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ARTICLE

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The use of B-type natriuretic peptide in the management of patients with diabetes and acute dyspnoea

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Abstract *Aims/hypothesis:* The aim of this study was to determine the impact of measurement of B-type natriuretic peptide (BNP) levels on the management of patients with diabetes presenting with acute dyspnoea. *Methods:* This study evaluated the subgroup of 103 patients with diabetes included in the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study (n=452). Patients were randomly assigned to a diagnostic strategy with (n=47, BNP group) or without (n=56, control group) the use of BNP levels assessed by a rapid bedside assay. Time to discharge and total cost of treatment were recorded as the primary endpoints. *Results:* Although similar with regard to age and sex, patients with diabetes more often had pre-existing cardiovascular and renal disease and heart failure as the cause of acute dyspnoea compared with patients without diabetes. In addition, medical and economic outcomes were worse in patients with diabetes. The use of BNP levels significantly reduced time to discharge (median 9 days [interquartile range (IQR) 2–16] in the BNP group vs 13 days [IQR 8–22] in the control group; p=0.016). At 30 days, the diabetic patients in the BNP group had spent significantly fewer days in hospital compared with the diabetic patients in the control group (9 days [IQR 2–19] vs 16 days [IQR 8–24], respectively; p=0.008). Total treatment costs at 30 days were US$5,705 (IQR 2,285–9,137) in the BNP group and US$7,420 (IQR 4,194–11,966) in the control group (p=0.036). *Conclusions/interpretation:* The results of this study indicate that measurement of BNP levels improves the management of patients with diabetes presenting with acute dyspnoea.

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Abbreviations BASEL: B-type natriuretic peptide for acute shortness of breath evaluation · BNP: B-type natriuretic peptide · COPD: chronic obstructive pulmonary disease · ED: emergency department · IQR: interquartile range

Introduction

The evaluation and management of patients presenting to the emergency department (ED) with acute dyspnoea is challenging. Among more than 30 diagnoses that may be responsible for the acute dyspnoea, heart failure is very common and therefore important [1–3]. Unfortunately, the rapid and accurate differentiation of heart failure from other causes of acute dyspnoea often remains elusive, particularly in patients with diastolic heart failure. Misdiagnosis of heart failure causes morbidity and increases time to discharge and treatment costs, because treatments for heart failure may be hazardous to patients with other conditions such as chronic obstructive lung disease (COPD), and vice versa [4–6]. Patients with diabetes have an increased risk of developing heart failure and are particularly affected by the diagnostic dilemma surrounding heart failure. The incidence of heart failure is two-fold higher in diabetic vs non-diabetic men and five-fold higher in diabetic vs non-diabetic women [7]. Patients with diabetic cardiomyopathy display clinical and anatomical features of heart failure that are different from those displayed by other heart failure patients [8]. Diabetic cardiomyopathy is a distinct entity characterised by left ventricular diastolic dysfunction caused by myocardial fibrosis and hypertrophy, which occur in response to hyperglycaemia and insulin resistance [9–11]. Using sensitive echocardiographic techniques, diastolic dysfunction can be detected in 50–60% of asymptomatic patients with diabetes [12, 13].

B-type natriuretic peptide (BNP) is a novel cardiac marker that is reliably elevated in the setting of heart failure,

and may therefore be very helpful in its diagnosis [14–16]. Observational studies have shown that the use of BNP levels significantly increases the accuracy of the clinical diagnosis in patients presenting with acute dyspnoea to the ED [14–16]. However, BNP levels are significantly lower in patients with left ventricular diastolic dysfunction—the predominant mechanism of heart failure in patients with diabetes—than in patients with left ventricular systolic dysfunction [15, 16]. In addition, diabetes is associated with kidney disease. This is considered a limitation for the diagnostic use of BNP, as kidney disease results in elevated BNP levels independently of heart failure [17, 18].

These differences and our previous findings in patients with diabetes [19, 20] have fostered the need to specifically evaluate whether the promising results obtained for BNP testing for acute dyspnoea in unselected patient cohorts [21, 22] can be extrapolated to patients with diabetes. This study sought to evaluate the impact of a BNP-guided diagnostic strategy on the evaluation and management of diabetic patients presenting with acute dyspnoea to the ED.

Subjects and methods

Setting and study population This study specifically evaluated the outcome of patients with diabetes in the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study [22]. The BASEL study was a prospective, randomised, single-blind study conducted in the ED of the University Hospital in Basel, Switzerland, from May 2001 to April 2002. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all participating patients.

To be eligible for the study, a patient had to present with shortness of breath as the primary complaint and no obvious traumatic cause of dyspnoea. Patients with severe renal disease (serum creatinine >250 μmol/l), patients in cardiogenic shock, and patients who requested an early transfer to another hospital were excluded. A total of 452 patients were enrolled in the BASEL study and randomly assigned according to a computer-generated randomisation scheme 1:1 without stratification to receive a diagnostic strategy with (n=225, including 47 patients with diabetes [BNP group]) or without (n=227, including 56 patients with diabetes [control group]) the use of BNP levels determined by a rapid bedside assay. Diabetes was defined as a known history of diabetes treated currently with diet, oral glucose-lowering agents or insulin.

Routine clinical assessment Patients underwent an initial clinical assessment that included clinical history, physical examination, ECG, pulse oximetry, blood tests (including arterial blood gas analysis when indicated) and chest X-ray. Echocardiography and pulmonary function tests were strongly recommended in the ED on an outpatient basis or in the hospital if the patient was admitted.

Measurement and interpretation of BNP levels During initial evaluation, at the time of venipuncture for routine blood tests, a venous specimen of blood (3 ml) was collected into tubes containing potassium EDTA. BNP was measured using a rapid fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). The precision, analytical sensitivity and stability characteristics of the system have been described previously [23]. In brief, the CVs for intra-assay precision have been reported to be 9.5, 12.0 and 13.9%, and the CVs for interassay precision are known to be 10.0%, 12.4 and 14.8% for BNP levels of 28.8, 584.0 and 1180.0 pg/ml, respectively [23]. The analytical sensitivity was <5.0 pg/ml, with a measurable range of 1–1,300 pg/ml.

In the BNP-guided group, diagnostic and therapeutic decisions were not based on BNP levels alone; rather, the information provided by the BNP level was integrated with the clinical results, as described previously [22]. In brief, we used two BNP cut-off levels (100 and 500 pg/ml) to differentiate heart failure from other causes of dyspnoea. In patients with a BNP level below 100 pg/ml, heart failure was considered unlikely and alternative causes of dyspnoea had to be pursued. In patients with a BNP level above 500 pg/ml, heart failure was considered likely and rapid therapy with diuretics, nitroglycerin, ACE inhibitors and morphine was recommended. For patients with BNP levels between 100 and 500 pg/ml, the protocol recommended clinical judgement and possible further diagnostic testing. Patients in the control group were evaluated and managed according to the most recent clinical practice guidelines [1–3].

Endpoints Time to discharge and cost of treatment were defined as the primary endpoints of this study. Time to discharge was defined as the time interval from presentation to the ED to hospital discharge. As cost:charge ratios have not been defined for the majority of services and departments at our institution, hospital charges were collected as the most appropriate estimate of true costs [24, 25]. To avoid imbalance introduced by varying hospital contracts with different insurances or different insurance classes, charges were standardised to the actual rates for patients with general insurance, living in Basel. For the measurement of BNP, the current reimbursement in Switzerland (US$47) was used. Endpoints were assessed by physicians not involved in patient care and blinded to the assigned group using all medical records pertaining to the patient.

Statistical analyses The statistical analyses were performed using the SPSS/PC software package (version 12.0; SPSS, Chicago, IL, USA). A statistical significance level of 0.05 was used. All data were analysed on an intention-to-treat basis. Comparisons were made using the t test for normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, Fisher's exact test for categorical

variables with any field including fewer than six patients, and the χ^2 test for the other categorical variables. All hypothesis testing was two-tailed.

Results

A total of 103 patients with diabetes were enrolled in this trial (Fig. 1). Although these patients were similar to the non-diabetic patients in terms of age and sex, diabetic patients more often had pre-existing cardiovascular and renal disease (Table 1). As regards symptoms, chest pain and nycturia were more frequent in diabetic subjects. Assessment of clinical signs revealed that rales and lower-extremity oedema were more frequent in diabetic patients. In addition, patients with diabetes had significantly lower haemoglobin and albumin, but higher serum creatinine and BNP compared with patients without diabetes.

The final discharge diagnosis was significantly different in patients with diabetes compared with patients without diabetes. Heart failure was more often the cause of acute dyspnoea in patients with diabetes (65 vs 43%), whereas obstructive pulmonary disease and anxiety disorder were less often the cause in these patients. Interestingly, medical and economic outcomes were different—to the detriment of patients with diabetes. BNP was similar in heart failure patients with or without diabetes (median 812 vs 795 pg/ml, p=0.236). BNP was also similar in patients without heart failure with or without diabetes (median 135 vs 57 pg/ml, p=0.134). Diabetic patients more often required hospitalisation and recovered more slowly, resulting in an increased time to discharge and an increase in the number of days in hospital at 30 days after initial presentation. Moreover, initial and 30-day total treatment costs were significantly higher in patients with diabetes.

The two groups of diabetic patients were well matched in terms of baseline characteristics (Table 2). The use of BNP levels significantly affected patient management. Patients assigned to the BNP group required hospitalisation less often. As shown in Fig. 2, the use of BNP levels significantly reduced time to discharge (median 9 days [interquartile range (IQR) 2–16] in the BNP group vs 13 days [IQR 8–22] in the control group; p=0.016). At 30 days, diabetic patients in the BNP group had spent significantly fewer days in hospital than the those in the control group (9 days [IQR 2–19] vs 16 days [IQR 8–24]; p=0.008). In-hospital and 30-day mortality were lower in the BNP group. However, the between-group differences were not statistically significant. Interestingly, this medical benefit was accompanied by an economic benefit, with a relative reduction in initial and 30-day treatment costs in the BNP group. Total treatment costs at 30 days were US $5,705 (IQR 2,285–9,137) in the BNP group and US $7,420 (IQR 4,194–11,966) in the control group (p=0.036).

Similar benefits of BNP testing were observed in non-diabetic patients. The use of BNP levels significantly reduced time to discharge (median 7 days [IQR 1–16] in the BNP group vs 10 days [IQR 3–18] in the control group; p=0.027) and total treatment costs at 30 days (US $3,841 [IQR 601–7,545] in the BNP group vs US$5,432 (IQR 2,572–9,930) in these subjects (p=0.014).

Discussion

In this study we examined the use of BNP levels in the management of diabetic patients presenting with acute dyspnoea to the ED. We report four major findings. First, patients with diabetes represent a high-risk group with increased cardiovascular and renal comorbidity. However,

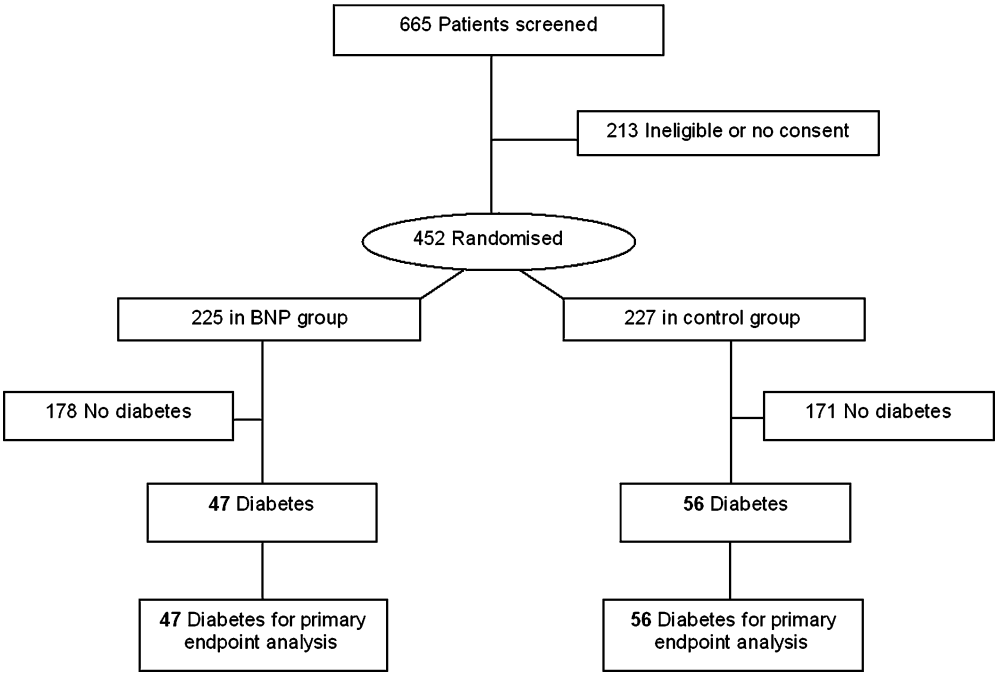

Fig. 1 Patient flow through trial

Table 1 Baseline characteristics in patients with and without diabetes mellitus

	Diabetes *n*=103	No diabetes *n*=349	*p* value
Age (years)	72±10	70±16	0.157
Sex			0.153
Male	66 (64)	196 (56)	
Female	37 (36)	153 (44)	
History			
Coronary artery disease	71 (69)	154 (44)	<0.001
Arterial hypertension	79 (77)	158 (45)	<0.001
COPD	33 (32)	107 (31)	0.790
Asthma	4 (4)	25 (7)	0.358
Pneumonia	15 (15)	43 (12)	0.550
Pulmonary embolism	12 (12)	19 (5)	0.029
Other pulmonary or pleural disease	15 (15)	31 (9)	0.094
Any pulmonary disease	57 (55)	169 (48)	0.217
Depressive disorder	9 (9)	27 (8)	0.741
Stroke or peripheral vascular disease	31 (30)	58 (17)	0.003
Chronic kidney disease	35 (34)	77 (22)	0.014
Deep vein thrombosis	10 (10)	31 (9)	0.798
Symptoms			
Shortness of breath[a]			0.474
Slight hill	14 (14)	51 (15)	
Level ground	55 (53)	202 (58)	
At rest	32 (31)	94 (27)	
Paroxysmal nocturnal dyspnoea	45 (44)	121 (35)	0.095
Nycturia	45 (44)	91 (26)	0.001
Weight gain	17 (17)	34 (10)	0.057
Chest pain	45 (44)	109 (31)	0.019
Coughing	46 (45)	178 (51)	0.258
Expectoration	34 (33)	125 (36)	0.600
Fever	22 (21)	87 (25)	0.457
Vital status			
Systolic blood pressure (mmHg)	153±27	143±28	0.003
Diastolic blood pressure (mmHg)	87±18	85±19	0.520
Heart rate (per min)	97±21	98±25	0.717
Temperature (°C)	37.4±1.0	37.4±1.0	0.735
Signs			
Tachypnoea (>20 per min)	52 (51)	158 (45)	0.351
Elevated jugular venous pressure	18 (18)	46 (13)	0.272
Hepatojugular reflux	7 (7)	42 (12)	0.133
Rales	61 (59)	146 (42)	0.002
Wheezing	22 (21)	78 (22)	0.832
Hyper-resonant percussion	8 (8)	31 (9)	0.723
Dullness	14 (14)	32 (9)	0.192
Lower-extremity oedema	48 (47)	108 (31)	0.003
Laboratory tests			
Haemoglobin (g/l)	128±24	137±27	0.005
Serum creatinine (μmol/l)	132±62	109±54	<0.001
Serum albumin (g/l)	32±5	34±5	0.009
Troponin I (μg/l)	6.1±16.9	6.1±35.3	0.997
B-Type natriuretic peptide (pg/ml)[b]	372 [144–961]	202 [35–770]	0.060
Final discharge diagnosis			
Congestive heart failure	67 (65)	150 (43)	<0.001
Left ventricular ejection fraction (%)[c]	40 [30–55]	40 [30–55]	0.761
Obstructive pulmonary disease	10 (10)	66 (19)	0.028
Pulmonary embolism	2 (2)	19 (5)	0.185

Table 1 (continued)

	Diabetes *n*=103	No diabetes *n*=349	*p* value
Pneumonia	14 (14)	48 (14)	0.967
Anxiety disorder	0	16 (5)	0.029
Other disease[d]	11 (11)	48 (14)	0.416
Unknown cause	6 (6)	14 (4)	0.432
Outcome			
Time to treatment (min)	62 [16–159]	73 [20–180]	0.160
Hospital admission	91 (88)	271 (78)	0.017
Time to discharge (days)	12 [5–19]	9 [1–17]	0.020
Initial treatment cost (US$)	5,740 [2,924–9,056]	4,457 [887–7,881]	0.018
In-hospital mortality	6 (6)	28 (8)	0.457
30-day in-hospital days	13 [6–22]	9 [2–18]	0.002
30-day treatment cost (US$)	6,110 [3,518–10,238]	4,827 [1,199–8,023]	0.001
30-day mortality	8 (8)	42 (12)	0.225

Data are presented as mean±SD, median [IQR] or number of patients (%)
[a]Two patients in each group had dyspnoea only when climbing a steep incline
[b]In the BNP group, *n*=225
[c]Available in 148 patients
[d]Including interstitial lung disease, pleural effusion, anaemia and sepsis

it is important to note that 30-day mortality was similar for diabetic and non-diabetic patients. Second, heart failure is the predominant cause of acute dyspnoea in patients with diabetes. Third, patients with diabetes had worse medical and economic outcomes compared with patients without diabetes. Fourth, used in conjunction with other clinical information, rapid measurement of BNP in the ED improves the management of diabetic patients presenting with acute dyspnoea, and thereby reduces the time to discharge, days in hospital at 30 days, and the total treatment cost. Given the predominance of left ventricular diastolic dysfunction, the distinct features of diabetic cardiomyopathy, and the high prevalence of kidney disease in patients with diabetes, this finding supports the clinical use of BNP in patients with diabetes [7–13]. Given both the significant morbidity associated with acute dyspnoea and the considerable cost associated with heart failure and other causative disorders [1–6], BNP testing seems to represent a major advance in the evaluation and management of diabetic patients who present with acute dyspnoea. Additional studies are necessary to further evaluate whether this improvement in patient management also reduces mortality.

The findings of the BASEL study build on the conclusions of observational studies in which BNP levels were validated by comparison with a retrospectively adjudicated 'gold standard' for the diagnosis of heart failure by two independent cardiologists [14–17]. In the Breathing Not Properly Multinational Study, BNP levels alone were more accurate than any historical or physical finding or laboratory value in identifying heart failure as the cause of acute dyspnoea. The diagnostic accuracy of BNP at a cut-off value of 100 pg/ml was 83%, with a sensitivity of 90% and a specificity of 76% [14, 17]. Our data show that a rapid and more accurate diagnosis avoids unnecessary hospitalisation, reduces the time to the initiation of the adequate therapy and reduces time to discharge, irrespective of the presence or absence of diabetes [26–30]. Recent subgroup analysis from the Breathing Not Properly Multinational Study suggested that a history of diabetes does not affect the accuracy of BNP levels in the detection of heart failure as the cause of acute dyspnoea [29]. There was no significant difference in median BNP levels between diabetes and no diabetes among patients without heart failure (32 vs 33 pg/ml), patients with heart failure (587 vs 494 pg/ml), and those with a history of heart failure (180 vs 120 pg/ml). In this study we were able to confirm this finding. Moreover, in contrast to kidney disease, the presence of diabetes does not seem to necessitate a change in cut-off values [17, 29]. Our data confirm and extend this finding by showing that the use of BNP as an accurate marker of heart failure without cut-off value adjustment for the presence of diabetes significantly improves medical and economic outcomes in diabetic patients presenting with acute dyspnoea to the ED. As heart failure is the cause of dyspnoea in two-thirds of diabetic patients with acute dyspnoea, the use of an accurate heart failure marker could have a considerable impact. Moreover, as diabetic patients with acute dyspnoea have higher rates of hospitalisation and longer in-hospital stays, this high-risk cohort has much to gain from the use of BNP level.

In normotensive non-insulin-dependent diabetic patients with microalbuminuria, a significant positive correlation between plasma BNP levels and urinary albumin excretion rate (r=0.58) was found [26]. Moreover, BNP testing may be helpful as a screen for left ventricular dysfunction in patients with diabetes. Epshteyn and colleagues screened diabetic patients with and without a clinical indication for echocardiography [27]. Irrespective of the clinical indication for echocardiography, BNP levels were significantly

Table 2 Baseline characteristics in patients with diabetes assigned to the control and the BNP groups

	Control group *n*=56	BNP group *n*=47	*p* value
Age (years)	72±10	73±11	0.777
Sex			0.962
Male	36 (64)	30 (64)	
Female	20 (36)	17 (36)	
History			
Coronary artery disease	36 (64)	35 (75)	0.266
Arterial hypertension	43 (77)	36 (77)	0.982
COPD	17 (30)	16 (34)	0.690
Asthma	2 (4)	2 (4)	1.000
Pneumonia	9 (16)	6 (13)	0.636
Pulmonary embolism	6 (11)	6 (13)	0.746
Other pulmonary or pleural disease	9 (16)	6 (13)	0.636
Any pulmonary disease	31 (55)	26 (55)	0.997
Depressive disorder	7 (13)	2 (4)	0.176
Stroke or peripheral vascular disease	18 (32)	13 (28)	0.621
Chronic kidney disease	18 (32)	17 (36)	0.667
Deep vein thrombosis	5 (9)	5 (11)	1.000
Symptoms			
Shortness of breath[a]			0.780
Slight hill	6 (11)	8 (17)	
Level ground	30 (54)	25 (53)	
At rest	19 (34)	13 (28)	
Paroxysmal nocturnal dyspnoea	26 (46)	19 (40)	0.541
Weight gain	9 (16)	8 (17)	0.897
Nycturia	27 (48)	18 (38)	0.312
Chest pain	25 (45)	20 (43)	0.831
Coughing	30 (54)	16 (34)	0.047
Expectoration	22 (39)	12 (26)	0.139
Fever	11 (20)	11 (23)	0.643
Vital status			
Systolic blood pressure (mmHg)	149±27	157±28	0.109
Diastolic blood pressure (mmHg)	88±19	85±17	0.502
Heart rate (per min)	99±24	94±17	0.266
Temperature (°C)	37.4±0.9	37.3±1.1	0.735
Signs			
Tachypnoea (>20 per min)	30 (54)	22 (47)	0.494
Elevated jugular venous pressure	11 (20)	7 (15)	0.527
Hepatojugular reflux	2 (4)	5 (11)	0.241
Rales	32 (57)	29 (62)	0.639
Wheezing	10 (18)	12 (26)	0.344
Hyper-resonant percussion	5 (9)	3 (6)	0.724
Dullness	10 (18)	4 (9)	0.249
Lower-extremity oedema	28 (50)	20 (43)	0.450
Laboratory tests			
Haemoglobin (g/l)	127±24	130±24	0.578
Serum creatinine (μmol/l)	136±70	128±51	0.523
Serum albumin (g/l)	32±5	33±5	0.395
Troponin I (μg/l)	6.4±17.3	5.8±16.7	0.892
Endpoints			
Time to treatment (min)	71 (17–207)	61 (13–133)	0.151
Time to discharge (days)	13 (8–22)	9 (2–16)	0.016
Hospital admission	53 (95)	38 (81)	0.036
Initial treatment cost (US$)	5,940 (3,641–10,731)	5,538 (1,200–8,673)	0.093
In-hospital mortality	4 (7)	2 (4)	0.686

Table 2 (continued)

	Control group *n*=56	BNP group *n*=47	*p* value
30-day in-hospital days	16 (8–24)	9 (2–19)	0.008
30-day treatment cost (US$)	7,420 (4,194–11,966)	5,705 (2,285–9,137)	0.036
30-day mortality	5 (9)	3 (6)	0.724

Data are presented as mean±SD, median [IQR] or number of patients (%)
[a]One patient in each group had dyspnoea only when climbing a steep incline

higher in patients with left ventricular dysfunction. The receiver operating characteristic curve revealed that the AUC was 0.91 for patients with a clinical indication for echocardiography and 0.81 for those without. For the latter group, a BNP level below 39 pg/ml had a negative predictive value of 91%.

The diabetic population in this study was highly representative of the elderly diabetic population currently presenting to the ED in the USA and Europe [1–4, 14, 19]. Comorbidity is extensive in this population and includes coronary artery disease in more than two-thirds of these patients, arterial hypertension in nearly 80%, and pulmonary disease in more than 50%. The rapid and accurate differentiation of heart failure from pulmonary causes of dyspnoea in the ED in these patients is often difficult, but is essential for cost-effective management.

Several limitations apply to this study. First, our interpretation of the BNP test results was based on the data available when the study protocol was devised. Subsequent studies have shown that the use of the two cut-off values (100 and 500 pg/ml) in the BASEL study is also appropriate in patients with diabetes, as BNP cut-off values need not be corrected for age, sex or diabetes [14, 29]. However, recent subgroup analyses from the Breathing Not Properly Multinational Study suggest that the use of a higher first cut-off value (200–225 pg/ml rather than 100 pg/ml, to exclude heart failure) seems to provide higher accuracy in patients with renal disease [17]. In contrast, a lower first cut-off value should be applied in obese patients [30]. Second, randomisation was not stratified for diabetes. Therefore, it is reassuring to note that the baseline characteristics of the diabetic patients in the two groups were well matched.

In conclusion, our results confirm the findings of observational studies and support the use of BNP testing in the assessment of diabetic patients presenting with acute dyspnoea. Used in conjunction with other clinical information, rapid measurement of BNP improved the evaluation and management of patients in the ED and thereby reduced time to discharge and total cost of treatment.

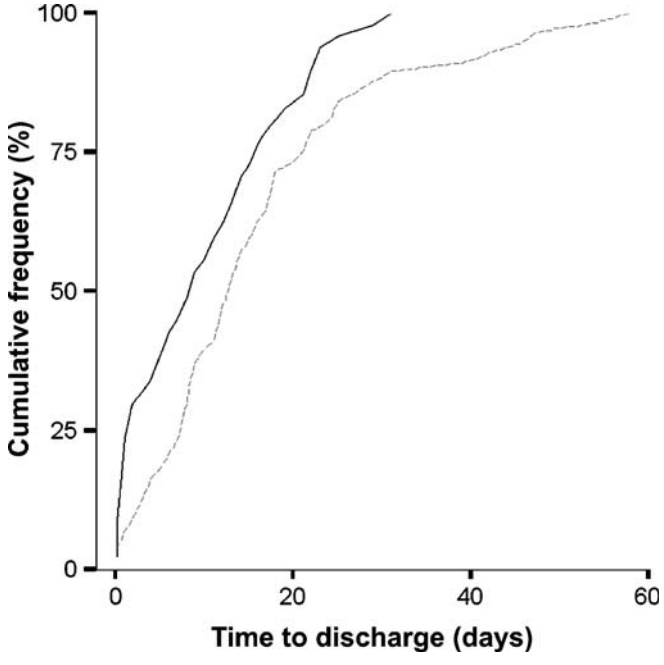

Fig. 2 Cumulative frequency distribution curve displaying the time to discharge of patients with diabetes in the BNP group (*solid line*) vs the control group (*dashed line*). *p*=0.016 by log-rank

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