NT-proBNP testing

A valuable and cost-effective option for the diagnosis and management of heart failure

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The economic burden of heart failure

Heart failure (HF) is one of the most costly medical conditions to manage, due to the high prevalence, prolonged duration of hospitalisation and frequent readmission rates for patients with suspected HF compared with other diseases. The cost-effective diagnosis of HF is challenging and places a high demand on healthcare resources.

Disease prevalence

In the developed world, approximately 3 % of the adult population have HF;[1,2] however, the prevalence of the disease increases dramatically with age, rising to ≥10 % among individuals over 70 years old.[3] Over the coming decades, the global burden of HF is predicted to increase (Figure 1) due to both the ageing of the population and the increased prevalence of risk factors such as hypertension, coronary heart disease, obesity, diabetes and hyperlipoproteinemia.[4,5] Projections of crude prevalence show that in 2010, 6.6 million US adults ≥18 years of age (2.8 %) had HF. Prevalence is predicted to increase to 3.5 % by 2030 (a 25 % increase), equating to an additional 3 million people with HF. Consequently, direct medical costs are expected to increase threefold in the next 20 years, representing an additional US$ 50 billion annual spending for HF patients.[4]

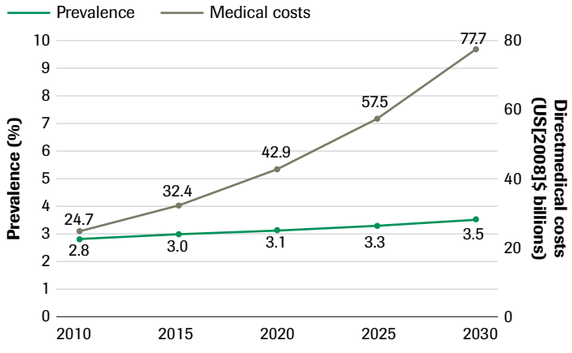

Figure 1: Predicted prevalence and cost of HF in the US[4]

Healthcare costs associated with HF

HF-related healthcare costs are substantial and account for approximately 2 % of total national healthcare expenditure in the US and Europe.[6] The majority of costs are associated with hospitalisation of patients (Figure 2).[2] Recent US data among adults aged 18 – 64 years estimated that the mean cost per hospitalisation due to HF was US$ 23,077.[7]

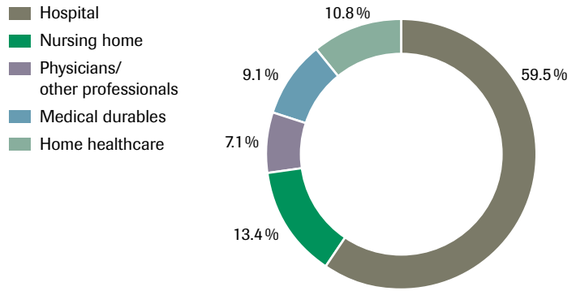

Figure 2: Breakdown of estimated direct HF-related healthcare costs (US data)[2]

Despite declining HF-related hospitalisation rates, HF remains the principal diagnosis in 21 % of hospital admissions.[8] With an average duration of 11 days, the length of stay due to HF is considerably longer than other diseases (average length of stay of 7.2 days for all-cause hospitalisation).[9,10] Furthermore, 27 % of patients with HF are readmitted within 30 days of discharge (7.6 % of all hospital readmissions).[11]

Identifying patients with HF is challenging

Identifying which dyspnoeic patients have HF is difficult. Diagnostic accuracy based on history and clinical assessment is poor, with up to 50 % of patients misdiagnosed.[12,13] Symptoms are non-specific and are difficult to interpret in obese or elderly patients, or those with lung disease,[14-16] therefore further diagnostic procedures are required to confirm the initial diagnosis. Echocardiography is the 'gold standard' for assessing cardiac pathology; however, echocardiographic screening of all dyspnoeic patients is not cost-effective, and many patients referred for imaging do not have serious heart disease.[17,18] Accurate and rapid rule-in or rule-out of HF has the potential to significantly reduce the costs associated with the management of this condition.

"It is evident that a sensitive 'gatekeeper' is needed to identify those with higher likelihood of HF while confidently excluding the diagnosis for those with lower likelihood."

"Baggish & Januzzi, 2006"[19]

NT-proBNP testing in the ED

Improved diagnosis and stratification of patient care

NT-proBNP measurement in the ED can reduce the uncertainty about the diagnosis of HF

Natriuretic peptides (NT-proBNP and BNP) are secreted from the heart in response to cardiac hemodynamic stress mediated by volume and/or pressure overload.[20] The amino terminal of proB-type natriuretic peptide (NT-proBNP) is a robust biomarker for diagnosing individuals with HF; the PRIDE and ICON trials established NT-proBNP as a sensitive and specific indicator of acute HF in patients presenting to the emergency department (ED; Table 1).[21,22] Both the American College of Cardiology and the European Society of Cardiology guidelines state that measurement of natriuretic peptides should be considered in patients with suspected HF to exclude alternative causes of dyspnoea.[15,23] Early measurement of NT-proBNP can reliably rule out symptomatic patients who do not have HF and provides further confidence that patients with HF will not be missed.

Category	Optimal cut-point pg/mL	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Confirmatory ('rule in') cut-points						
<50 years (n = 184)	450	97	93	76	99	94
50 – 75 years (n = 535)	900	90	82	83	88	85
>75 years (n = 535)	1,800	85	73	92	55	83
Rule in, overall		90	84	88	66	85
Exclusionary ('rule out') cut-points						
All patients (n = 1,256)	300	99	60	77	98	83

Table 1: Optimal NT-proBNP cut-points for the diagnosis or exclusion of acute HF among dyspnoeic patients (ICON trial)[21]
N/PPV, negative/positive predictive value

Improved stratification of patient care

The prospective, randomised, controlled, multicentre PROMPT trial demonstrated the benefit of rapid NT-proBNP testing in the ED.[24] When NT-proBNP results were communicated to attending ED physicians, an improved stratification of patient care regarding hospital and intermediate/intensive care unit admission was seen. Knowledge of an elevated NT-proBNP level facilitated early and more aggressive patient management.

Patients with high levels of NT-proBNP (>1,800 pg/mL) were more likely to be admitted to a higher level of care (21.9 % vs. 12.9 %, p<0.05), and those with lower levels (<150 pg/mL) were less likely (4.6 % vs. 13.8 %, p<0.05), when treated by physicians with knowledge of NT-proBNP levels compared with the blinded group (Figure 3). The rate of admission to intermediate/intensive care in the intermediate group did not differ between the open and blinded groups.

The higher use of intermediate/intensive care in patients with the highest NT-proBNP was associated with a trend toward a reduction in mortality and rehospitalisation rate. A similar trend towards lower mortality and rehospitalisation rates were also seen in patients in the intermediate group. This suggests that improved patient stratification has the potential to lower mortality and rehospitalisation rates.

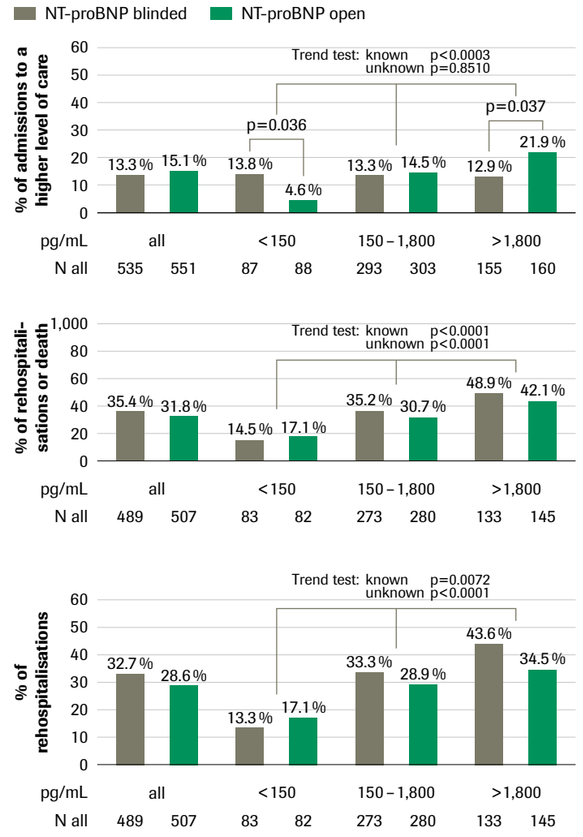

Figure 3: Rates of: admission to higher level of care, rehospitalisation or death and rehospitalisation, according to NT-proBNP strata in patients treated by physicians with (open group) or without (blinded) knowledge of NT-proBNP levels (PROMPT study population, n=1,086)[24]

NT-proBNP testing in the ED
Improved resource utilisation

Incorporating NT-proBNP testing into the diagnostic work up of dyspnoeic patients can reduce the number of clinical examinations required

Combining NT-proBNP testing with clinical assessment can improve initial patient selection for further investigations. Consequently, the allocation of additional diagnostic resources can be optimised and the number of unnecessary tests performed in both patients with HF and those without HF will be reduced. Incorporating NT-proBNP testing into clinical decision making would have resulted in a more efficient utilisation in clinical examinations in patients from the MANPRO study (Table 2).[25]

Type of examination	% savings*
Chest X-ray	34 %
Daily weight control	22 %
Daily blood withdrawal	19 %
Pulmonary function test	17 %
Daily pulse oximetry	11 %
ECG	10 %
ECHO	9 %
Daily balancing	8 %
Daily monitoring	4 %
Computed tomography	2 %

** compared with the number of examinations performed in patients with NT-proBNP ≥300 pg/mL. This cut-off level was optimum to rule out HF; ECG, electrocardiograph; ECHO, echocardiography*

Table 2: Proportion of clinical examinations saved in patients presenting to the ED with acute dyspnoea or peripheral oedema with NT-proBNP levels <300 pg/mL[25]

Incorporating NT-proBNP into the diagnostic algorithm could improve allocation of cardiac imaging

Pre-screening patients with suspected HF using NT-proBNP has been shown to allow more efficient utilisation of echocardiography, both in patients presenting to the ED and in those referred from primary care (Table 3).

In 220 primary-care patients referred for echocardiography, an NT-proBNP value >280 pg/mL identified all cases of HF.[26] In patients with NT-proBNP above this cutoff, the probability of having HF increased from 23.6 % pre-test to more than 72 % post-test. Echocardiographic study would only have been necessary in the 72 (33 %) patients with NT-proBNP levels >280 pg/mL. Similarly, a 58 % reduction in the number of required echocardiograms was predicted by a decision-analytical model analysis of dyspnoeic patients presenting to the ED (PRIDE study population), if diagnosis was based on NT-proBNP measurement.[27]

The optimisation of further diagnostic pathways and more efficient allocation of imaging resources achieved by adding NT-proBNP testing into routine patients assessment reflects the very high negative predictive value of NT–proBNP to exclude even subtle cardiovascular abnormalities.[27]

Reference	Population	Rule-out cutoff	Sn/Sp/PPV/NPV	% ECHO saved*
Verdu (2012)[26]	Patients referred from primary care (n = 220)	<280 pg/mL	N/A	67 %
Fuat (2006)[28]	Patients referred from primary care (n = 297)	<150 pg/mL	Sn 94 %, Sp 40 %, PPV 48 %, NPV 92 %	24 %
Goode (2008)[30]	Patients referred from primary care (n = 94)	<180 pg/mL	Sn 100 % (fxd) Sp 47 %	38 %
		LR model***	Sn 100 % (fxd) Sp 54 %	44 %
Goode (2007)[29]	High-risk** patients referred from primary care (n = 427)	LR model***	Sn 100 % (fxd), Sp 54 %, PPV 8.8 %, NPV 100 %	50 %
Behnes (2009)[25]	Patients presenting to the ED (n = 401)	LR model***	Sn 96 %, Sp 48 %, PPV 45 %, NPV 96 %	9 %

Table 3: Percent of echocardiography procedures that could be saved with the addition of NT-proBNP to clinical assessment for ruling out HF.[25,26,28-30]

*** IHD, previous MI, AF, diabetes for ≤10 years, hypertension for ≤10 years; or currently taking a loop diuretic*
**** Logistic regression model combining Log NT-proBNP levels with QRS width; ECHO, echocardiography; fxd, 'fixed at'; N/PPV, negative/positive predictive value; Sn, sensitivity; Sp, specificity*

NT-proBNP testing in the ED
Reduce the burden on healthcare resources

Including NT-proBNP testing in the assessment of patients presenting to the ED with dyspnoea can reduce time spent in the ED

NT-proBNP testing in the ED can improve the efficiency of care by establishing the correct diagnosis more quickly. In the randomised, double-blind, prospective multicentre IMPROVE-CHF study of 500 dyspnoeic ED patients, the duration of the initial ED visit was reduced by 11 % when physicians were provided with NT-proBNP results, compared with patients randomised to usual care (Figure 4).[31] Reduction in ED time was greatest in patients with an intermediate (20 – 80 %) likelihood of HF (5.4 hours with NT-proBNP-based treatment vs 7.5 hours with usual care; p = 0.0028).

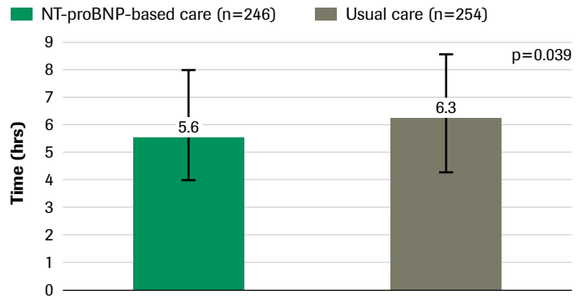

Figure 4: Median (IQR) duration of ED visit (IMPROVE-CHF study population, n = 500)[31]

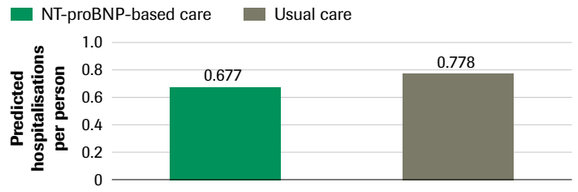

Figure 5: Predicted number of initial hospitalisations in patients presenting to the ED (PRIDE study population, n =599)[27]

NT-proBNP-based care in ED dyspnoeic patients can reduce the number of hospitalisations

A cost-effectiveness analysis of NT-proBNP testing in the PRIDE study population (599 patients presenting to the ED with acute dyspnoea) predicted a 13 % reduction in initial hospitalisations if clinical assessment incorporated NT-proBNP testing compared with standard clinical assessment (Figure 5).[27] This was associated with a 1.6 % relative reduction of serious adverse event risk and a 1.0 % relative reduction in post-discharge mortality.

Shorter duration of stay in hospitalised patients with NT-proBNP testing in the ED

NT-proBNP-based diagnosis and management of patients presenting to the ED with dyspnoea was associated with a predicted 12 % reduction in the average length of stay in the study by Siebert et al. (Table 4).[27]

In the MANPRO study, NT-proBNP levels were measured in all dyspnoeic patients on presentation to the ED.[25] Clinical routine care and diagnostic assessment was performed by physicians blinded to NT-proBNP levels. The treatment of patients (clinical examinations performed, medical therapy and period of hospitalisation) was retrospectively validated by two independent cardiologists un-blinded to the NT-proBNP levels, and the period of hospitalisation that could have been saved if NT-proBNP levels were known at presentation was estimated. In patients with NT-proBNP <300 pg/mL, 14 % of the total hospitalisation time (corresponding to a monetary value of US$ 481 per patient) could have been saved. No evidence of acute HF was found in 96 % of these patients. Furthermore, in patients with NT-proBNP ≥300 pg/mL, the saving potential was still 5 % (US$ 199 per patient) of the hospitalisation time).

Randomising ED patients (n = 477) presenting with acute dyspnoea to either rapid NT-proBNP measurement or usual care resulted in a significant reduction in the time from ED admission to hospital discharge (1.9 days [IQR: 0.12 – 9.4] in the NT-proBNP group vs 3.9 days [IQR: 0.16 – 11.0] with usual care; p = 0.04).[32]

Reference	Study group	Duration of hospitalisation
Siebert (2006)[27]	NT-proBNP group	Median 3.88 days
	Usual care	Median 4.41 days
Behnes (2009)[25]	NT-proBNP <300 pg/mL (n = 139)	14 % saving in hospitalisation time
	NT-proBNP ≥300 pg/mL (n = 262)	5 % saving in hospitalisation time

Table 4: Reduction in duration of stay in hospitalised patients[25,27] Duration of hospitalisation refers to length of stay from admission from the ED to discharge

NT-proBNP-based care of dyspnoeic patients

Cost effective option for diagnosis and management

NT-proBNP-based care of dyspnoeic patients reduces overall treatment costs

The reductions in use of diagnostic resources, hospitalisations and lengths of stay achieved by incorporating NT-proBNP testing in the diagnosis of HF translates into lower overall healthcare costs (Figure 6).

Direct medical costs up to 60 days were reduced by 15 % (p = 0.0232) in the IMPROVE-CHF trial when NT-proBNP testing was combined with clinical assessment in patients presenting to the ED with dyspnoea.[31] Cost savings were due in part to fewer patients in the NT-proBNP group undergoing advanced diagnostic tests on an outpatient basis after initial discharge. Knowledge of NT-proBNP results appeared to have the greatest impact on the costs of the initial and subsequent ED visits in patients with a 20 – 80 % likelihood of HF, compared with the entire cohort. This prospective, randomised analysis demonstrated that a management strategy that involves NT-proBNP testing improves the overall management of patients presenting to the ED with suspected HF.

In a prospective randomised trial of NT-proBNP-based care versus usual care in 477 patients presenting to the ED with dyspnoea, the addition of NT-proBNP testing to standard clinical assessment was associated with a trend towards a reduction in costs related to hospital admission and diagnostic investigations of US$ 1,364 per patient (95 % CI US$ -246 to US$ 3,215).[32] Post-hoc subgroup analyses indicated that the effect on costs was largest in patients with cardiac dyspnoea (mean reduction in costs, US$ 2,627; 95 % CI US$ -1,506 to US$ 6,753) compared with patient with non-cardiac dyspnoea (mean reduction in costs, US$ 150; 95 % CI US$ -1,386 to US$ 1,626).

Direct medical costs due to hospitalisations and echocardiograms were reduced by 9.4 % (or US$ 474 per patient) with NT-proBNP-based care in ED patients with dyspnoea compared with standard clinical assessment.[27] This study applied a decision-analytic model to patients from the PRIDE study to examine the cost-effectiveness of testing NT-proBNP in the ED setting. Over 90 % of savings were attributable to prevented or shortened hospitalisations.

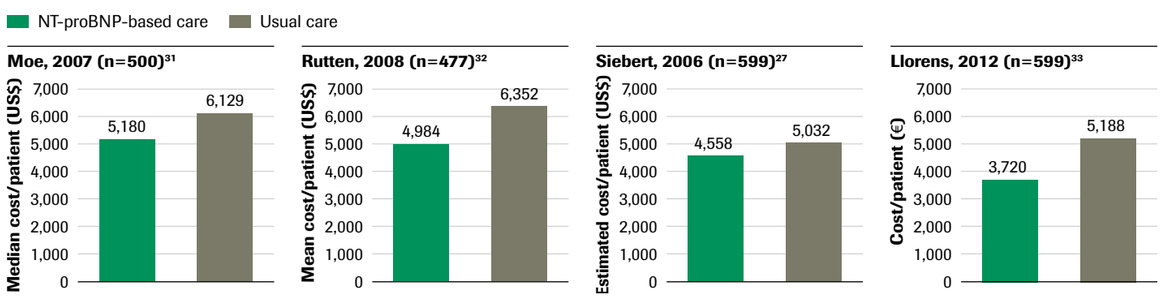

Figure 6: Reduction in direct medical costs per patient when management of patients presenting to the ED with dyspnoea incorporates assessment of NT-proBNP levels[27,31-33]
Figure shows the reduction in direct medical costs (diagnostic costs and hospitalisation costs) to 60 days (30 days for Rutten, 2008). Data for Moe, 2007 includes outpatient services

NT-proBNP-based care of dyspnoeic patients

No adverse effect on patient outcomes
Reduced rehospitalisation rates

Safety is maintained: No difference in mortality rates

The reductions in healthcare utilisation accomplished with the addition of NT-proBNP to routine clinical assessment of dyspnoeic patients are achieved without compromising patient outcomes (Figure 7). Sixty-day mortality rates in the IMPROVE-CHF trial were similar in patients treated based on NT-proBNP levels (5.4 %) than those receiving usual care (4.5 %; p = 0.58).[31] In-hospital mortality was also not significantly different (4.5 % and 2.4 %, respectively; p = 0.1932). In patients with an intermediate pre-test probability of HF, 60-day mortality (3.8 % vs 2.6 %, respectively; p = 0.6250) and in-hospital mortality (5.0 % vs 5.4 %, respectively; p = 0.8814) were also unchanged.

Similarly, the mean US$ 1,364 per patient reduction in costs reported by Rutten et al. with NT-proBNP testing in the ED did not adversely affect 30-day mortality (6 % with NT-proBNP-based treatment and 8 % with usual care).[32]

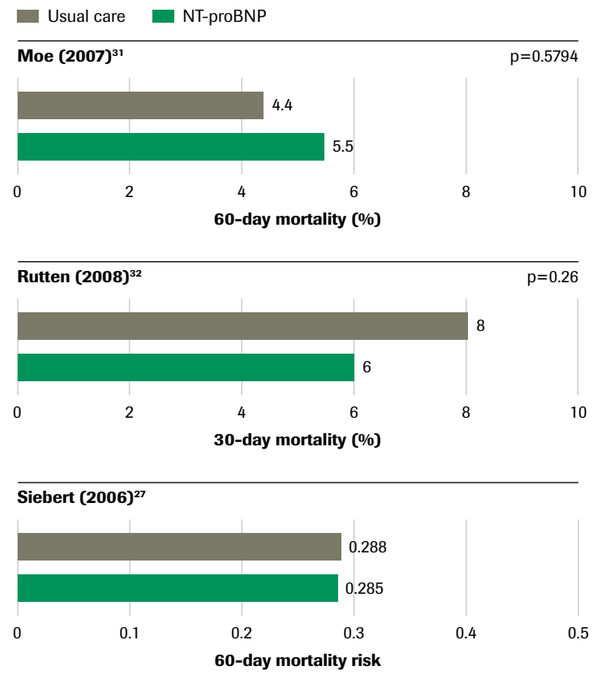

Figure 7: Mortality rates are similar with NT-proBNP-based care and usual care [27,31,32]

Readmission rates for HF are reduced when patients are treated based on NT-proBNP assessment compared with usual care

Over a quarter of patients with a discharge diagnosis of HF will be readmitted within 6 months, greatly adding to the cost of care.[11] In the IMPROVE-CHF study, patients treated based on NT-proBNP levels measured in the ED were significantly less likely to be rehospitalised within 60 days (13 % vs 20 %; p = 0.0463; Figure 8).[31]

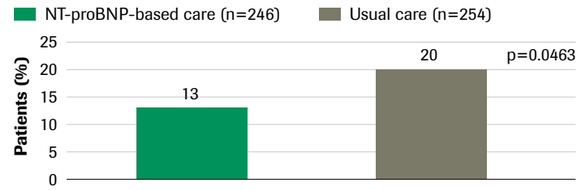

Figure 8: Rehospitalisation rates at 60 days[31]

As well as the established benefit of more accurate diagnosis at presentation, NT-proBNP measured prior to discharge may represent an effective strategy for preventing subsequent rehospitalisation. Subclinical congestion at the time of discharge is one of the biggest risk factors for early readmission[34] and many patients are discharged with persistent signs and symptoms of congestion and/or a high left ventricular filling pressure.[35] In the IMPROVE-CHF study, NT-proBNP measurements were also obtained 72 hours after admission in hospitalised patients to provide pre-discharge values to guide subsequent management.

Pre-discharge levels of NT-proBNP predict adverse prognosis following acute left ventricle failure.[36] A discharge NT-proBNP level that has not substantially decreased from admission levels may indicate that the patient is still congested, has impending kidney disease or has a high amount of end-diastolic wall stress. [34] Therefore, measuring NT-proBNP levels at discharge and/or shortly afterwards may identify those patients who are in need of further treatment before being discharged, or a higher level of care as an outpatient, and provide valuable information for preventing rehospitalisation and further reducing the economic burden of HF.

NT-proBNP-based care of dyspnoeic patients

Cost-effective in the outpatient setting

NT-proBNP in home-based specialist HF care is a cost-effective strategy

HF management programmes using nurse intervention have been shown to improve quality of care for HF patients and reduce the number of re-hospitalisations.[37] Combining NT-proBNP assessment into a home-based nurse care programme further improves patient outcomes and is cost effective and cheaper than usual care.[5] In 190 congestive HF patients randomised to usual care, home-based nurse care, or NT-proBNP-based care, rehospitalisation rates due to HF (25 % vs 60 %, respectively; $p<0.001$) and mortality rates (17 % vs 45 %, respectively; $p = 0.017$) were lower with NT-proBNP-based care than usual care. In the NT-proBNP-based group, additional visits to a HF out-patient clinic were triggered if NT-proBNP levels increased (>2,200 pg/mL) at one of four three-monthly home consultations. Rehospitalisation costs adjusted for mortality were significantly lower with NT-proBNP-based specialist care compared with both usual care ($p = 0.012$) and home-based nurse care ($p = 0.016$; Figure 9).

Assessment of NT-proBNP levels in the outpatient setting may enable congestion to be detected before it becomes severe enough to require hospitalisation.

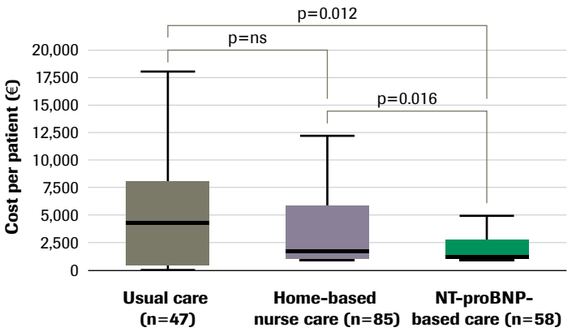

Figure 9: Rehospitalisation costs due to HF adjusted for mortality over 18 months in discharged CHF patients[5]

Conclusions

The global economic burden of HF is high and expected to increase. Measuring NT-proBNP in patients presenting to the ED with acute dyspnoea offers you a cost-effective method for identifying patients with suspected HF.

Incorporating NT-proBNP testing into the routine assessment of your patients can:

- Reduce uncertainty about the diagnosis of HF and establish a diagnosis more quickly
- Improve risk stratification
- Reduce the rehospitalisation occurrence rate
- Shorten lengths of stay
- Improve cost containment of patient management
- Allow optimal allocation of diagnostic resources to dyspnoeic patients suspected of having HF
- Improve the overall management of patients presenting to the ED with suspected acute HF

Managing patients with suspected HF based on NT-proBNP levels is superior to clinical assessment alone and reduces the overall cost to healthcare systems, and cost savings can be accomplished without compromising the care of your patients.

Early diagnosis and treatment are crucial for the prognosis of HF.

Both Roche NT-proBNP assays for laboratory and for Point of Care play a significant role in improving clinical decision-making when patients present with symptoms suggestive of HF.

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