EDITOR'S CHOICE

Natriuretic peptides and troponins in pulmonary embolism: a meta-analysis

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► Details of the search strategy and additional tables and figures are published online only at http://thorax.bmj.com/content/vol64/issue10

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ABSTRACT

Background: The role of biomarkers such as B-type natriuretic peptides (BNP and NT-proBNP) and troponins in risk stratification of acute pulmonary embolism (APE) is still debated. A meta-analysis was performed to assess the association between raised natriuretic peptide levels, alone or in conjunction with troponins, and all-cause and APE-related mortality, serious adverse events and echographic right ventricular dysfunction.

Methods: MEDLINE and EMBASE databases were searched and conference abstracts were hand searched up to February 2008. Studies were included if a 2×2 table could be constructed based on natriuretic peptide results and at least one of the outcomes.

Results: Twenty-three studies were included (1127 patients). Raised natriuretic peptide levels were significantly associated with all-cause mortality (odds ratio (OR) 6.2; 95% confidence interval (CI) 3.0 to 12.7), APE-related mortality (OR 5.0; 95% CI 2.2 to 11.5) and serious adverse events (OR 6.7; 95% CI 3.9 to 11.6), with homogeneity across studies. Among patients with raised natriuretic peptide levels, increased serum troponins were associated with a further increase in the risk of adverse outcomes. Analysis of the accuracy of natriuretic peptides in detecting right ventricular dysfunction was limited by heterogeneity across studies. BNP appeared to have better sensitivity and specificity than NT-proBNP in detecting right ventricular dysfunction.

Conclusions: Raised levels of B-type natriuretic peptides identified a subset of patients with APE at higher risk of adverse outcomes. Among patients with raised natriuretic peptide levels, increased troponins were found to be an independent prognostic marker. The results of this meta-analysis may have important clinical implications in the management of APE.

Acute pulmonary embolism (APE) may present with a wide spectrum of manifestations ranging from lack of symptoms to massive embolism resulting in right ventricular failure and sudden death.[1 2] Although most patients initially have normal blood pressure, some patients rapidly deteriorate and develop systemic hypotension, cardiogenic shock and death despite appropriate anticoagulation. Early risk stratification is the cornerstone of the modern management of APE as it largely influences patient management.[1 2] Patients at risk for adverse clinical events will require close monitoring or even more aggressive therapy, whereas early discharge and outpatient treatment will be considered for those at low risk.[2] Among patients with normal blood pressure on admission, major adverse clinical events attributable to APE are generally confined to patients with echocardiographic signs of right ventricular dysfunction. However, major drawbacks of echocardiography include its limited round-the-clock availability, occasional poor imaging quality and absence of consensus criteria for right ventricular overload.[1]

A number of biomarkers, including natriuretic peptides and cardiac troponins, have recently raised interest for risk stratification in patients with APE. Natriuretic peptides are secreted by the heart in response to pressure or volume overload and are also influenced by patients' age, body mass index and renal function.[3] In the setting of APE, increases in natriuretic peptide levels (BNP and NT-proBNP) are presumably related to enhanced right ventricular shear stress and right ventricular dysfunction.[4] Increased cardiac troponin T and I, two related muscular proteins released in response to myocardial ischaemia, were recently shown to be associated with higher mortality in APE.[5] The objectives of this meta-analysis were to assess (1) the prognostic significance of BNP and NT-proBNP alone or in conjunction with troponins, and (2) the diagnostic accuracy of natriuretic peptides in detecting right ventricular dysfunction in patients with APE.

METHODS

The methods that we used were in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group.[6]

Literature search

We searched EMBASE (1974–February 2008) and MEDLINE (1966–February 2008) for original articles published in any language. Search criteria combined free text search, exploded MESH/EMTREE terms and all synonyms of pulmonary embolism and brain natriuretic peptides (see further details in online supplement). We also searched for additional articles from the reference list of relevant papers obtained from the electronic search. In addition, the grey literature was explored by hand searching the conference abstracts of the American Heart Association, American College of Cardiology, European Society of Cardiology, American Thoracic Society, American College of Chest Physicians, European Respiratory Society and British Thoracic Society from January 1999 to February 2008.

Study selection

Observational studies were included if they reported on patients with an objective diagnosis of APE, and if a 2×2 table could be constructed based on BNP or NT-proBNP results and at least one of four outcomes: all-cause mortality, APE-related mortality, serious adverse events and/or

right ventricular dysfunction. All-cause mortality was considered as the primary outcome. Serious adverse events were defined as the composite of death and any of the following: shock, need for thrombolysis, need for catheter fragmentation, need for surgical embolectomy, endotracheal intubation, catecholamine infusion for sustained hypotension, cardiopulmonary resuscitation or recurrent pulmonary embolism.

Two reviewers (JCL, SP) independently applied these criteria to the titles and abstracts of all citations obtained. When there was any possibility that it might be relevant, the paper was retrieved and independently assessed by the same reviewers for a final decision about its inclusion into the meta-analysis. Throughout this process the reviewers were blinded to authors' names, journal and year of publication of the papers. Those published in languages other than English and French were translated into French. When we identified studies that had been reported in multiple papers, the analysis was limited to the largest cohort unless the necessary data had appeared only in another paper. Any disagreement was resolved by consensus. A log of reasons for rejection of citations identified from the searches was kept. The agreement between the two primary reviewers was measured using the quadratic weighted kappa statistic.[7]

We determined "a priori" that the effect of publication bias should be minor if the plot of the magnitude of risk in each study (ie, odds ratio (OR)) versus its precision estimate (ie, standard error of OR) showed a roughly symmetrical funnel shape.[8] We also formally tested the presence of publication bias using the standard error- and study size-based funnel plot and related asymmetry tests.[9]

Assessment of methodological quality

The methodological quality of the selected studies was evaluated by systematically considering three important sources of bias in observational studies:[10] (1) whether the study included consecutive patients (selection bias); (2) whether the professionals who influenced the outcomes (eg, need for thrombolysis) were blinded to the natriuretic peptide result at study entry (information bias); and (3) whether comorbidities which might influence BNP or NT-proBNP levels and accuracy (eg, renal failure or chronic heart failure) were included (confounding bias). Each of these three criteria was evaluated separately.

Information extraction

In addition to the data related to natriuretic peptides alone, the same reviewers independently noted the results when cardiac troponin levels were measured in conjunction with natriuretic peptides. This meta-analysis therefore differed from that of Becattini *et al*[5] who studied the value of cardiac troponins alone in APE. The abstracted information for each study included: (1) patients' characteristics (number of patients, mean age, gender distribution, methods for diagnosis of pulmonary embolism, haemodynamic status at study entry, length of follow-up); (2) test methods (assay, manufacturer, diagnostic threshold, time between admission and measurement); and (3) number of patients with or without the outcome of interest among those with positive or negative BNP, NT-proBNP and troponin when available. In cases of missing data, the authors were contacted for additional information.

Meta-analysis

In the main analysis we considered increased natriuretic peptide levels as a risk factor for adverse outcome. Accordingly, for each study we constructed 2×2 tables for each outcome at a given natriuretic peptide threshold level. All-cause mortality and APE-related mortality were considered separately. We also performed specific analyses of studies including only haemodynamically stable patients. When several thresholds were reported in the same studies, the one that approached the most frequently used threshold across studies was selected. The ORs were weighted by the inverse of their variance and combined according to a random effects model.[11] Homogeneity was tested with Cochran's χ^2 and I^2 tests. Statistically significant heterogeneity was considered present at $p<0.10$ and $I^2>50\%$.[12]

We also conducted a meta-analysis of the studies that assessed the combination of natriuretic peptides and troponins to predict adverse outcome in APE. In order to explore the added prognostic value of cardiac troponins over natriuretic peptides, patients with both positive natriuretic peptides and troponins were compared with those with positive natriuretic peptides and negative troponins.

We decided "a priori" to conduct subgroup analyses to identify sources of heterogeneity (if any) in the main analysis. Separate analyses were planned for studies (1) that assessed BNP and NT-proBNP assays; (2) that included patients with haemodynamic instability at study entry; and (3) that limited their analysis to short-term events (<6 weeks). Subgroup analyses were also conducted according to the criteria of methodological quality described above. The meta-analyses were performed with Review Manager (Version 4.2, The Cochrane Collaboration).

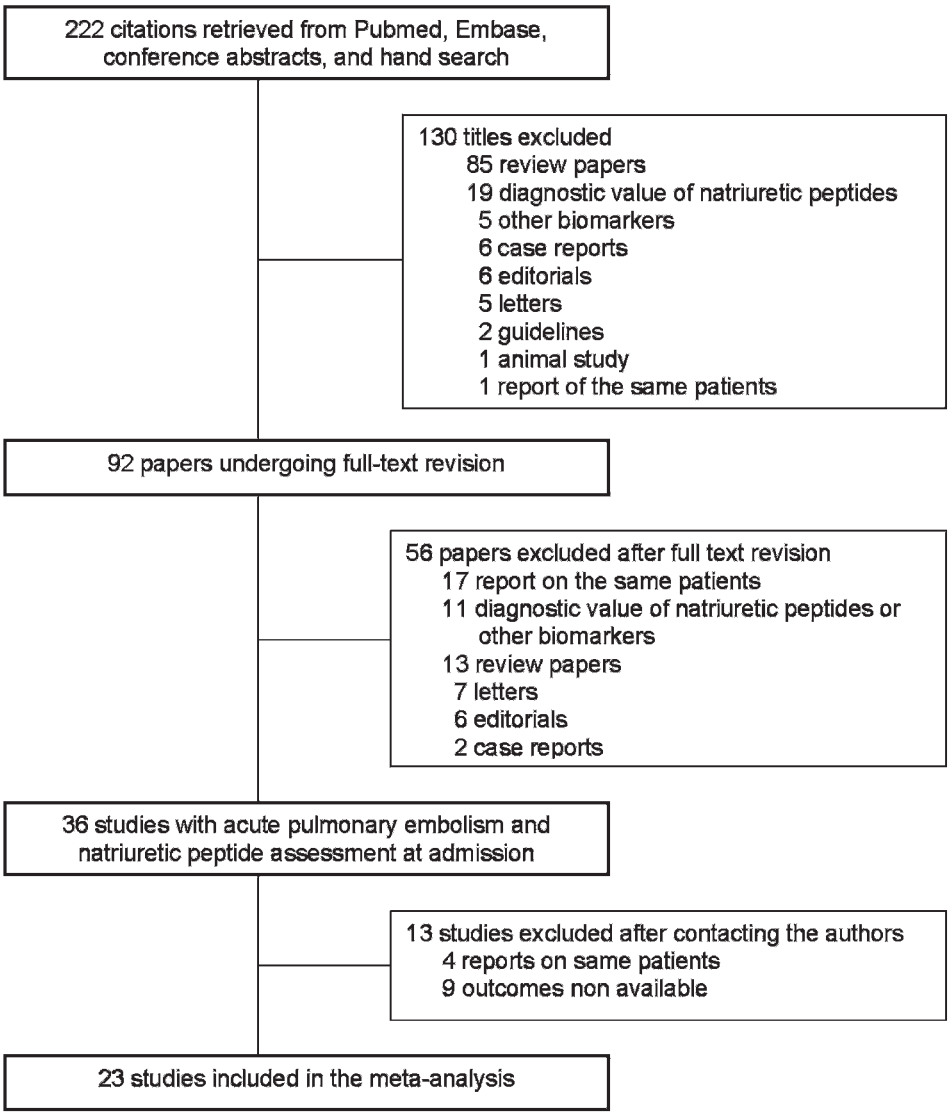
In secondary analyses we considered the measurement of natriuretic peptides as a diagnostic test for right ventricular dysfunction. For each study a receiver operating characteristics (ROC) curve was constructed from the true positive rate (sensitivity) and the false positive rate (1 – specificity) at the reported threshold levels of natriuretic peptide. The ROC curves were then pooled with an additional random effect term.[11 13] We computed the area under the curve that indicated the probability that a random pair of patients would be correctly classified as to their disease state.[14] In addition, for each assay we calculated the pooled sensitivity, specificity and the corresponding likelihood ratios at the most frequently used threshold value.[13] All the secondary analyses were performed with R software 2.5.1 (www.r-project.org).

RESULTS

Literature search/agreement studies

Two hundred and twenty-two separate publications were retrieved (fig 1). Both primary reviewers agreed to include 19 independent cohorts[4 15–32] that contributed to 23 separate studies[4 15–36] (quadratic weighted kappa 0.79; 95% confidence interval (CI) 0.43 to 1). Two studies assessed the value of BNP and NT-proBNP in the same cohort.[24 36] Three articles[33–35] reported on the same patients as those included in larger studies;[18–20] these three articles were included only to perform specific analyses such as mortality in haemodynamically stable patients. Two other studies that were suspected of minimal overlap (<5% of patients) with each other that could not be confirmed by contact with the authors were also included.[22 26] The reasons for exclusion are shown in fig 1. No indication of publication bias was found from the visual inspection of the funnel plot (fig 2) and from the standard error- and study size-based funnel plot and related asymmetry tests (both $p = 0.11$).

Figure 1 Flow diagram for study selection.



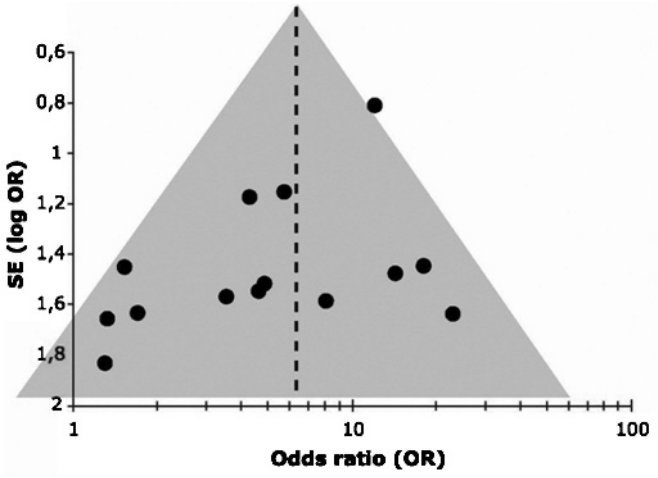


Figure 2 Study of publication bias: funnel plot for the primary outcome of the meta-analysis (all-cause mortality). OR, odds ratio; SE (log OR), standard error of log OR. The studies with no events[17 31] could not be represented.

Selected studies

The characteristics of the selected studies are shown in table 1S in the online supplement. Six studies assessed the combination of natriuretic peptides and troponins to predict adverse outcome[15 19 28 32 33 35] and six studies included haemodynamically stable patients only.[17 18 21 28 33 35] The length of follow-up ranged from hospital discharge to 365 days following admission to hospital. Right ventricular dysfunction was defined as right ventricular hypokinesis of the free wall in three studies,[15 24 36] severity of tricuspid regurgitation in one study,[16] right ventricular dilatation in one study[31] and by a composite criteria in 10 studies, all including increased RV/LV end-diastolic diameter ratio.[4 17 20–23 25 26 28 32]

Assessment of methodological quality

All 23 studies included consecutive patients with APE and none reported any patients lost to follow-up. The physicians who influenced the outcomes and the echographists were blinded to the biomarker results in 10[17 20–22 26 28 31 32 34 35] and 13[4 15–17 20–23 25 26 28 31 32] studies, respectively. Patients with comorbidities susceptible to influence natriuretic peptides levels were excluded

in 10 studies.[4 15 16 18 21 23 25 28 31 33] In one study, no data regarding the methodology used was available.[27] The validity assessment of the included studies is shown in table 2S in the online supplement.

Natriuretic peptide and troponin assays

The value of BNP and NT-proBNP was assessed in 15[4 15 16 18 21 23–25 27 28 30–34] and 8 studies,[17 19 20 22 26 29 35 36] respectively. In all studies the biomarkers were measured at patient admission. For the BNP studies four different assays were used, whereas only one NT-proBNP assay was used. Threshold levels defining positive and negative results were determined "a priori" in 5 studies[17 19 23 24 26] and "a posteriori" in 18 studies, mainly by ROC analysis. For the seven studies that reported the results according to multiple threshold levels,[18 20 21 23 24 28 34] the following range of thresholds was chosen to facilitate between-study comparisons: BNP: 80–100 ng/ml for the Biosite Diagnostics assay and 35–75 ng/ml for the Shionogi assay; NT-proBNP: 600–1000 ng/ml for the Roche assay. Troponins I[15 19 28 32] and T[33 35] were assessed by four and two studies, respectively. Three different assays were used with different thresholds ranging from 0.01 to 0.1 μg/l. The test methods used for troponins or BNP were not available in two studies.[27 33] The characteristics of the natriuretic peptide and troponin assays are shown in table 3S in the online supplement.

Meta-analysis

Natriuretic peptides in APE prognosis

The association between raised natriuretic peptide levels and adverse outcome in APE is shown in table 1. Overall, 52% (587/1127) of patients with APE had raised natriuretic peptides. Increased levels of natriuretic peptides were associated with an increased risk for all-cause mortality (fig 3), APE-related mortality and serious adverse events (figs 1S and 2S in the online supplement). The prognostic significance of raised natriuretic peptide levels was similar in studies that only included haemodynamically stable patients for all-cause mortality (OR 8.2; CI 2.5 to 26.4), APE-related mortality (OR 6.6; CI 1.7 to 25.6) and serious adverse events (OR 15.6; CI 3.0 to 81.9). Homogeneity was found across the studies in the meta-analyses for these outcomes so no further subgroup analyses were performed.

Cardiac troponins in addition to natriuretic peptides in APE prognosis

Among natriuretic peptide-positive patients, 46% (103/222) also had positive troponin values. Only 4% (14/383) of patients were positive for troponins and negative for natriuretic peptides. Among natriuretic peptide-positive patients, raised troponin levels were associated with further increase in risk for all-cause mortality, APE-related mortality and serious adverse events (table 2). The results were still significant in haemodynamically stable patients with homogeneity across studies for all-cause mortality (OR 6.9; CI 2.3 to 20.7),[28 33 35] APE-related mortality (OR 8.4; CI 2.1 to 33.4),[28 33 35] but not for serious adverse events (OR 15.5; CI 0.8 to 284.7).[28] The rate of all-cause mortality, APE-related mortality and serious adverse events in natriuretic- and troponin-negative patients were 0.2% (1/443), 0% (0/341) and 1.6% (7/443), respectively.

Natriuretic peptide for the diagnosis of right ventricular dysfunction

A total of 899 patients with right ventricular dysfunction assessment contributed to the analysis. The overall prevalence of right ventricular dysfunction was 41% (CI 37% to 44%). The interpretation of the risk of right ventricular dysfunction with an increased natriuretic peptide level was limited by our finding of significant heterogeneity among the 14 studies that contributed to this meta-analysis (table 1 and fig 3S in the online supplement). None of the subgroup analyses that we planned "a priori" satisfactorily explained this heterogeneity (see table 4S in the online supplement).

The summary ROC curve is shown in fig 4. For BNP, the area under the curve was 0.92 (CI 0.88 to 0.94). Due to the paucity of studies, we could not compute a reliable area under the curve for NT-proBNP. Nevertheless, visual inspection of fig 4 suggested that BNP was more accurate than NT-proBNP in the diagnosis of right ventricular dysfunction. This was substantiated by the pooled sensitivities and specificities. For the BNP Triage Biosite assay, pooled sensitivity and specificity at the threshold of 90 ng/ml were 96% (CI 93% to 99%) and 91% (CI 86% to 96%) respectively ($p_{homogeneity} = 0.73$, $I^2 = 0\%$), which correspond to positive and negative likelihood ratios of 10.7 and 0.04, respectively. For the NT-proBNP Roche assay, pooled sensitivity and specificity at a threshold of 1000 ng/ml were 82% (76% to 88%) and 59% (CI 52% to 66%) respectively, with homogeneity among studies ($p_{homogeneity} = 0.25$, $I^2 = 27\%$), which correspond to positive and negative likelihood ratios of 2.0 and 0.31, respectively.

DISCUSSION

Our meta-analysis shows that raised B-type natriuretic peptide levels are associated with increased risk of mortality, serious

Table 1 Natriuretic peptides in APE prognosis: primary results of the meta-analysis

Outcome	No of studies	References	Proportion of events (95% CI)	Pooled OR (95% CI)	Homogeneity	
					p Value	I^2 (%)
All-cause mortality	16	4, 15–22, 24, 27–32	(+): 62/491, 12.6% (9.6% to 15.5%)	6.2 (3.0 to 12.7)	0.96	0.0
			(−): 5/433, 1.1% (0.1% to 2.1%)			
APE-related mortality	14	4, 15–18, 21, 24, 27–31, 34, 35	(+): 40/378, 10.6% (7.9% to 14.1%)	5.0 (2.2 to 11.5)	0.97	0.0
			(−): 3/298, 1.0% (0.3% to 2.9%)			
Serious adverse events	9	15, 19, 21, 22, 24, 26, 28, 32, 35	(+): 115/416, 27.6% (23.4% to 32.0%)	6.7 (3.9 to 11.6)	0.83	0.0
			(−): 17/319, 5.3% (2.8% to 7.7%)			
Right ventricular dysfunction	14	4, 15–17, 20–26, 28, 31, 32	(+): 352/487, 72.3% (68.3% to 76.3%)	24.2 (11.4 to 51.3)	0.001	61.1
			(−): 71/412, 17.2% (13.6% to 20.9%)			

APE, acute pulmonary embolism; CI, confidence interval; OR, odds ratio.
(+) indicates the proportion of patients with the outcome of interest among those with positive natriuretic peptides; (−) indicates the proportion of patients with the outcome of interest among those with negative natriuretic peptides.

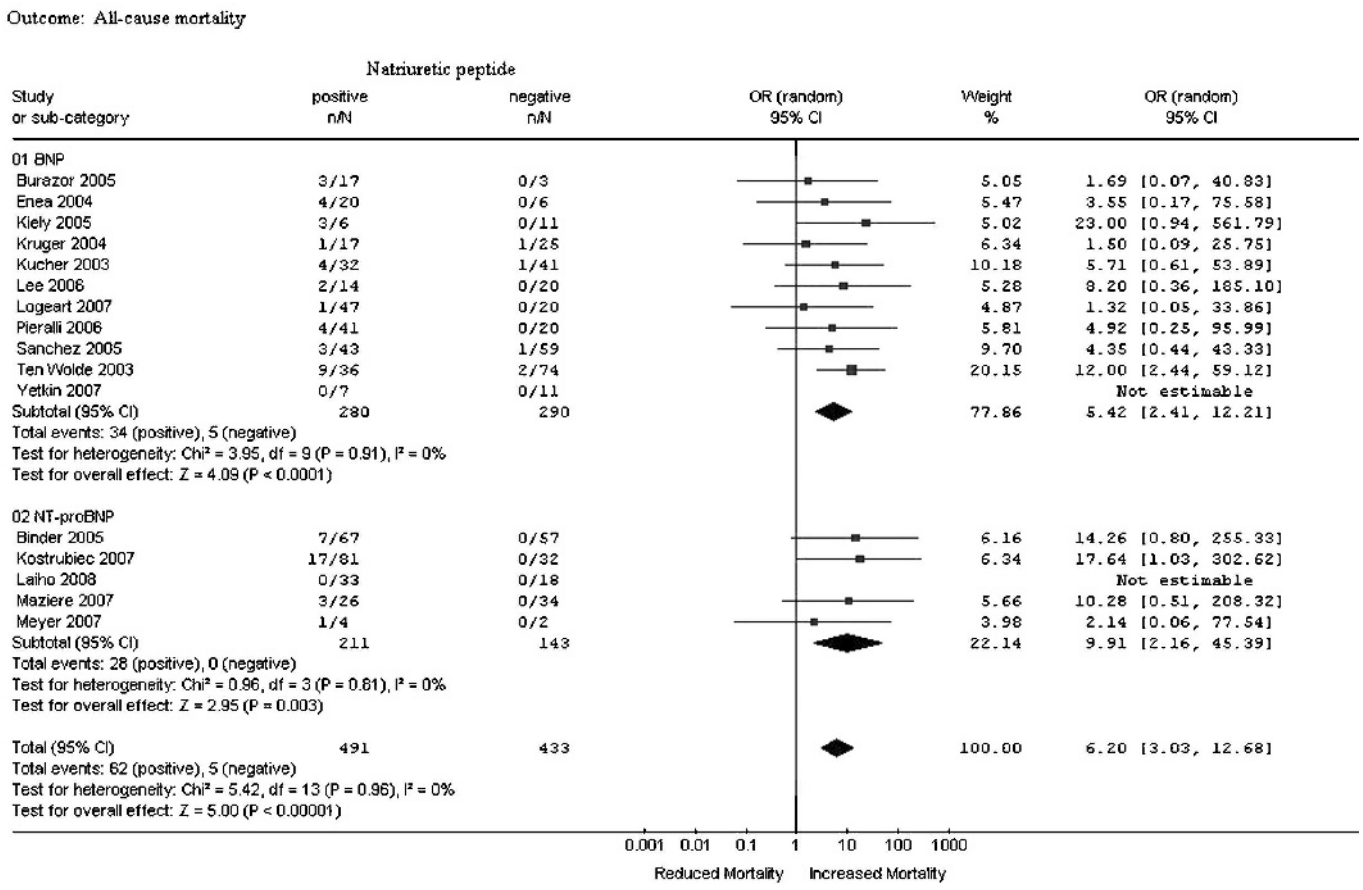


Figure 3 Meta-analysis of B-type natriuretic peptides BNP and NT-proBNP to predict all-cause mortality in acute pulmonary embolism. Data of studies with patient overlap were not pooled together in the overall odds ratio (OR).[19 34]

adverse events and right ventricular dysfunction in APE. In most analyses the results were consistent across studies regardless of the patient's haemodynamic status at admission and the presence of medical conditions with the potential to influence natriuretic peptide levels such as chronic heart failure and renal failure. Among patients with raised natriuretic peptide levels, increased troponin levels were also found to be an independent prognostic marker of morbidity and mortality in APE. Conversely, patients with negative natriuretic peptides and troponins were at very low risk of complications.

In the meta-analysis, BNP appeared to be more accurate than NT-proBNP for detecting right ventricular dysfunction. Similar results were recently reported by others in a meta-analysis for the diagnosis of heart failure.[37] Several physiopathological processes may explain the higher accuracy of BNP, including the fact that the NT-proBNP assay is affected to a greater extent by glomerular filtration rate.[3] Another potential explanation is the absence of consensus for right ventricular dysfunction definition,[1] which differed among the studies included in the analysis.

Table 2 Increased cardiac troponins in patients with positive natriuretic peptides: results of the meta-analysis

Outcome	No of studies	References	Proportion of events (95% CI)	Pooled OR (95% CI)	Homogeneity	
					p value	I^2 (%)
All-cause mortality	6	15, 19, 28, 32, 33, 35	(+): 37/97, 38.1% (28.4% to 47.9%) (−): 7/119, 5.9% (1.7% to 10.1%)	8.0 (3.0 to 21.4)	0.72	0.0
APE-related mortality	4	15, 28, 33, 35	(+): 13/74, 17.6% (8.8% to 26.3%) (−): 2/79, 2.5% (0.0% to 5.9%)	8.6 (2.2 to 34.1)	0.57	0.0
Serious adverse outcome	4	15, 19, 28, 32	(+): 27/79, 34.2% (23.7% to 44.7%) (−): 8/49, 16.3% (5.8% to 26.8%)	13.3 (2.4 to 74.2)	0.83	0.0
Right ventricular dysfunction	2	15, 28	(+): 44/50, 88.0% (78.9% to 97.1%) (−): 12/17, 70.6% (50.8% to 90.3%)	1.67 (0.4 to 6.6)	NA	NA

APE, acute pulmonary embolism; CI, confidence interval; NA, not applicable; OR, odds ratio.
(+) indicates the proportion of patients with the outcome of interest among those with both positive troponins and natriuretic peptides; (−) indicates the proportion of patients with the outcome of interest among those with negative troponins and positive natriuretic peptides.

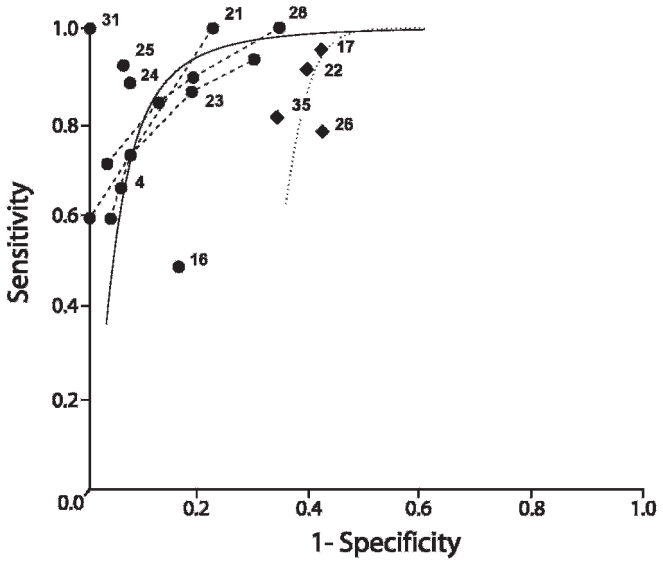


Figure 4 Estimation of natriuretic peptide accuracy by ROC curves. BNP studies are represented by circles and NT-proBNP studies by diamonds. Results from different cut-off points within the same study are joined by dotted lines. The studies are identified by their reference numbers.

In the subgroup analysis of studies that excluded patients with comorbidities which might influence natriuretic peptide levels and accuracy, increased natriuretic peptides tended to predict right ventricular dysfunction better than studies which included patients with these comorbidities (table 4S in online supplement). Although this difference did not reach statistical significance, we interpret it as a consequence of the confounding effect of renal and congestive heart failure. Notwithstanding this confounding effect, natriuretic peptides remained similarly accurate in predicting mortality and serious adverse events among patients with these conditions. The inclusion of patients with these comorbidities better reflects current clinical practice and enhances the external validity of the results.

The relation between natriuretic peptide level and prognosis in APE has recently been explored in four other systematic reviews.[38–41] They differed from ours in several important methodological aspects. Their literature search was limited to the published literature and two considered only the English literature.[39 40] As a consequence, we included a larger number of studies by also searching the grey literature and contacting the authors when data were missing to complete the analysis.[15–17 27 29 31 32] A more important difference is that the authors inadvertently included the results of studies from totally or partially duplicated cohorts,[19 22 24 33–36 42–44] corresponding to a significant proportion of their total sample size (17–28%).

We acknowledge limitations to our systematic review that are inherent to the available data. First, the thresholds for natriuretic peptide positivity often differed across studies. In the main analysis, this precluded our computing of pooled sensitivities and specificities at given thresholds. We therefore limited the meta-analyses to the pooling of ORs. Only full access to individual data could have resolved this problem. Second, ORs provided by this meta-analysis are unadjusted for other risk factors of adverse events in APE, with the exception of impaired haemodynamic status. Third, the causes of deaths were not analysed in most studies. This situation may have influenced the rate of APE-related deaths. Finally, despite the fact that all authors were contacted when data were missing to complete our analysis, we estimated that 615 additional patients from published articles or meeting abstracts could not be included in the present analysis.

The results of our meta-analysis have important clinical implications in the management of APE. While massive APE is undoubtedly associated with poor prognosis and requires an aggressive therapeutic approach, the role of such treatment in submassive APE remains controversial.[1 2] Increases in natriuretic peptide levels at admission clearly identify a subgroup of patients at higher risk of APE-related death, whatever their haemodynamic status. Patients with increased levels of both natriuretic peptides and troponins are at a particularly high risk of adverse outcomes. Also, natriuretic peptides appear to be especially helpful in identifying low-risk patients, given their very low positive rate among those with a poor outcome (table 1). Nevertheless, large-scale prospective randomised controlled trials are clearly necessary to define the precise role of cardiac biomarkers and the optimal cut-off values to select patients with APE who may benefit from thrombolysis or outpatient treatment.[45]

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Lung alert

WISP-1, a novel target for treatment of pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is characterised by formation of fibroblast foci and deposition of extracellular matrix (ECM) in the lung interstitium. This results in distorted lung architecture, impaired gas exchange and reduced respiratory function. Impaired crosstalk between alveolar type 11 (AT11) cells and subepithelial fibroblasts has previously been shown to contribute to ECM deposition in IPF.

This study investigated the gene regulatory networks behind AT11 cell dysfunction in IPF. Genetic analyses highlighted WNT-inducible signalling protein-1 (WISP-1) as a key mediator of AT11 cells. WISP-1 was highly upregulated in AT11 cells in a mouse model of fibrosis and also in human lung tissue from patients with IPF.

The investigators treated murine primary AT11 cells with recombinant WISP-1 and induced epithelial-mesenchymal transition (EMT). EMT is recognised as a possible mechanism underlying the formation of fibroblast foci that occurs in IPF.

Recombinant WISP-1 treatment of lung fibroblasts in vitro led to increased ECM deposition. Furthermore, WISP-1 neutralisation resulted in attenuation of lung fibrosis in mouse models as evidenced by decreased lung ECM deposition. A marked reduction in expression of genes associated with fibrosis and reversal of EMT gene expression was noted. Interestingly, this was shown to partially restore normal lung function and significantly improve survival.

Currently available treatment options for IPF are limited. This study puts forward WISP-1 as a novel potential therapeutic target in IPF. Whether or not the findings in mouse models will translate to humans remains to be seen.

► Konigshoff M, Kramer M, Balsara N, *et al*. WNT1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis. *J Clin Invest* 2009;**119**:772–87.

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