



## **Early detection of heart failure in high-risk patients**

*The value of NT-proBNP*

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# Heart failure

Common, costly, disabling and life-threatening

Early diagnosis and categorisation may allow for more effective therapy and prognosis improvement.<sup>13,14</sup>

## Definition

Heart failure (HF) is a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.<sup>1</sup> Initial causative myocardial injury may be either sudden and obvious (e.g. myocardial infarction), gradual and insidious (e.g. longstanding hypertension), or entirely unknown – however, once injury occurs a series of compensatory, yet maladaptive, mechanisms ensue.<sup>2</sup> Worsening HF on a background of chronic HF is the most common form, leading to frequent hospital admissions.<sup>3</sup>

## Epidemiology

HF is a major, global health problem that affects 25 million people worldwide.<sup>4</sup> HF or asymptomatic ventricular dysfunction is evident in approximately 4% of the total population of Europe.<sup>3</sup> In the UK, around 900,000 people have HF<sup>5</sup> and in the USA, 550,000 new cases are diagnosed annually.<sup>6</sup> The prevalence of HF rises sharply in the elderly, with a prevalence of over 10% in those over 70 years of age.<sup>7</sup>

Chronic HF accounts for 1–2% of the total healthcare expenditure in developed countries<sup>8</sup>, with about two-thirds of this economic burden accounted for by hospitalisation cost.<sup>2</sup> With an increasing cost tendency in the future, real medical costs of heart disease and HF are projected to increase by about 200% between 2010 and 2030.<sup>9</sup>

HF is associated with high morbidity and mortality. One in five patients die within one year of diagnosis, with sudden cardiac death occurring at six to nine times the rate of the general population.<sup>10</sup> The detection of HF in the earlier stages is a key objective in improving patient outcomes, life expectancy and quality of life.<sup>11,12</sup>

## The progression of HF

In 2001, the American College of Cardiology introduced a new classification of HF (Stage A to Stage D, Table 1) which highlights the importance of pre-HF (Stage A) in patients who are at high risk of developing HF.<sup>15</sup> Early identification of subjects with asymptomatic

structural or functional damage (e.g. left ventricular systolic dysfunction [LVSD] and left ventricular hypertrophy [LVH]) may allow preventative therapies to be initiated in the preclinical phase of disease, thus delaying or preventing the progression to HF.<sup>16</sup>

### Stages of HF

Stage A: At high risk for HF but without structural heart disease or symptoms of HF

Stage B: Structural heart disease but without signs or symptoms of HF

Stage C: Structural heart disease with prior or current symptoms of HF

Stage D: Refractory HF requiring specialised intervention

### Can be found in patients with the following:

Hypertension, atherosclerotic disease, diabetes, obesity, metabolic syndrome, patients using cardiotoxins or patients with a family history of cardiomyopathy

Previous MI, LV remodeling including LVH and low EF, asymptomatic valvular disease

Structural heart disease with symptoms of heart failure

Marked symptoms at rest despite maximal medical therapy

Table 1: Stages of HF according to the ACCF/AHA classification guidelines.<sup>15</sup>

EF: Ejection fraction; LV: Left ventricular; LVH: Left ventricular hypertrophy; MI: Myocardial infarction.



# Natriuretic peptides

## *From science to clinical routine*

## Initial clinical assessment of HF

### *How sensitive and specific is it?*

Signs and symptoms suggestive of HF typically include shortness of breath (dyspnea), fatigue, signs of fluid retention (pulmonary congestion or ankle swelling) and objective evidence of an abnormality of the structure or function of the heart at rest, such as an abnormality on the echocardiogram.<sup>3</sup>

The European Society of Cardiology (ESC) HF Guidelines, 2012<sup>7</sup>, highlight the following limitations of HF-related physical examinations:

- Symptoms are often non-discriminatory between HF and other co-morbidities, are of limited diagnostic value, and can poorly correlate with ventricular function

- Symptoms and signs may be particularly difficult to identify and interpret in obese individuals, the elderly and in patients with chronic lung disease
- Lack of symptom specificity leads to unnecessary echocardiogram referral, often revealing no important abnormalities
- Echocardiography referral may not be available in a timely manner or may not be cost-effective
- Chest X-ray can be of limited use in the diagnostic work-up of patients with suspected HF

The above limitations make the diagnosis of HF difficult, particularly in a primary care setting.<sup>11</sup>

### BNP and NT-proBNP

The heart attempts to maintain cardiovascular homeostasis by releasing natriuretic peptides (NPs), which promote natriuresis and diuresis, act as vasodilators and exert antimitogenic effects on cardiovascular tissues. B-type natriuretic peptides (BNP) and N-terminal-proBNP (NT-proBNP) are produced predominantly in ventricular myocytes due to increased myocardial wall stress.<sup>17</sup>

BNP and NT-proBNP are synthesised as a pre-proBNP molecule consisting of 134 amino acids. Pre-proBNP is then cleaved by proteolytic enzymes into a 108-amino acid prohormone (proBNP) and a 26-amino acid signal peptide. Upon secretion, proBNP is cleaved into BNP, the biologically active peptide, and NT-proBNP, the more stable N-terminal fragment (Figure 1).<sup>18</sup>

NT-proBNP is an ideal biomarker for HF in the primary care setting.<sup>19</sup> This is not only due to its strong prognostic value, but also because NT-proBNP is more stable at room temperature than BNP, thus making it the superior marker in an outpatient setting.<sup>20</sup>

### Synthesis of B-type natriuretic protein in response to increased volume and filling pressures

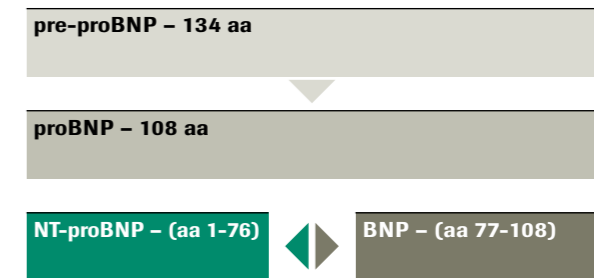


Figure 1: Schematic diagram showing the synthesis of NT-proBNP and BNP from the pre-proBNP protein by cardiomyocytes.<sup>18</sup>

*NT-proBNP measurement fulfils the criteria of being a robust test to exclude reduced left ventricular systolic function.<sup>4</sup>*

## HF diagnosis in the primary care setting

### *The importance of NT-proBNP*

NT-proBNP levels are inversely associated with left ventricular ejection fraction (LVEF) and positively associated with LV mass.<sup>16</sup>

In 721 primary care patients, NT-proBNP yielded the highest diagnostic value when added to patient history and physical examination, resulting in a reclassification improvement of 69%.<sup>21</sup>

When applied to patients with symptoms of HF in the primary care setting, NT-proBNP:

- Has a high negative predictive value (NPV) of 92 – 99% for ruling out HF (Table 2).<sup>19</sup>
- Could provide a powerful tool for detecting early stages of the disease.<sup>22</sup>
- Pre-selects high-risk patients for urgent echocardiogram when NT-proBNP values are between 200 – 300 pg/mL.<sup>23</sup>
- Is cost-effective and could substantially decrease echocardiogram referrals when utilising a decision limit value of 125 pg/mL.<sup>4</sup>

Study	N	Optimal cut-off limits (ng/L)	NPV	PPV
Zaphiriou et al, 2005	306	125	97%	44%
Nielsen et al, 2004	345	93 and 144*	97%	57% and 48%
Gustafsson et al, 2005	367	125	99%	15%
Fuat et al, 2006	279	150	92%	48%
Al-Barjas et al, 2004	220	125	97%	76%

Table 2: Studies of NT-proBNP cut-off limits for excluding heart failure in the primary care setting.<sup>19</sup>

\*Age adjusted, N = Number, NPV= Negative predictive value, PPV = Positive predictive value.

## Guideline recommendations

### *Recommendations for NP testing to aid HF diagnosis and risk prediction*

Many major practice guidelines recommend NP testing for the diagnosis and treatment of acute and chronic HF. In the primary care setting, routine

screening is not currently advocated, but high-risk patients with symptoms of HF should be referred for a diagnostic workup.

#### International guideline recommendations for measurement of NPs in HF diagnosis and management

- The European Society of Cardiology (ESC) states that a normal NP level in untreated patients virtually excludes significant cardiac disease and serves as a means to risk stratify echocardiogram referral. In addition, measurement of NPs should be considered to exclude alternative causes of dyspnea and to obtain prognostic information.<sup>7</sup>
- The American College of Cardiology (ACC)/American Heart Association (AHA) recommends that NP should be tested in patients presenting in the urgent care setting with dyspnea of unknown cause, where a clinical diagnosis of HF is uncertain. A final diagnosis requires interpreting the results in a context of all available clinical data. In addition, NP can be useful in risk stratification.<sup>24</sup>
- The Heart Failure Society of America (HFSA) recommends that NP levels should be tested in patients with dyspnea who have signs and symptoms compatible with HF, and that concentrations should not be interpreted in isolation, but in context of all available clinical data. However, routine measurement of NP in non-symptomatic patients is not recommended.<sup>12</sup>
- The National Institute for Health and Clinical Excellence (NICE) recommends NP measurement before echocardiogram in patients with suspected HF who have not suffered a prior myocardial infarction. NT-proBNP values >2,000 pg/mL should be referred urgently for echocardiography and specialist assessment.<sup>5</sup>



*Outcomes in HF are highly variable; established risk markers do not fully explain the mortality risk and underestimate an individual's prognosis.<sup>26</sup>*

## Risk stratification in the primary care setting

### *The role of NT-proBNP*

NT-proBNP has a good prognostic impact as a predictive marker of HF risk, due to its ability to detect subtle preclinical cardiac changes.<sup>25</sup>

Measuring NT-proBNP in primary care patients with suspected HF identified those with substantial increases in the risk of cardiovascular hospitalisation and death. An elevated NT-proBNP in these patients was associated with a 90% increased risk for cardiovascular hospitalisation (Figure 2) and an 80% increased risk of death.<sup>23</sup>

Traditional risk factors are less predictive in the elderly.<sup>22</sup> The Cardiovascular Health Study, a risk prediction study, demonstrated that elevated levels of NT-proBNP correlated to an increased risk of incident HF (Figure 3) and death in 2,975 enrolled community-dwelling adults aged over 65 years without HF. This study confirmed that a NT-proBNP value of 190 pg/mL divided the patients into a lower-risk and higher-risk group for the development of HF and cardiovascular death.<sup>22</sup>

**Hazard ratio for CV hospitalisations per NT-proBNP decile**

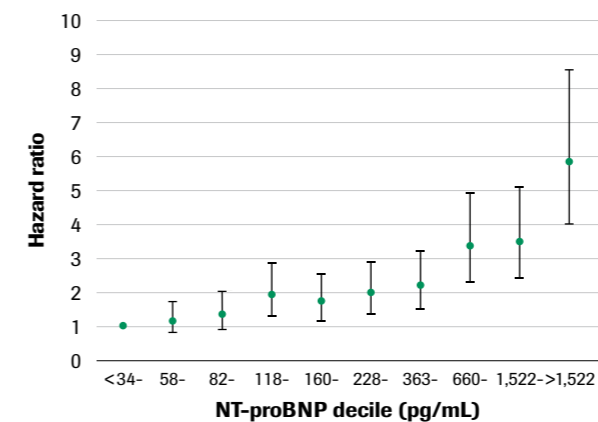


Figure 2: Effect of NT-proBNP decile on the hazard ratio with 95% CI for cardiovascular hospitalisation after adjustment for age, sex, previous hospitalisation, CV disease and chronic disease (95% CI: 30–190,  $p < 0.01$ ).<sup>23</sup>

**Hazard ratios for new-onset HF by decile of NT-proBNP**

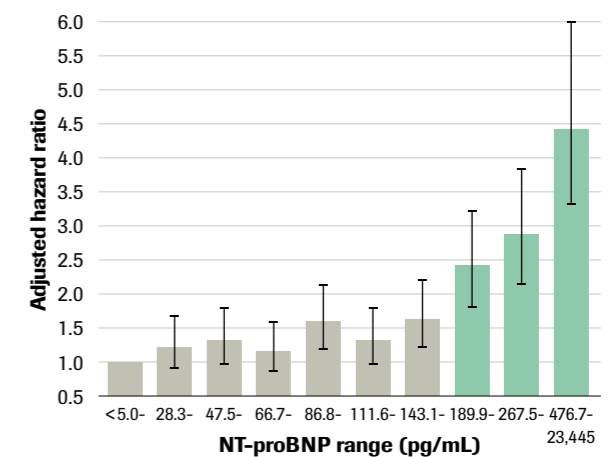


Figure 3: Demographic-adjusted hazard ratios for developing new-onset HF by decile of NT-proBNP.<sup>22</sup>

*NT-proBNP level is an independent, long-term predictor of new-onset HF and cardiovascular death.<sup>22</sup>*

## Risk prediction

### *NT-proBNP improves risk prediction models*

Utilising clinical risk scores, which include NT-proBNP, may facilitate risk-stratified waiting lists for echocardiogram referrals. This may, in turn, positively impact mortality and morbidity.<sup>23</sup> Recently, the addition of NT-proBNP to an optimised risk prediction model (Atherosclerosis Risk in Communities [ARIC] HF risk function) demonstrated that the inclusion of NT-proBNP markedly improved the 10-year risk prediction of HF in 15,792 enrolled middle-aged adults.<sup>27</sup>

Indeed, prevalence of NT-proBNP levels >190 pg/mL increased according to 5-year risk prediction scores utilising the health aging and body composition (ABC) HF risk score and data from 3,752 participants from the Cardiovascular Health Study (CHS) (Figure 4).<sup>28</sup>

Both NT-proBNP and echocardiogram score improved risk classification when added to the health ABC HF risk score. This resulted in a clinically relevant risk

reclassification among the 35.7% of participants deemed to be at intermediate risk (5–10% and 10–20% predicted 5-year HF risk).<sup>28</sup>

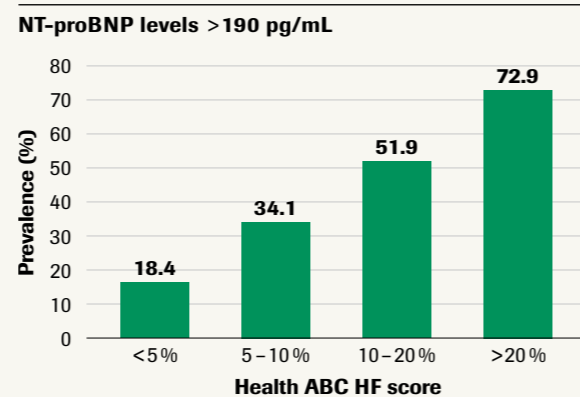


Figure 4: Prevalence of increased NT-proBNP levels according to projected health ABC HF risk.  $p < 0.001$  for linear trend across categories.<sup>28</sup>

## Prognosis in at-risk subjects

*Elevated NT-proBNP levels are associated with increased negative patient outcomes*

Stage A patients with coronary artery disease (CAD), hypertension, and diabetes have an increased risk of developing HF.<sup>15,20</sup> Prediction of cardiovascular events in these high-risk subjects can be challenging.<sup>25</sup> Patients are at an increased risk for hospitalisation and death once signs and symptoms of HF are present.<sup>29</sup>

Elevated levels of NT-proBNP are correlated to an increased risk of death<sup>25</sup>, cardiovascular events<sup>30,31</sup>, and HF.<sup>31</sup> One of the most significant steps in limiting the public health impact of the incidence and associated cost of HF is the early identification and treatment of risk factors.<sup>12</sup> Identification of high-risk patients with high levels of NT-proBNP might be helpful in the selection of more aggressive primary prevention.<sup>32</sup>

Elevated levels of NT-proBNP were associated with an increased risk of hospitalisation in high-risk individuals in the primary care setting, even if LVEF was normal (Figure 5). Furthermore, the negative predictive value (NPV) was excellent in predicting hospitalisation using a cut-off of 125 pg/mL; 86% for all-cause, 98% for cardiac and 100% for HF-related hospitalisation.<sup>33</sup>

### Significant increase in event rate in high-risk patients with elevated NT-proBNP, even when LVEF normal

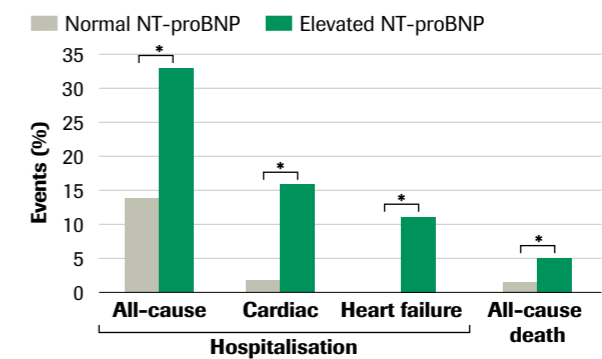


Figure 5: Hospitalisation and mortality rates in high-risk primary care patients with elevated NT-proBNP (>125 pg/mL) vs normal NT-proBNP ( $\leq 125$  pg/mL).<sup>33</sup>

\*  $p < 0.001$

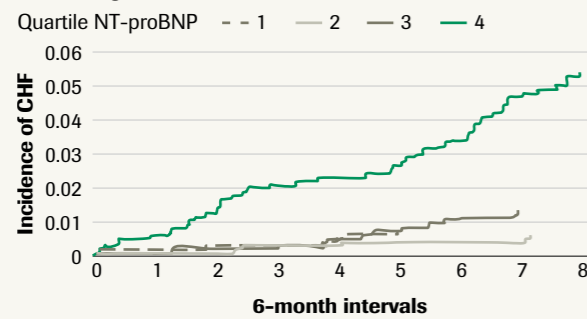
“In the future, algorithm building will take into consideration clinical and echocardiographic parameters as well as NP measurements, and this may better ensure the correct diagnosis and categorisation for patients with worsening prognosis.”<sup>14</sup>

### Coronary artery disease

CAD is by far the most common cause of myocardial disease and is the initiating factor in ~70% of patients with HF.<sup>3</sup>

CAD can be described as stable or unstable, depending on the frequency of symptoms, triggering factors and severity.<sup>34</sup> Patients with stable CAD have a high rate of clinically suspected HF (up to 60%)<sup>31</sup> whereas patients with unstable CAD have varying severity of the underlying CAD, prognosis and response to treatment.<sup>35</sup>

**a) NT-proBNP levels are predictive of congestive heart failure**



**b) NT-proBNP levels are predictive of cardiovascular death**

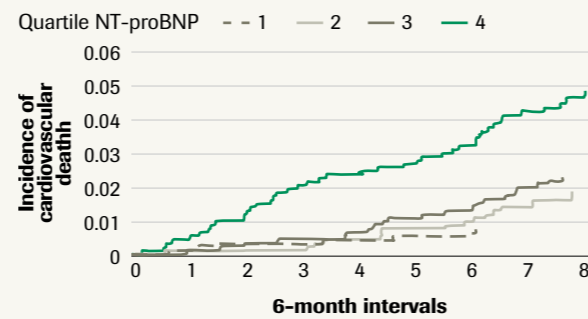


Figure 6: Kaplan-Meier curves showing the cumulative incidence of a) fatal or non-fatal congestive HF and b) death due to cardiovascular cause in patients according to quartiles of NT-proBNP concentrations in pg/mL. Quartile 1: Men 5–66, women 5–105; Quartile 2: men 66–127, women 105–196; Quartile 3: men 127–253, women 196–372; Quartile 4: men 253–5,590, women 372–4,593.<sup>31</sup>

### Stable CAD

In the PEACE (Prevention of Events With Angiotensin-Converting Enzyme Inhibition) study, elevation of NT-proBNP levels measured in 3,761 patients with stable mortality, fatal or non-fatal congestive HF and fatal or non-fatal stroke after accounting for other risk factors (Figure 6).<sup>31</sup>

### Unstable CAD

Unstable CAD refers to unstable angina or non-ST-segment elevated acute myocardial infarction (non-STEMI), both of which are acute coronary syndromes with similar pathogenesis and clinical presentations but with differing severity.<sup>36</sup>

NT-proBNP levels have been found to be highly predictive of adverse outcomes independent of other biomarkers in patients presenting with symptoms suggestive of unstable CAD.<sup>37</sup> NT-proBNP was analysed on arrival in 755 patients admitted to the coronary care unit with symptoms suggestive of non-ST-segment elevated acute coronary syndrome (including unstable angina and non-STEMI). Relative risk of death at 40 months (95% CI) was 4.2 (1.6–11.1), 10.7 (4.2–26.8) and 26.6 (10.8–65.5) for patients in the second, third and fourth quartile, respectively, compared to the lowest quartile (Figure 7).<sup>35</sup>

**High levels of NT-proBNP associated with increased mortality in patients with CAD**

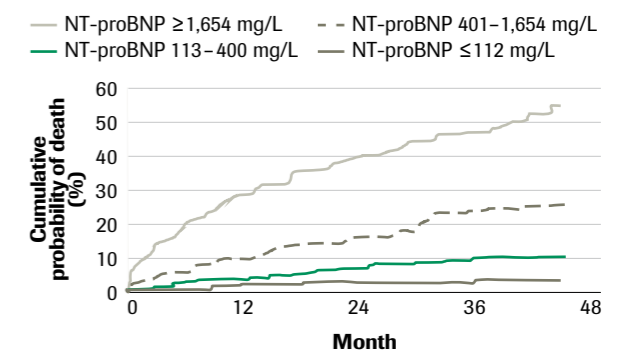


Figure 7: Kaplan-Meier curves regarding probability of death during 40 months for patients according to quartiles of NT-proBNP. 1<sup>st</sup> vs 2<sup>nd</sup> quartile:  $p = 0.005$ , log rank, 2<sup>nd</sup> vs 3<sup>rd</sup> and 3<sup>rd</sup> vs 4<sup>th</sup> quartiles:  $p < 0.001$ .<sup>35</sup>

While methods exist for detection of cardiac damage in hypertensive patients, there is still room for new cardiac markers to be used for risk stratification.<sup>25</sup>

### Hypertension

Seventy-five percent of HF cases have preceding hypertension.<sup>10</sup> Hypertension with resultant LVH and MI result in cardiac remodelling, followed by the development of subclinical left ventricular diastolic and systolic dysfunction. The sequence of events that eventually lead to the final stage of the disease (HF) are not fully understood, but are thought to include changes in ventricular shape and load, change in chamber mechanics, loss of atrioventricular synchrony, neurohormonal activation and atrial fibrillation (Figure 8).<sup>38</sup>

NT-proBNP levels are higher in patients with hypertension and LVH compared to levels in healthy subjects.<sup>25</sup> In the Losartan Intervention For Endpoint

Reduction in Hypertension (LIFE) substudy, patients with severe hypertension and LVH, NT-proBNP values >184 pg/mL were associated with a 2.8-fold increased risk of cardiovascular death, non-fatal stroke, and non-fatal MI.<sup>39</sup> Furthermore, elevated NT-proBNP values predicted subsequent HF hospitalisations (p <0.01).<sup>40</sup> Paget et al (2011) found that the prognostic value of NT-proBNP was independent of and superior to the electrocardiogram indexes of LVH and Sokolov-Lyon index in hypertensive patients of various severities.<sup>25</sup> Garcia et al (2010) found that patients in the highest NT-proBNP quartile were twice as likely to die during a 9-month follow up when compared to patients in the lowest quartile.<sup>41</sup>

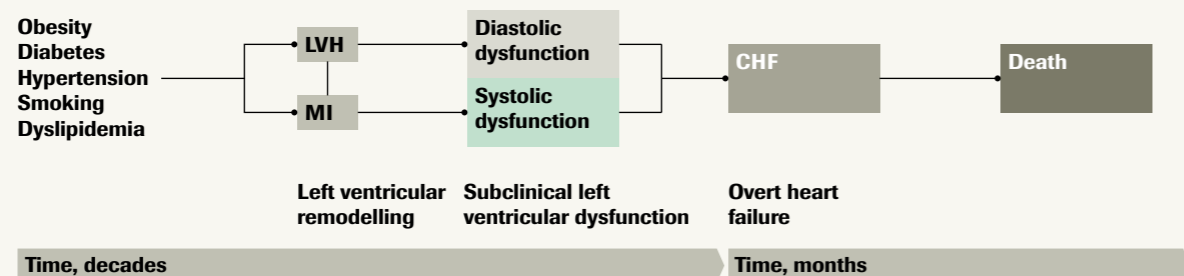


Figure 8: Hypertension is a major risk factor for developing HF, leading to left ventricular remodeling and subsequent dysfunction.<sup>38</sup>

“Early identification of vascular risk is the cornerstone of diabetes management and facilitates tailored intervention at an early stage when a beneficial response is more likely to be obtained.”<sup>42</sup>

### Diabetes

The Framingham study confirmed that diabetes was an independent risk factor for developing chronic HF, lending diabetic men and women a relative risk of 2.36 and 5.14, respectively, for developing HF when compared to non-diabetics.<sup>43</sup> Thus, risk stratification in diabetic patients and targeted, individualised management is of great importance.<sup>44</sup>

In recent years, NT-proBNP has been found to be an excellent predictor of cardiovascular risk and mortality in patients with diabetes.<sup>44,45</sup> NT-proBNP levels >125 pg/mL were a better predictor of short-term cardiovascular events compared to 17 other variables, including glycated hemoglobin (HbA1c) and a history of heart disease.<sup>45</sup> To predict a combined end point (unplanned cardiovascular hospitalisation and death), the ROC for a NT-proBNP value of 125 pg/mL was 0.785, with a sensitivity of 0.795 and a NPV of 97.6%, making NT-proBNP an excellent predictor to rule out short-term cardiovascular events in diabetes patients (Figure 9).<sup>45</sup>

Similar results were found in a population of patients with diabetes mellitus treated at a tertiary care centre, where levels of NT-proBNP at baseline and at one-year follow up accurately predicted the 40-month outcome (all-cause mortality, cardiovascular and all-cause hospitalisation).<sup>44</sup> Furthermore, elevated NT-proBNP

was a strong long-term (15.5 years) predictor of cardiovascular mortality in patients with diabetes, with all-cause mortality increased in patients with NT-proBNP in the second and third tertiles (52 – 80 pg/mL and 139 – 428 pg/mL, respectively) compared to the first tertile (17 – 32 pg/mL, HR 95% CI, 1.70 [1.08 – 2.67] and 5.19 [3.43 – 7.88], p <0.001).<sup>42</sup>

### Kaplan-Meier lifetime analyses

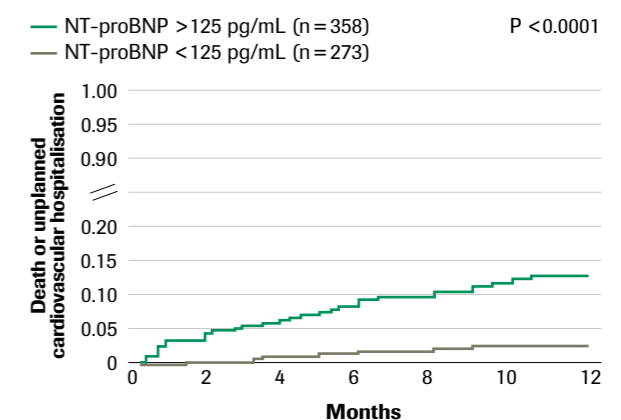


Figure 9: NT-proBNP prediction of all-cause mortality or unplanned hospitalisations in 631 diabetic patients using NT-proBNP cut-off levels of 125 pg/mL. Log rank test for overall difference, p <0.0001.<sup>45</sup>



*Early diagnosis and treatment are crucial for the improvement of HF prognosis.<sup>12</sup>*

## **Roche NT-proBNP assays** *Supporting clinicians in the early detection of HF*

### **Early detection of at-risk patients** *A role for NT-proBNP*

As the previously listed studies demonstrate, NT-proBNP is a biomarker that is able to stratify patients with CAD, hypertension and diabetes into high- and low-risk groups for mortality and developing HF.

In addition to traditional tools that are available for the evaluation of high-risk patients for HF, NT-proBNP is a useful and, indeed, recommended additional test to help clinicians decide which patients could benefit from aggressive management.<sup>7,12</sup>

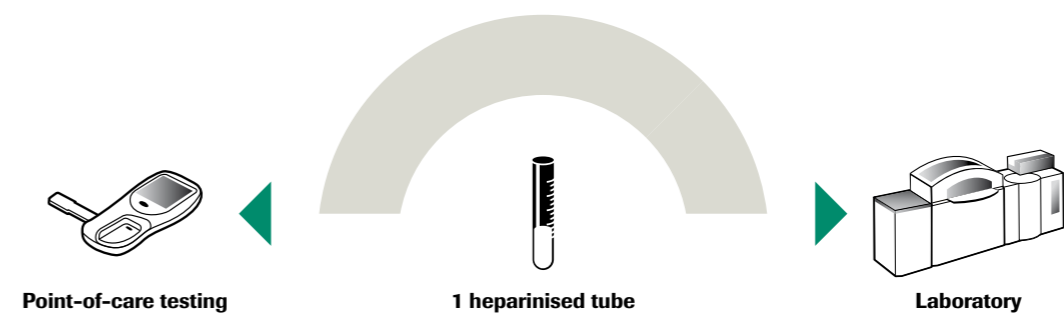
#### **A low NT-proBNP level:**

Has an excellent negative predictive value for ruling out HF (92 – 99 %)<sup>19</sup>

#### **An elevated NT-proBNP level:**

- Is associated with an increased risk of a first major cardiovascular event<sup>30</sup>, a new onset of HF<sup>22</sup> and cardiovascular death<sup>22,23,30,33,41</sup>
- Provides improved risk stratification compared to several established biomarkers and risk scores<sup>27,28</sup>
- Identifies high-risk patients with co-morbidities which are often associated with HF<sup>25,35,40,45</sup>
- Facilitates echocardiogram referral decision-making<sup>23</sup>

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



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