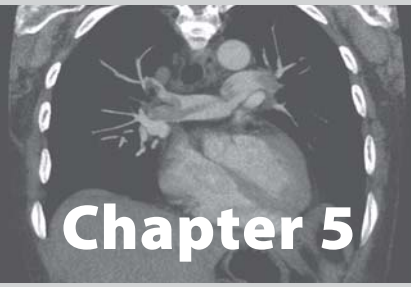
Pulmonary embolism : diagnostic management and prognosis

Klok, F.A.



Chapter 5

Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: systematic review and meta-analysis

F.A. Klok†, I.C.M. Mos† and M.V. Huisman

†Equally contributed

Am J Respir Crit Care Med 2008; 178:425-30

ABSTRACT

Background

The potential role of elevated brain-type natriuretic peptides (BNP) in the differentiation of patients suffering from acute pulmonary embolism (PE) at risk for adverse clinical outcome has not been fully established.

Methods

Articles reporting on studies that evaluated the risk of adverse outcome in patients with PE and elevated BNP or N-terminal-pro-BNP (NT-pro-BNP) levels were abstracted from Medline and EMBASE. Information on study design, patient and assay characteristics as well as clinical outcome was extracted. Primary endpoints were overall mortality and a predefined composite outcome of adverse clinical events.

Results

Data from 13 studies were included. In 51% (576/1132) of the patients, BNP or NT–pro-BNP levels were increased. Elevated levels of BNP or NT-pro-BNP were significantly associated with right ventricular dysfunction (odds ratio [OR] 39; 95% confidence interval [CI] 17-89). Patients with high BNP or NT–pro-BNP concentration were at higher risk of complicated in-hospital course (OR 6.8; 95% CI 4.4-10) and 30-day mortality (OR 7.6; 95% CI 3.4-17). Patients with a high BNP or NT-pro-BNP had a 10% risk of dying (68/671; 95% CI 8.0-13%), whereas 23% (209/909; 95% CI 20-26%) had an adverse clinical outcome.

Conclusions

High concentrations of BNP or NT-pro-BNP distinguish patients with PE at higher risk of complicated in-hospital course and death from those with low BNP levels. Increased BNP or NT–pro-BNP concentrations alone, however, do not justify more invasive treatment regimens.

INTRODUCTION

Right ventricular dysfunction on echocardiography is a common clinical finding in patients with acute pulmonary embolism (PE) and predicts poor outcome.[1-3] Prognostic stratification after measuring right ventricular function in hemodynamically stable patients with acute PE can potentially be used for making treatment decisions: patients identified with a low risk of complicated outcome may be eligible for outpatient management whereas high risk patients may benefit from more aggressive treatment.[1,2]

Several cardiac biomarkers have emerged as indicator of right ventricular dysfunction and predictor of clinical outcome in patients with acute PE. A recent meta-analysis demonstrated that elevated Troponin levels identify patients with PE at high risk of short-term death and adverse outcome.[4] Brain-type natriuretic peptide (BNP) is also a marker of ventricular dysfunction. This hormone is released in response to myocyte stretch. It is synthesized as an inactive prohormone (pro-BNP) that is split into the active hormone BNP and the inactive N-terminal fragment (NT–pro-BNP).[5] Several prospective studies have been performed to identify the potential role of either BNP or NT–pro-BNP in the risk stratification of patients with PE.[6-18] However, reported studies have limited patient numbers, used different cut-off points and involved different clinical endpoints. Therefore, we performed a meta-analysis of studies in patients with acute PE with the aim of evaluating the predictive value of elevated levels of BNP or NT–pro-BNP for clinical outcome after PE.

METHODS

Data sources

A literature search was performed to identify all published prospective studies on BNP or NT–pro-BNP levels and clinical outcome in patients with acute PE. Medline and EMBASE were searched using predefined search terms between January 1980 and October 2007. Search criteria included "pulmonary embolism" and "pro–brain natriuretic peptide" or "brain natriuretic peptide" or "natriuretic peptide." Also, by searching the reference lists of all established studies, the researchers aimed to identify additional relevant articles. Articles were not limited to the English language. Only complete articles were applicable for this analysis.

Study outcome

Objectively adjudicated short-term adverse clinical events were used as a primary outcome of this meta-analysis. Adverse clinical outcome was defined as the occurrence of any of the following: death, cardiopulmonary resuscitation, mechanical ventilation, use of vasopressors, thrombolysis, thrombosuction, open surgical embolectomy or admission to the intensive care unit. Right ventricular dysfunction was used as secondary endpoint.

Study selection and data extraction

Two independent researchers performed the study selection. In case of disagreements, a third researcher was consulted. Criteria for selection were as follows: prospective design, consecutive inclusion of patients, clear description of inclusion and exclusion criteria, objective criteria for diagnosis of PE, predefined endpoints, standardized treatment and the possibility of creating a 2 by 2 table based on BNP or NT–pro-BNP levels and clinical endpoints. Study sample size was not an eligibility criterion. Objective criteria for PE were positive findings on computed tomography (CT) or conventional pulmonary angiography, high-probability ventilation perfusion scintigraphy, or clinical suspicion of PE in combination with ultrasonography proven deep venous thrombosis. This latter criterion is supported by the findings of Le Gal and colleagues who recently described that a positive compression ultrasonography of the lower limb veins is highly predictive of PE on CT in suspected patients.[19] Data regarding patient characteristics, exclusion criteria, diagnostic criteria for PE, severity of PE (inclusion of hemodynamically unstable patients and use of thrombolytic therapy), completeness of follow-up, immunoassay, timing of sampling, cut-off level, follow-up period and endpoints were abstracted.

Statistical Analysis

Data were entered in Review Manager (version 4.2 for Windows; The Nordic Cochrane Center, 7 2003, Copenhagen, Denmark). Individual and pooled odds ratios (OR) were calculated to assess the relation between elevated BNP or NT–pro-BNP levels and clinical outcome. Mantel-Haenszel methods for combining trials were used for weighting the studies. Cochran's Chi-Square test and the I^2 test for heterogeneity were used to assess interstudy heterogeneity. The Chi-Square test assesses whether observed differences in results are compatible with chance alone. The I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. Statistically significant heterogeneity was considered present at Chi-Square $p<0.10$ and $I^2>50\%$.

RESULTS

Study selection

After the literature search, 124 potentially relevant studies were identified. Articles were excluded by review of title and abstract in case of review articles (48), animal studies (2), case reports (5), editorials, letters or author replies (13), studies not covering the clinical course of PE (6) and if the article concerned studies on other diseases than PE (17). After full review, an additional 20 studies were excluded because our predefined endpoints were not reported (17) or cut-off points were not mentioned (3). The remaining 13 studies met our criteria and were included in this meta-analysis.[6-18]

Characteristics of included studies

Demographic characteristics of the patients were comparable between all included studies (Table 1). Mean age of the patients varied between 53 and 75 years; the proportion of females ranged from 36 to 74%. In most patients, the diagnosis of PE was confirmed by CT, high-probability ventilation perfusion scintigraphy or pulmonary angiography. In three studies, hemodynamically unstable patients were excluded.[7,11,17] Noticeably, in two of these latter studies, some patients received thrombolytic therapy during their hospital stay.[7,11] Two included studies reported on partially overlapping patient cohorts.[16,18] Because one of these studies used BNP[16] and the other NT-pro-BNP[18] levels as an outcome parameter, both studies could be incorporated into subgroup analyses based on type of BNP testing.

Assays and cut-off points

As shown in Table 1, all studies reporting NT-pro-BNP levels used a Roche analyzer (two types: Elecsys 2010 analyzer, Meylan France; electro-chemiluminescence method-ECLIA, Roche Diagnostics GmbH, Mannheim, Germany), with three different cut-off levels, varying from 500 to 1000 pg/mL. In the BNP studies, two assays with four different cut-off levels varying between 75 and 100 pg/mL were used. In all included studies, the timing of sampling was comparable. Cut-off levels were not predefined in 10 studies. In these articles, receiver operating characteristic (ROC) analyses were performed to retrospectively determine optimal cut-off values with regard to complicated PE. Normal levels are defined as levels beneath or equal to the cut-off point.

Clinical outcome

Overall, in 51% (576/1132) of the patients, the assays showed elevated plasma concentrations of BNP or NT-pro-BNP. Data on overall mortality were reported in four studies using BNP[10,11,14,17] and four studies using NT–pro-BNP.[8,12,13,15] In the BNP cohort, 17 of 123 patients (14%; 95% confidence interval [CI] 8.3–21%) with elevated BNP levels died compared with 3 of 138 (2.2%; 95% CI 0.45–6.2%) of those with normal BNP levels. This resulted in an overall OR for death of 6.5 (95% CI 2.0–21; Figure 1). One study had a follow-up of three months[17], as compared with the other three, which had only in-hospital follow-up. If this single study was left out of the analysis, overall OR decreased to 3.3 (95% CI 0.6–18). In the NT-pro-BNP cohort, 46 of 250 patients (18%; 95% CI 14-24%) with elevated NT–pro-BNP levels died in comparison with 2 of 160 (1.3%; 95% CI 0.15–4.4%) of those with normal NT–pro-BNP levels; OR for death was 8.7 (95% CI 2.8–27%; Figure 1). Numbers on PE-related mortality were only available in three studies.[11,13,17] Because follow-up time was dissimilar between these studies and not all mortality cases were adjudicated by an independent, blinded committee to determine the cause of death, we could not include PE-related mortality as an outcome of this meta-analysis.

Ten studies provided data on adverse clinical outcome[6,8-13,15,16,18] of which six had NT-pro-BNP levels as an outcome parameter.[6,8,12,13,15,18] Overall, criteria for adverse clinical outcome were comparable throughout all studies. In the BNP study group, 47 of 128 (37%; 95% CI

Table 1. Characteristics of included studies.

Marker	Ref	n	Female (%)	Age*	Assay†	Timing of sampling	Cut-off	Follow-up	PE diagnosis	Hemodynamic instability¥	Thrombolysis (n, %)
NT-pro-BNP	6	60	60	72 ±15	Roche, Elecsys 2010 analyzer	Admission	1000pg/mL§	In hospital	PA, V/Q, ultrasonography∂	Yes	1 (1.7)
	8	107	63	61 ±6	Roche, Elecsys 2010 analyzer	Admission, 4h, 8h, 24h	1000pg/mL	30 days	PA, V/Q, ultrasonography∂	Yes	–¤
	12	124	60	60 ±18	Roche, Elecsys 2010 analyzer	Admission, 4h, 8h, 24h	1000pg/mL	In hospital	PA, V/Q, ultrasonography∂	Yes	12 (11)
	13	100	65	63 ±18	Roche, ECLIA	Admission	600pg/mL	40 days	PA, V/Q	Yes	7 (7.0)
	15	79	63	63 ±17	Roche, Elecsys 2010 analyzer	Admission	600pg/mL	In hospital	PA, V/Q	Yes	8 (10)
	18	73	41	61 ±18	Roche, Elecsys 2010 analyzer	Admission	500pg/mL	In hospital	PA, V/Q	Yes	10 (14)
BNP	7	67	41	64 ±17	Biosite Diagnostics, Triage	Admission	100 pg/mL	NA‡	CT, V/Q	No	6 (9.0)
	9	181	58	53 ±17	Biosite Diagnostics, Triage	Admission	90pg/mL§	6 months	PA, V/Q	Yes	13 (22)
	10	51	65	79 ±9	Biosite Diagnostics, Triage	Admission	100 pg/mL	In hospital	PA, V/Q, ultrasonography∂	Yes	0 (0)
	11	61	74	75 ±14	Biosite Diagnostics, Triage	Admission	89 pg/mL	In hospital	PA, pulmonary angiography	No	7 (11)
	14	46	36	57 ±19	Biosite Diagnostics, Triage	Admission	90 pg/mL	In hospital	PA, V/Q, echocardiography∆	Yes	22 (48)
	16	73	41	61 ±18	Biosite Diagnostics, Triage	Within 4 hours	90pg/mL§	In hospital	PA, V/Q, embolectomy	Yes	6 (8.2)
	17	110	-¶	58 ±18	Immuno radiometric assay, Shionoria	Admission	75 pg/mL	3 months	PA, V/Q, ultrasonography	No	0 (0)

*Mean ±SD; †manufacturer and kind of assay (all were quantitative assays); ‡not applicable: endpoint was right ventricular dysfunction at time of diagnosis; ¶information was not provided; §predefined cut-off point; ∂typical clinical presentation and positive ultrasonography of lower limbs; ∆typical presentation and suggestive echocardiography; ¤specific information was not provided; ¥patients with hemodynamic instability were eligible for the study. PA=computed tomography or conventional pulmonary angiography, V/Q=ventilation perfusion scintigraphy, PE=pulmonary embolism, SD=standard deviation, n=number.

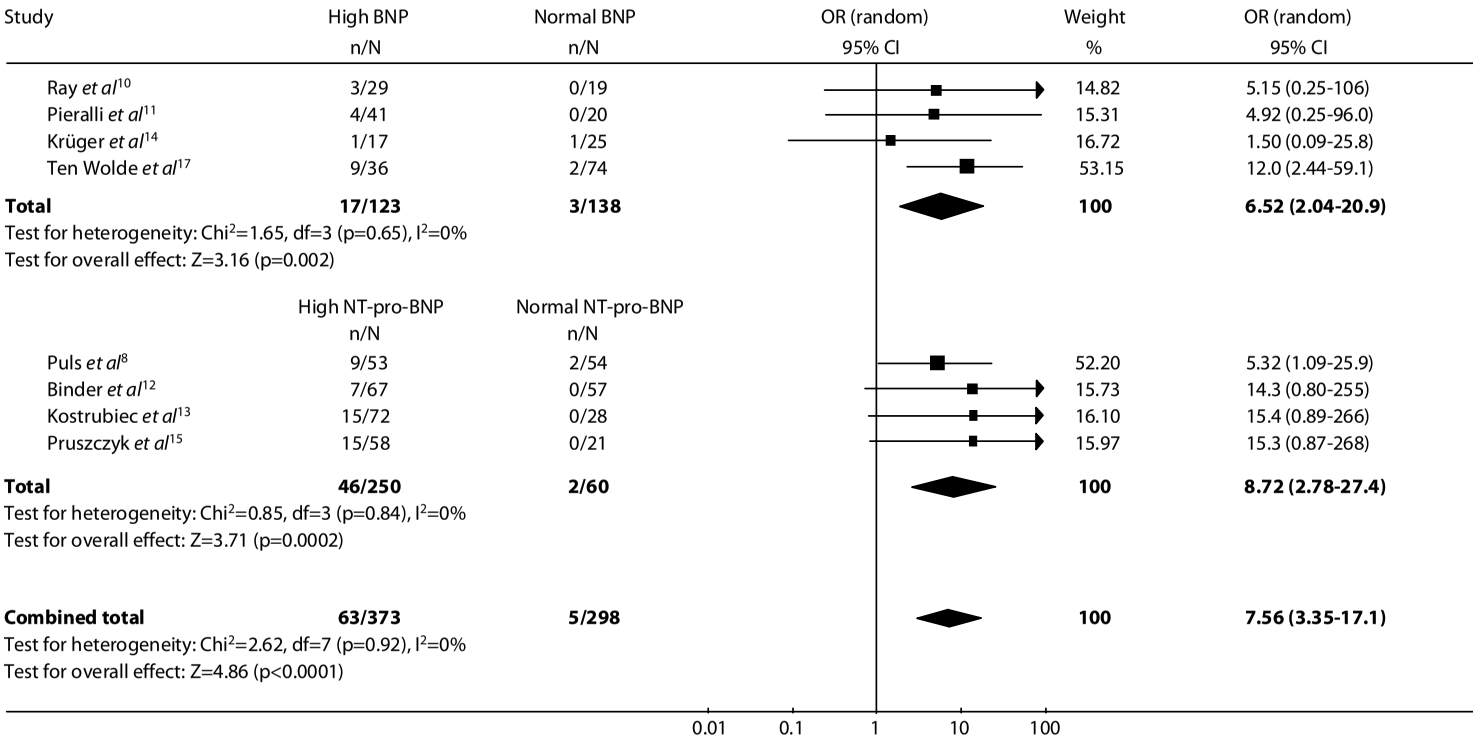


Figure 1. Odds ratio (OR) for overall mortality based on elevated BNP or NT–pro-BNP levels. Different cut-off points were used for different studies; Mantel-Haenszel methods for combining trials were used for weighting the studies. CI indicates confidence interval.

28-46%) patients with elevated BNP levels had adverse advents during follow-up in comparison with 28 of 208 (13%; 95% CI 9.1-19%) patients with normal plasma concentrations. High BNP levels were associated with a higher risk of occurrence of adverse clinical events (OR 6.3; 95% CI 3.6–11; Figure 2). This OR was even higher (9.5; 95% CI 3.5-25) after exclusion of one study with six months of follow-up[9], thereby limiting the outcome to in-hospital clinical course. Of the 318 patients with elevated NT-pro-BNP levels, 102 experienced short-term adverse events (32%; 95% CI 27-38%) as compared with 12 of 225 (5.3%; 95% CI 2.8-9.1%) patients with normal NT-pro-BNP levels. Patients with high NT-pro-BNP serum concentration were at higher risk of complicated in-hospital course compared with patients with normal levels (OR 7.5; 95% CI 3.8-15; Figure 2). Pooled data of all assays showed elevated BNP or NT-pro-BNP levels in 52% of the patients with a risk of 23% (209/909; 95% CI 20–26%) and an OR of 6.8 (95% CI 4.4-10) toward complicated clinical course.

Right ventricular dysfunction

Data on right ventricular dysfunction were reported in six studies (Figure 3). Four studies were evaluating BNP (243 patients)[7,11,14,16] and two studies evaluated NT–pro-BNP levels (197 patients).[12,18] The incidence of right ventricular dysfunction was 85% (116/137; 95% CI 78-90%) and 12% (13/106; 95% CI 6.7-20%) in patients with and without elevated BNP levels respectively. A positive association was found between increased concentration of BNP and the presence of right ventricular dysfunction (OR 81; 95% CI 27-238). In the NT-pro-BNP studies, the incidence of right ventricular dysfunction was 45% (49/109; 95% CI 35-55%) in patients with elevated NT-pro-BNP levels compared with 4.5% (4/88; 95% CI 1.3-11%) in patients with normal NT-pro-BNP levels. Elevated NT-pro-BNP levels were associated with the presence of right ventricular dysfunction (OR 17; 95% CI 5.7–49). Pooled data of all assays revealed a combined OR of 39 (95% CI 17-89).

DISCUSSION

This meta-analysis demonstrates a significant relation between high levels of BNP or NT-pro-BNP and deterioration of clinical condition in patients with acute PE. This is physiologically plausible because BNP is released in reaction to right ventricular stress, which has been shown to predict a non-benign course in patients with PE.[1-3] This latter relation is also demonstrated in this analysis: we found a very strong correlation between increased levels of BNP or NT-pro-BNP and right ventricular dysfunction on echocardiography (Figure 3).

There are some points for discussion if BNP or NT-pro-BNP levels would be incorporated in clinical risk stratification and treatment strategies for patients with acute PE. First, timing of blood sampling has consequences for the established BNP concentration. The BNP pro-hormone (pro-BNP) in normal ventricular myocytes is not stored to a significant amount. As a consequence, it takes several hours for the plasma natriuretic peptide levels to increase after

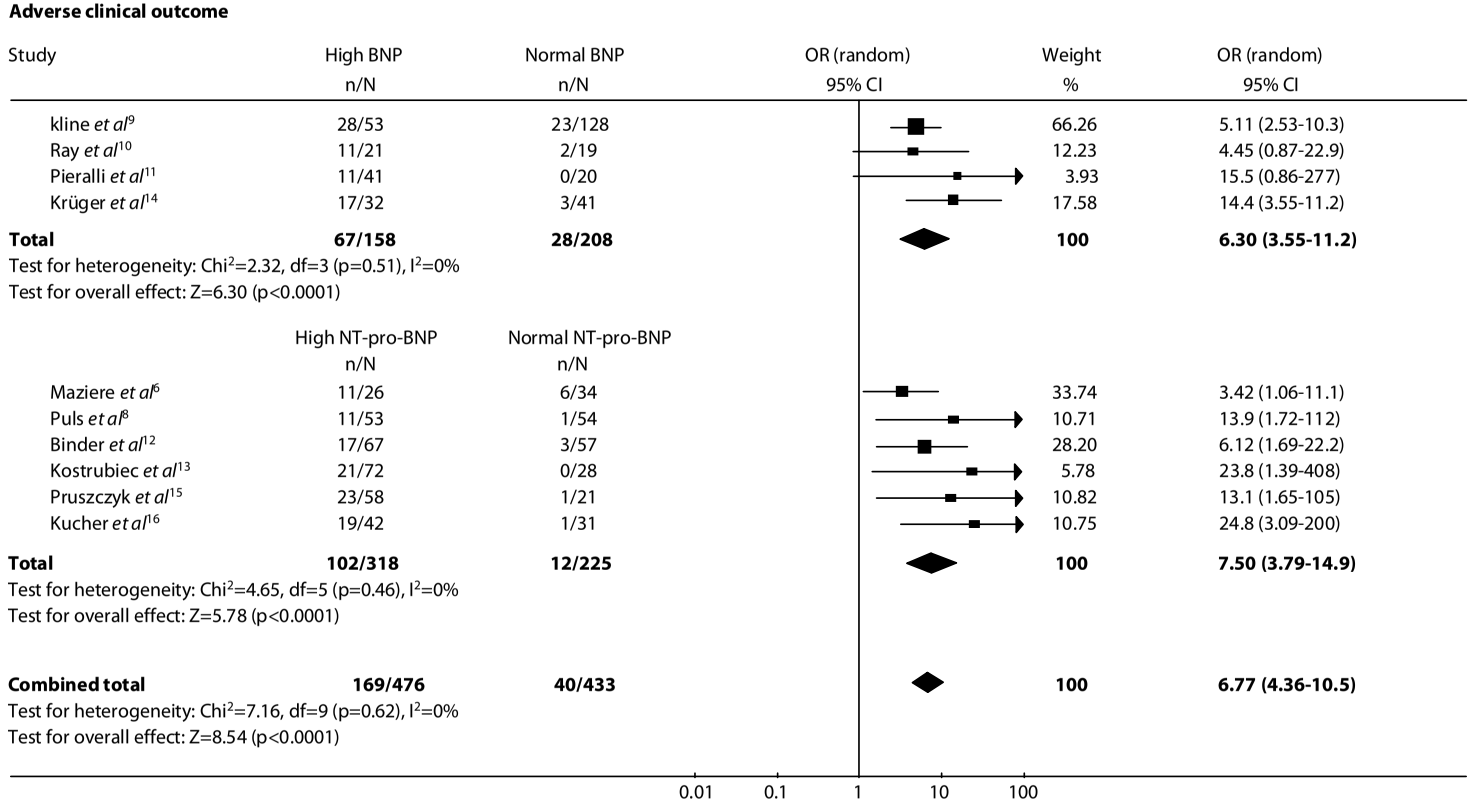


Figure 2. Odds ratio (OR) for adverse clinical outcome based on elevated BNP or NT–pro-BNP levels. Different cut-off points were used for different studies; Mantel-Haenszel methods for combining trials were used for weighting the studies. CI indicates confidence interval.

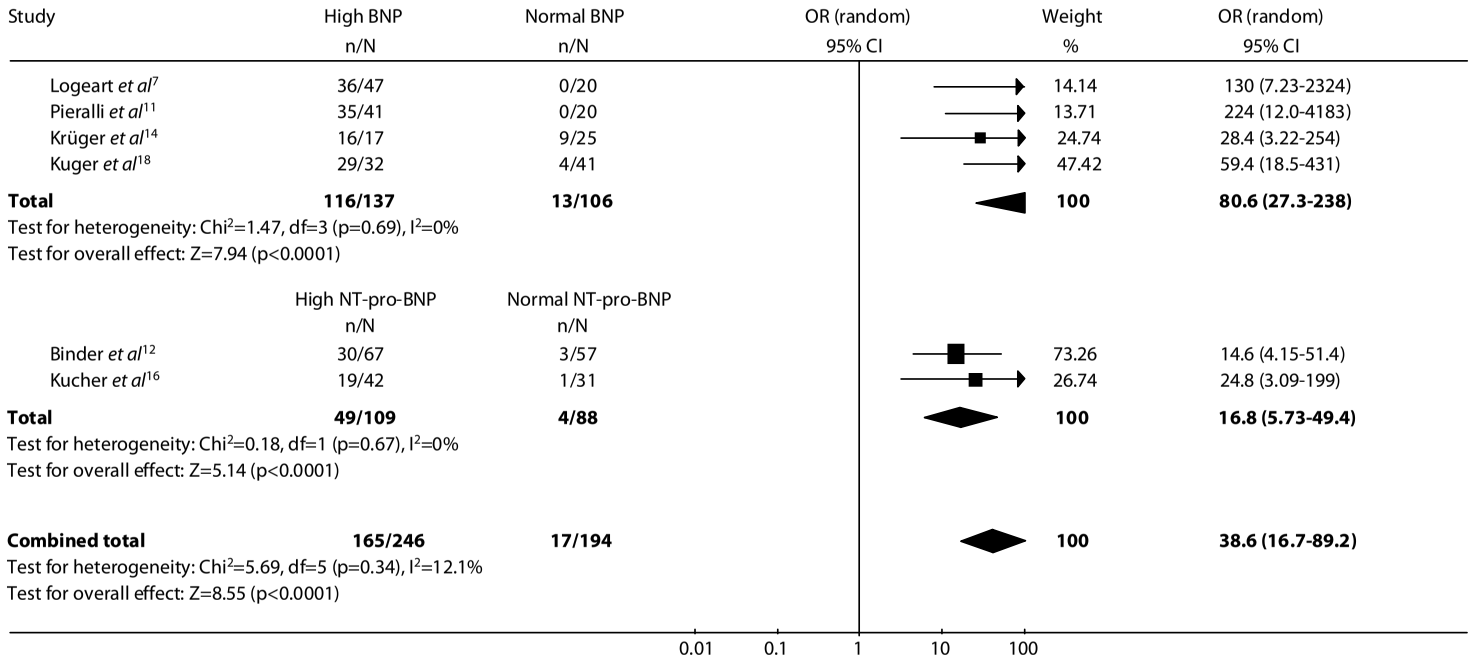


Figure 3. Odds ratio (OR) for right ventricular dysfunction on echocardiography based on elevated BNP or NT–pro-BNP levels. Different cut-off points were used for different studies; Mantel-Haenszel methods for combining trials were used for weighting the studies. CI indicates confidence interval.

the onset of acute myocardial stretch.[20] A very recent onset of complaints could therefore result in false-negative BNP or NT–pro-BNP test results. Second, many different cut-off levels for BNP or NT–pro-BNP are proposed in the literature.[21,22] The variation may be related to patient selection, sex, and age.[22] Nonetheless, despite the different cut-off levels and different assays, the prognostic value of both NT–pro-BNP and BNP was consistent in all included studies.

What are the potential implications of our findings? First, normal levels of BNP have a high negative predictive value for unfavorable clinical outcome. Therefore, patients with normal levels of BNP or NT-pro-BNP have low risks for death as well as for hemodynamic deterioration resulting in any adverse events. Conversely, elevated concentrations of B-type natriuretic peptides are a non-specific finding occurring in more than half of the patients. An explanation for this phenomenon is the elevation of natriuretic peptides in a multitude of other conditions, including preexisting left ventricular dysfunction, older age, renal impairment and chronic lung disease.[23] The combination of BNP with other clinical risk factors for adverse outcome may improve sensitivity and positive predictive value for clinical deterioration. Such algorithms for risk stratification would be clinically useful if they were able to identify patients eligible for outpatient management or for standard or intensive in-hospital treatment. Proposals for such algorithms including markers or biomarkers of right ventricular function (e.g. BNP or NT–pro-BNP, Troponin, Growth Differentiation Factor-15 or heart-type fatty acid-binding protein) have been made but not yet validated prospectively in clinical outcome studies.[4,8,12,13,24,25] Future studies are required to determine the clinical benefits of more aggressive treatments in patients with adverse prognosis as identified by these risk stratifications and less intensive treatment, including out of hospital treatment, in patients with normal values of BNP.

This meta-analysis has limitations. First, included studies used different assays with different retrospectively calculated cut-off points. Second, duration of follow-up and definitions of endpoints varied among the studies. In addition, most studies did not mention completeness of follow-up. Nonetheless, we have included a large cohort of prospectively followed patients and our analysis showed no evidence of heterogeneity between the outcomes of the incorporated studies. Third, the relative risk for mortality is not adjusted for confounding factors, thus part of the effect ascribed to high BNP values may be related to clinical conditions associated with PE. Fourth, we could not determine the ideal cut-off for the two BNP tests because we did not retrieve the raw data of the included studies to perform ROC and other analyses. Finally, in the included studies, it is not stated whether thrombolytic therapy or intensive care unit admission was the result of the clinical condition or a high BNP or NT-pro-BNP value.

In summary, elevated levels of BNP or NT-pro-BNP are indicators of right ventricular dysfunction in patients with acute PE and strong risk factors for short term mortality as well as for overall short term complicated clinical outcome. It remains to be demonstrated whether it could play a role in risk stratification algorithms identifying patients who could benefit from differentiated forms of therapy, of which thrombolytic therapy and home treatment are two poles of the spectrum.

REFERENCES

1. Frémont B, Pacouret G, Jacobi D, et al. Prognostic value of the echocardiographic right/left ventricular end-diastolic diameter ratio in patients with acute pulmonary embolism: results from a monocenter registry of 1416 patients. Chest 2008; 133:358-62
2. Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000; 101:2817-22
3. Goldhaber SZ. Pulmonary embolism. N Engl J Med 1998; 339:93-104
4. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007; 116:427-33
5. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail 2004; 6:257-60
6. Maziere F, Birolleau S, Medimagh S, et al. Comparison of troponin I and N-terminal-pro B-type natriuretic peptide for risk stratification in patients with pulmonary embolism. Eur J Emerg Med 2007; 14:207-11
7. Logeart D, Lecuyer L, Thabut G, et al. Biomarker-based strategy for screening right ventricular dysfunction in patients with non-massive pulmonary embolism. Intensive Care Med 2007; 33:286-92
8. Puls M, Dellas C, Lankeit M, et al. Heart-type fatty acid-binding protein permits early risk stratification of pulmonary embolism. Eur Heart J 2007; 28:224-29
9. Kline JA, Hernandez-Nino J, Rose GA, et al. Surrogate markers for adverse outcomes in normotensive patients with pulmonary embolism. Crit Care Med 2006; 34:2773-80
10. Ray P, Maziere F, Medimagh S, et al. Evaluation of B-type natriuretic peptide to predict complicated pulmonary embolism in patients aged 65 years and older: brief report. Am J Emerg Med 2006; 24:603-7
11. Pieralli F, Olivotto I, Vanni S, et al. Usefulness of bedside testing for brain natriuretic peptide to identify right ventricular dysfunction and outcome in normotensive patients with acute pulmonary embolism. Am J Cardiol 2006; 97:1386-90
12. Binder L, Pieske B, Olschewski M, et al. N-terminal pro-brain natriuretic peptide or troponin testing followed by echocardiography for risk stratification of acute pulmonary embolism. Circulation 2005; 112:1573-9
13. Kostrubiec M, Pruszczyk P, Bochowicz A, et al. Biomarker-based risk assessment model in acute pulmonary embolism. Eur Heart J 2005; 26:2166-72
14. Krüger S, Graf J, Merx MW, et al. Brain natriuretic peptide predicts right heart failure in patients with acute pulmonary embolism. Am Heart J 2004; 147:60-5
15. Pruszczyk P, Kostrubiec M, Bochowicz A, et al. N-terminal pro-brain natriuretic peptide in patients with acute pulmonary embolism. Eur Respir J 2003; 22:649-53
16. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003; 107:2545-7
17. ten Wolde M, Tulevski II, Mulder JW, et al. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. Circulation 2003; 107:2082-4
18. Kucher N, Printzen G, Doernhoefer T, et al. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. Circulation 2003; 107:1576-8
19. Le Gal G, Righini M, Sanchez O, et al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. Thromb Haemost 2006; 95:963-6
20. Hama N, Itoh H, Shirakami G, et al. Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. Circulation 1995; 92:1558-64
21. Maisel AS, Krishnaswamy P, Nowak RM, et al. Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161-7

22. Giannitsis E, Katus HA. Risk stratification in pulmonary embolism based on biomarkers and echocardiography. Circulation 2005; 112:1520-1
23. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003; 362:316-22
24. Puls M, Dellas C, Lankeit M, et al. Heart-type fatty acid-binding protein permits early risk stratification of pulmonary embolism. Eur Heart J 2007; 28:224-9
25. Lankeit M, Kempf T, Dellas C, et al. Growth-differentiation Factor-15 for Prognostic Assessment of Patients with Acute Pulmonary Embolism. Am J Respir Crit Care Med 2008; 177:1018-25