heart failure.

Due to the large number of included studies and difficulties of comparability, we observed considerable heterogeneity among all primary analyses, with an $I^2 > 75\%$.

In order to preclude publication bias we performed publication bias analysis. Overall, the funnel plots did not suggest that publication bias was of relevant concern (Supporting Information, *Figure S3*). Only for the analysis using log transformed BNP/NT-pro BNP values, there was a signal that was caused by the study of D'Amato *et al*. However, effect sizes remained stable when removing the study of D'Amato *et al*. from the analysis (detailed data not shown).

Figure 1 PRISMA flowchart for the search strategy of selected studies.



Discussion

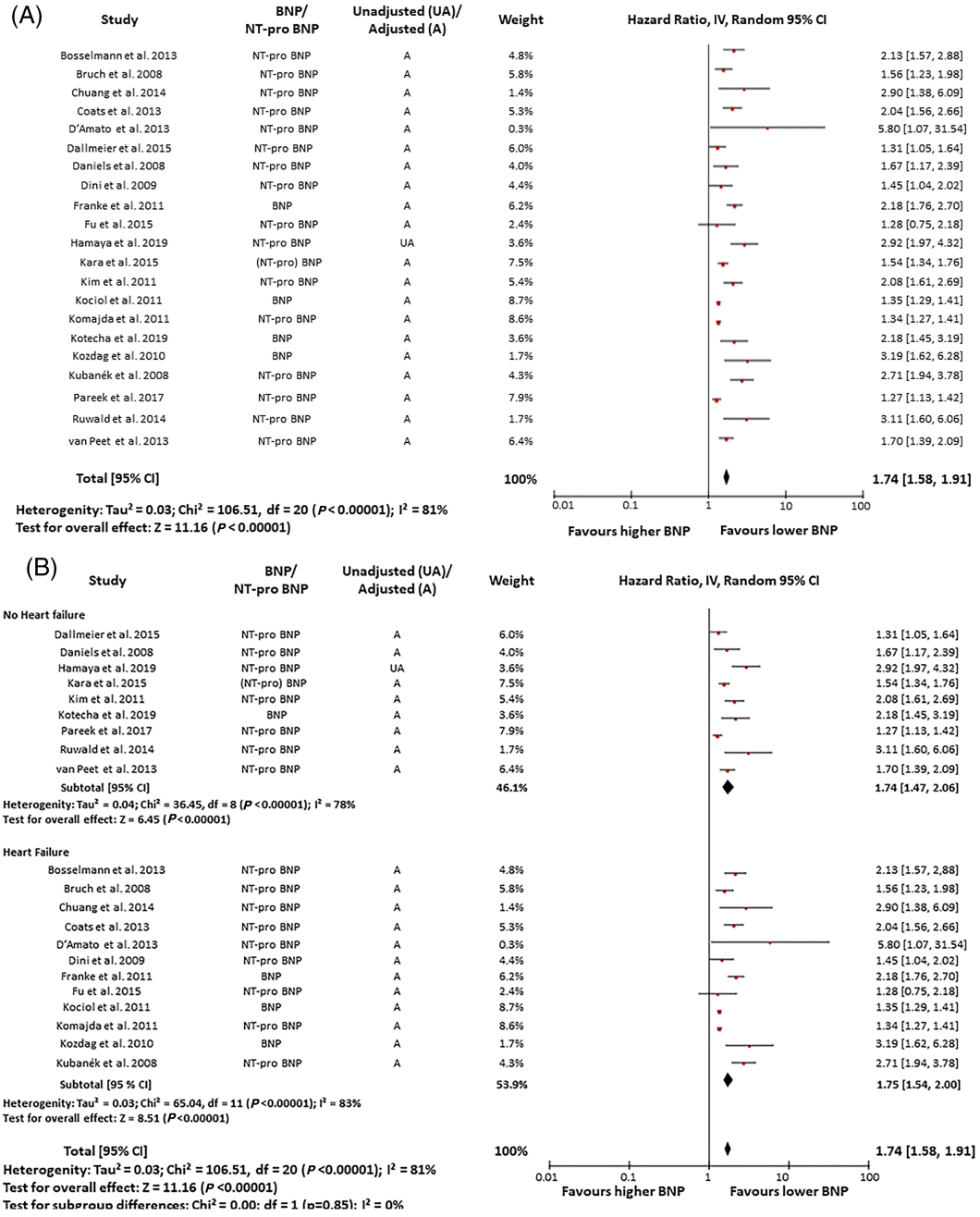
BNP/NT-proBNP is a well-established marker used in routine clinical practice for the diagnosis of heart failure and the evaluation of therapeutic response. Moreover, in patients with heart failure, BNP/NT-proBNP levels provide prognostic information. In addition, recent data suggest that in general population cohorts and cohorts of patient without heart failure, BNP/NT-proBNP levels can be used to identify individuals at increased cardiovascular risk. In this meta-analysis, we confirmed that BNP is a strong predictor of MACEs. Effect sizes were comparable for patients with and without heart failure and were independent of the thresholds used. Our results indicate that in general population cohorts or clinical cohorts of patients without heart failure, BNP/NT-proBNP levels can be used for the assessment of cardiovascular risk, with lower cut-off values than those used in heart failure cohorts.

When using BNP/NT-proBNP levels in clinical practice, several influencing factors should be considered: with increasing age, BNP/NT-proBNP levels normally increase. Sex-based cut-off values are reasonable, given that BNP levels are significantly higher in women than in men.[21] Furthermore, kidney function is a matter of concern, because decreasing kidney function is associated with elevated levels of BNP/NT-proBNP. We found a stable association of BNP/NT-proBNP with MACEs in heterogeneous cohorts, including diverse age groups and populations with high proportions of patients with chronic kidney disease, and after the application of a wide variety of cut-off values, suggesting that despite the observation of various ranges in different cohorts, BNP/NT-proBNP levels can be used as reliable predictors of the risk of MACEs.

BNP versus NT-proBNP

NT-proBNP, which is a biologically inactive peptide, is secreted from cardiomyocytes at the same time as BNP, which is the biologically active peptide.[1,2] Due to different elimination mechanisms, the half-life of NT-proBNP is longer and its plasma concentrations are higher.[22] Additionally, the stability of NT-proBNP makes it easier to measure in routine clinical practice. Previous data showed that NT-proBNP is a more

Figure 2 (A) Forest plot of all included studies using log-transformed BNP/ NT-pro BNP. (B) Forest plot of all included studies using log-transformed BNP/NT-pro BNP, subgroups.



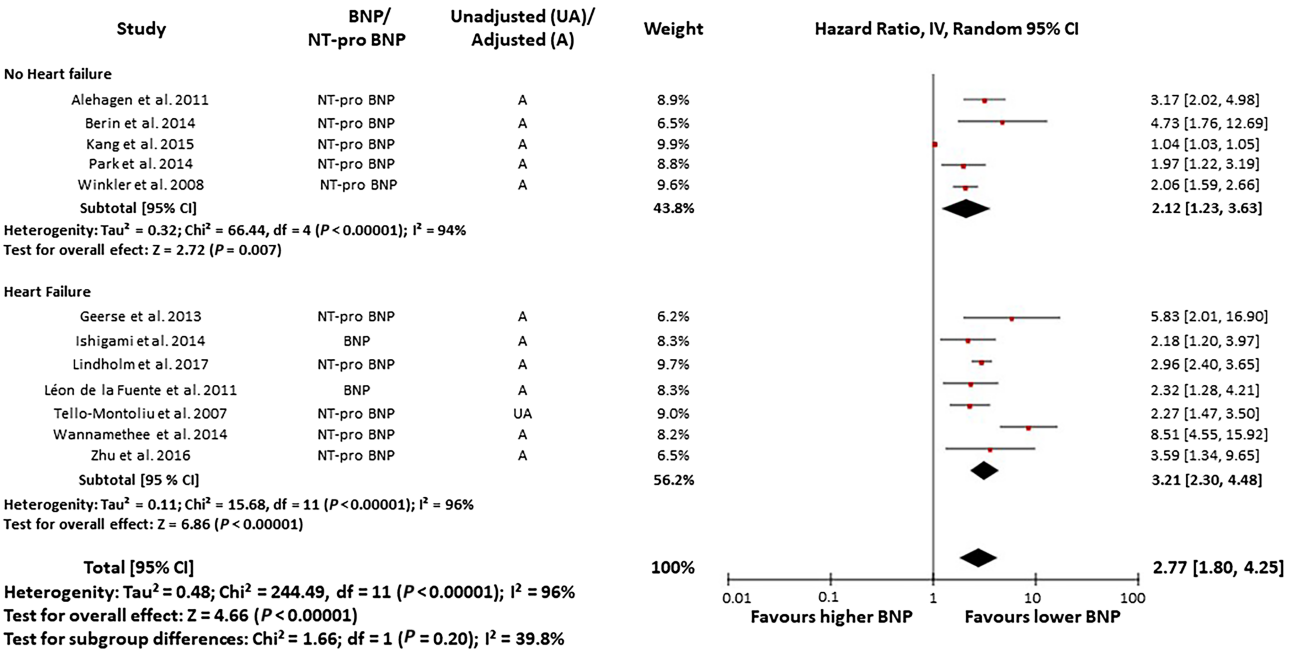
sensitive predictor of MACEs in the general population[4]; however, this finding was not confirmed in a clinical cohort.[23] For the primary analysis, we combined BNP and NT-pro BNP in the same analysis. However, when stratifying by specific BNP and NT-proBNP thresholds, we observed no relevant difference of the effect sizes based on whether BNP or NT-proBNP was used in the studies (*Figure 5A,B*). This observation is in line with the current ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, where cut-off values for BNP and NT-proBNP are defined without preferring one biomarker over the other.[3]

Thresholds in non-heart failure cohorts

While clinical cut-off values have been established for patients with heart failure, the thresholds associated with in-

Figure 3 Forest plot of all included studies using BNP/NT-pro BNP levels per 1 SD increase.

Figure 4 Forest plot and subgroup analysis of all included studies using quartiles.

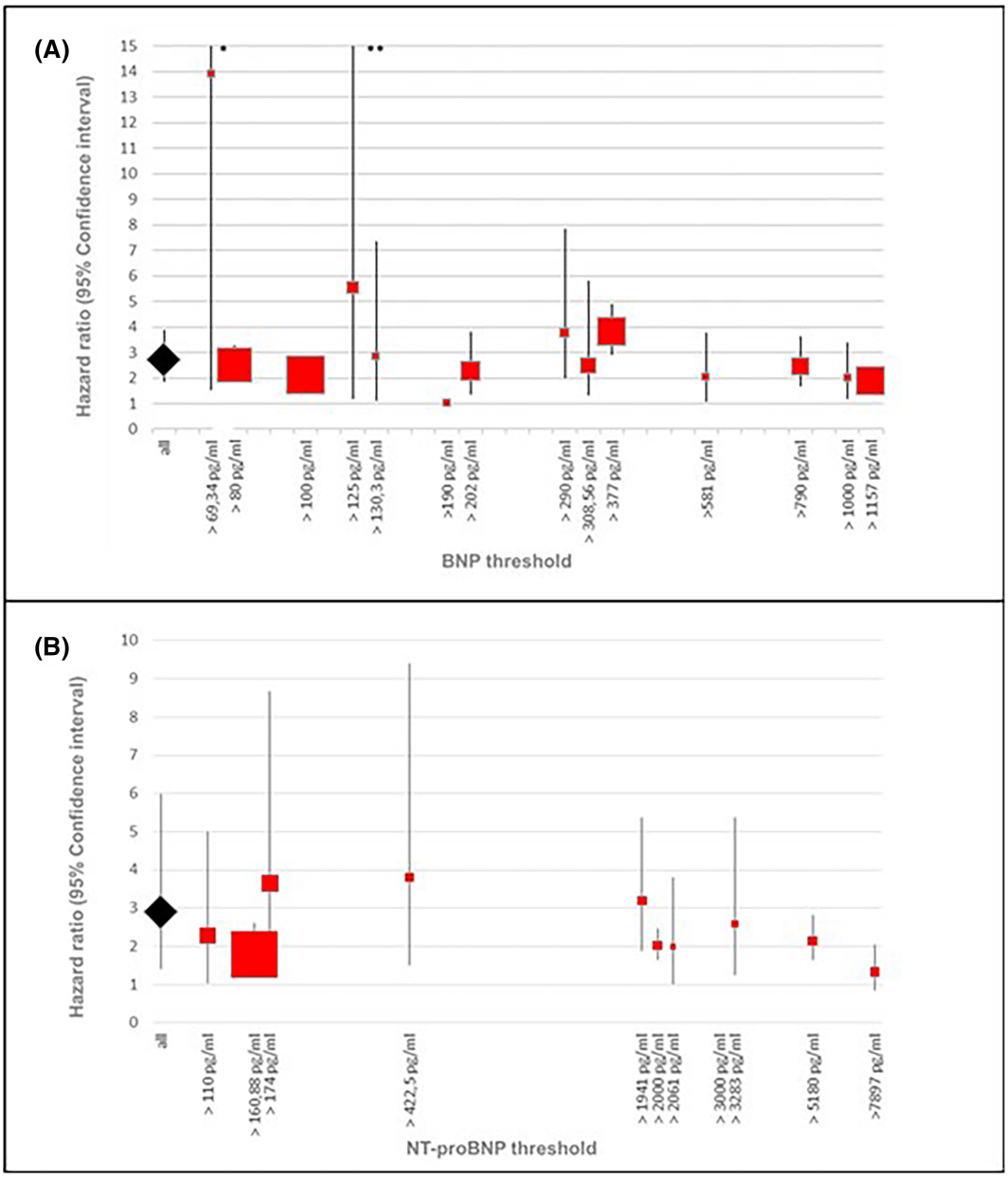


creased cardiovascular risk in patients without heart failure are unclear. In a large general population cohort, cut-off values for BNP/NT-proBNP were determined by the 90th percentile in healthy subjects, resulting in values of 31.3 pg/mL (men) and 45.5 pg/mL (women) for BNP and 106 pg/mL (men) and 173 pg/mL (women) for NT-proBNP. Applying these thresholds in a general population cohort improved the prediction of the risk of cardiovascular events independent of the presence of traditional cardiovascular risk factors over a follow-up period of 9 years.[4] In accordance with the findings of the present meta-analysis, these findings suggested that lower cut-off values for BNP/NT-proBNP than those used for the diagnosis of heart failure could be used for risk stratification in patients without heart failure. Therefore, our findings highlight the need for additional research to establish and validate the thresholds for the levels of BNP and NT-pro BNP in patients without heart failure that are indicative of an increased cardiovascular risk.

Strengths and limitations

The strengths of our analysis include the large number of studies, including more than 89 000 subject, and the broad spectrum of inclusion criteria. However, due to the variability in cohorts, the endpoints also varied in the included studies. Furthermore, whenever available, fully adjusted multivariate hazard ratios were used in this meta-analysis; however, the

Figure 5 Association of elevated BNP (A) and NT-proBNP (B) values with MACE events, stratified by level of threshold.



* HR (95%CI): 13.92 (1.52-127.79)

** HR (95%CI): 5.54 (1.19-25.79)

variables used for adjustment differed among the studies. In some included studies, multivariable models were not available, so univariate models were used.[13,24–28] Furthermore, a total of 11 studies had to be excluded due to a lack of comparability of the increments used. Last, we did not stratify studies according to acute or chronic heart failure status.

Conclusions

BNP/NT-proBNP can be used as predictors of the long-term prognosis in patients with and without heart failure patients. Our results also support the routine assessment of natriuretic peptides for the assessment of risk in non-heart failure co-

horts, highlighting the need for studies establishing and validating the thresholds for the levels of BNP and NT-pro BNP in patients without heart failure that are indicative of an increased cardiovascular risk.

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Conflict of interest

The authors of this work have nothing to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Forest plot of all included studies using predetermined cut-off levels of BNP/NT-pro BNP.
Figure S2. Subgroup analysis of clinical vs population based cohorts.
Figure S3. Funnel plot of all included studies using log-transformed BNP/NT-pro BNP.
Supporting information. All references.

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