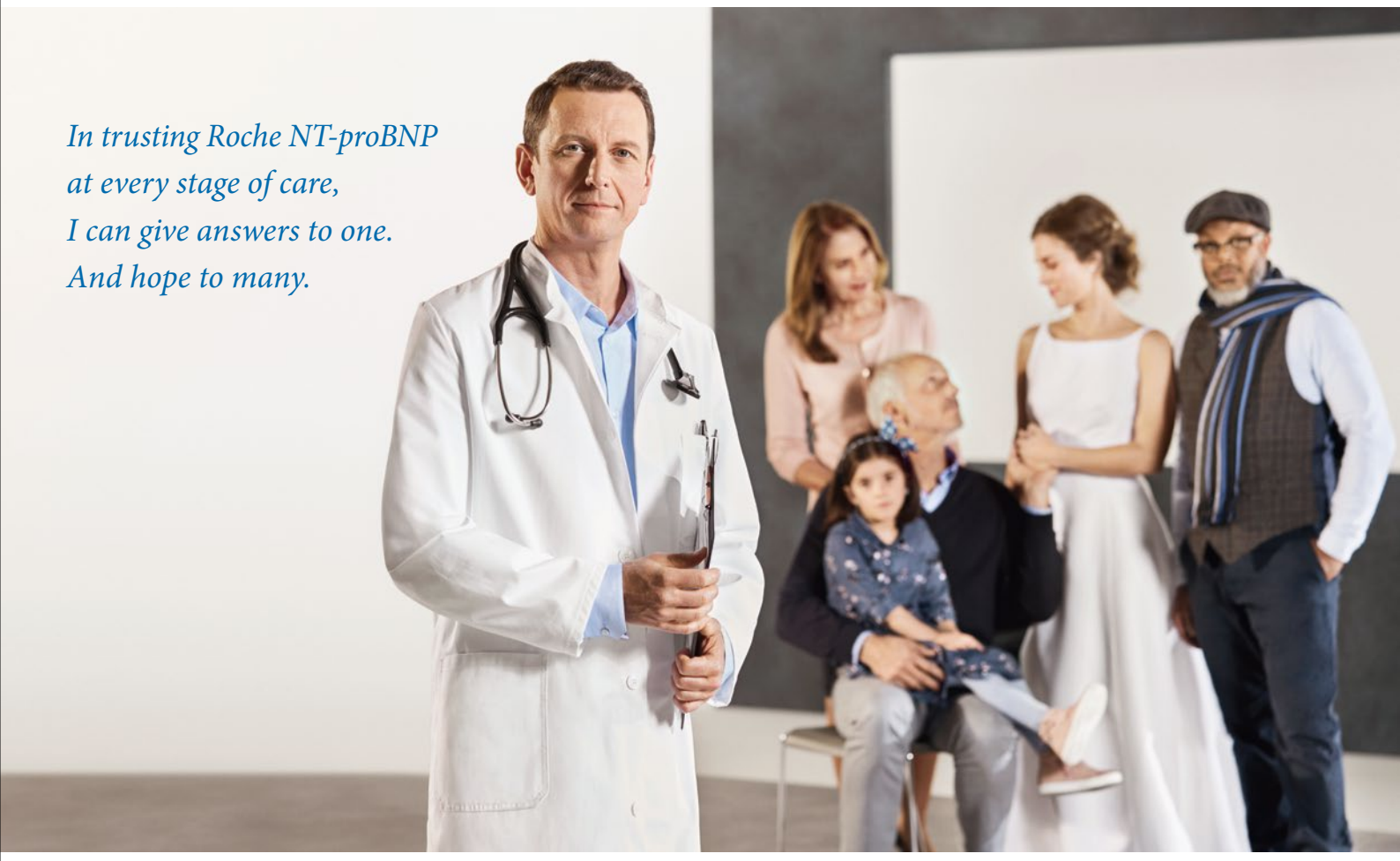
How Roche NT-proBNP can help all along the HF patient journey

Based recent International Heart Failure Guidelines for heart failure and clinical cases



Heart failure is very common and management can be challenging

Heart failure (HF) is a life-threatening condition affecting more than 26 million people worldwide[1]

HF is associated with high morbidity and mortality

- 1 in 5 patients die within 1 year of diagnosis, with sudden cardiac death occurring at 6 to 9 times the rate of the general population[2]
- More than 1 in 2 patients die within 5 years, with survival rates worse than major cancers like bowel, breast and prostate cancer[1]

Improved management of HF is key to improve patients' outcomes and quality of life[1,3,4]

From diagnosis to disease long term monitoring – HF management can be challenging.

HF diagnosis can be challenging

- In the early stages of heart failure (NYHA I), patients do not present any symptom or they can be transient[5]
- Symptoms of HF are unspecific and the typical clinical signs can be found in less than 50 % of the patients[6]
- Lack of symptom specificity leads to unnecessary echocardiogram referral, often revealing no important abnormalities[3]

HF hospitalization remains a burden for patients and society

- Hospitalization due to HF is the leading cause of hospitalization in the United States and Europe[7]
- 25 % of patients return to hospital for worsening progression one month after having left the hospital[8-9]
- As a consequence of the high level of hospitalization, the costs of HF to society is high, accounting for approximately 1–2 % of direct healthcare expenditure[8]

HF long term management can be improved

- Enhanced discharge planning could help to better coordinate care and to reduce hospitalization[10]
- In chronic HF, prescribing inertia is common and is associated with long-term risk[11]

How Roche NT-proBNP can support clinical decision making from diagnosis to monitoring

Major guidelines recommend the use of natriuretic peptides at every stage of patient management in HF.[5,12,13]

With over 15 years of clinical evidence generation and proven clinical use, you can trust Roche NT-proBNP to support your clinical decision at every stage of care in heart failure[14-15]

Diagnosis

Initial test for diagnosis before echocardiography in acute and non-acute setting

In-hospital management

Prognostic biomarker to asses disease severity at admission and to support discharge planning

Disease monitoring

Biomarker to monitor over time disease progression or patient status improvement

Major role of Roche NT-proBNP as the initial diagnostic test for the diagnosis of HF

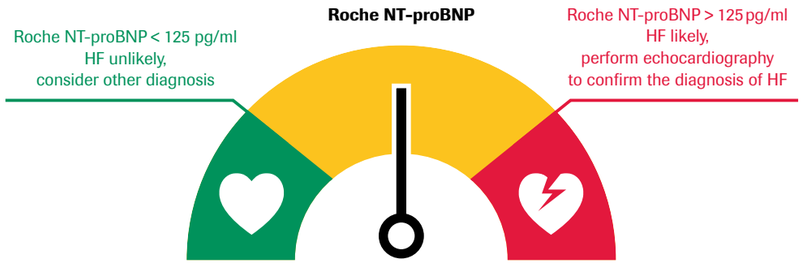
Gatekeeper for improved diagnosis and better use of resources

In association with clinical evaluation, natriuretic peptides are recommended as initial diagnostic test with the highest level of recommendation (IA) in major guidelines[5,12,13]

Roche NT-proBNP is clinically validated and can support your decision making in heart failure diagnosis procedure in both non-acute and acute setting [15]

- Exclude HF in a timely manner with a high sensitivity and NPV[12,13,16,17], thus avoid unnecessary echocardiography and shorten the length of stay in the emergency department [16,18-23]
- Identify patients with high probability of having HF who need further cardiac investigation to confirm the diagnosis and initiate treatment [5,12,13]
- In primary care, identify patients who need referral to the specialist [16,18-19]

How to use and interpret the results in patients presenting in non-acute setting [5,12,16,18,20]



How to use and interpret the results in patients presenting in acute setting [12,17,21]

- In the acute setting higher natriuretic peptides values should be used [12]
- Roche NT-proBNP is the only clinically validated biomarker with age specific cutoffs which helps to improve the specificity and the accuracy when diagnosis HF in patients presenting acute dyspnea in emergency department [18,21]

HF unlikely	Grey zone	Confirmation by imaging
Roche NT-proBNP **< 300 pg/mL** **Search for other symptoms**	**Roche NT-proBNP** **> 300 pg/mL but under "rule-in" cut-offs** **Diagnosis by imaging**	**Roche NT-proBNP** > 450 pg/mL if < 50 years > 900 pg/mL if 50 – 75 years > 1,800 pg/mL if > 75 years

Results in the grey zone have to be interpreted in the clinical context as other causes beyond heart failure can lead to elevation of natriuretic peptides[12]

Roche NT-proBNP is an objective tool to assess risk of events before discharge from hospital

Changes in Roche NT-proBNP levels reflect HF prognosis can help with discharge planning

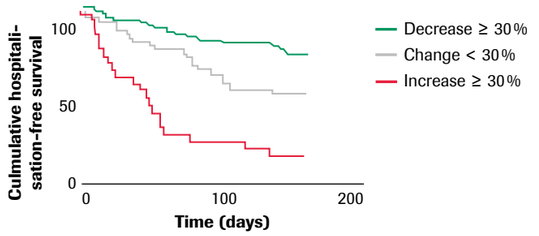
Measuring natriuretic peptides during the hospital stay can help with discharge planning: Patients whose natriuretic peptide concentrations fall during admission have lower cardiovascular mortality and readmission rates at 6 months.[12]

Studies demonstrated that **pre-discharge Roche NT-proBNP** absolute value and **relative changes in Roche NT-proBNP** levels during hospitalization provide **important prognostic** information and can help to **identify patients at risk** of hospital readmission or death at 6 months.[24-26]

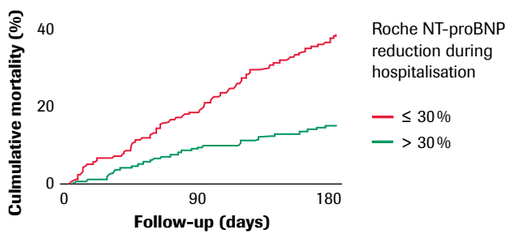
Role of relative changes in Roche NT-proBNP levels to predict risk for hospital readmission and mortality

A **lack of significant decrease** in **Roche NT-proBNP levels (≥ 30 %)** during hospitalization identifies patients with **high risk** of hospital readmission.[24]

Patients who didn't achieve significant reduction in Roche NT-proBNP level during hospitalization (> 30 %), have 2 times higher mortality rates at 6 months than those who did achieve it.[25]



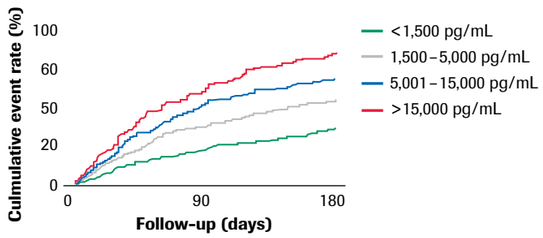
Cumulative hospitalization-free survival according to patterns of response of Roche NT-proBNP [24]



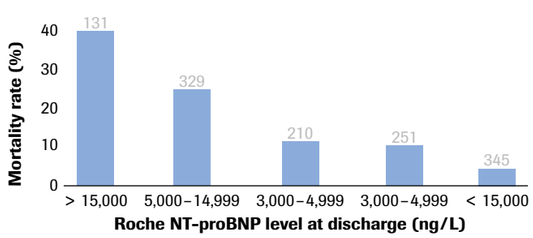
Kaplan–Meier curves for all-cause mortality at 6 months according to the dichotomised Roche NT-proBNP percentage reduction during hospitalization [25]

Role of absolute value of NT-proBNP at discharge to predict risk for hospital readmission and mortality

Patients **with higher levels of Roche NT-proBNP** at discharge have **higher risk** of event, including hospital readmission and mortality in the following 6 months.[25-26]



Kaplan–Meier curves for composite endpoint (all-cause mortality/cardio-vascular readmissions) at 6 months according to the quartiles of the absolute Roche NT-proBNP values at discharge[25]



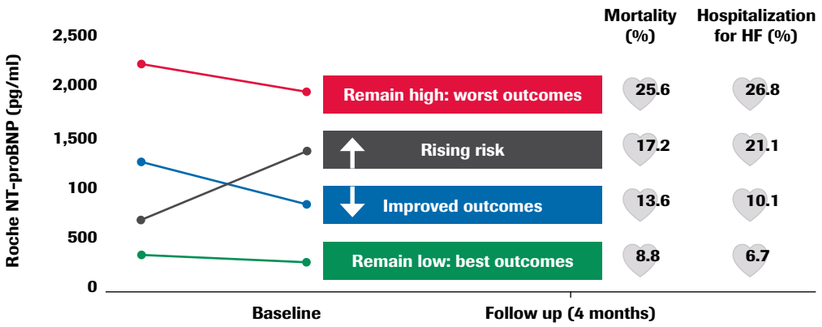
Mortality rates at 6 months in patients admitted for acute decompesated heart failure discharged with different absolute Roche NT-proBNP levels[26]

Roche NT-proBNP is a powerful prognosticator of outcomes regardless of the therapy

Changes in levels give an objective insight into patients' disease progression

Why monitoring natriuretic peptides over the course of HF?

- Prescribing inertia is common and could be reduced by biomarker like Roche NT-proBNP, which helps to identify that although the patient appears symptomatically to be 'doing quite well' their underlying disease is not yet under control [11]
- High circulating natriuretic peptides predict unfavorable outcomes in patients with HF, and a decrease in natriuretic peptides levels during recovery from circulatory decompensation is associated with a better prognosis [12-13]



Trend in Roche NT-proBNP concentration gives important prognostic information (adapted from Masson et al. 2008 and Januzzi et al. 2012) [27,28]

NT-proBNP or BNP in the era of ARNi therapy: time for a choice

- BNP is not a suitable biomarker of heart failure in patients treated with sacubitril-valsartan because BNP is a neprilysin substrate [13,29-33]
- "NT-proBNP is the gold standard for a powerful prognostic biomarker, especially when employing pharmacological agent that inhibits the degradation of natriuretic peptides", such as ARNi therapy [33]

Roche NT-proBNP can help your clinical decision-making in heart failure at every stage of care, regardless of the therapy

- **In PARADIGM-HF, changes in Roche NT-proBNP over the course of HF provided important prognostic information and can help to identify patients at risk of hospitalization for HF and mortality** [27,28,32]
- **Elevated Roche NT-proBNP values are strongly predictive of adverse outcomes and rising values identify a rising risk** [32,35-36]
- **Significant lowering of Roche NT-proBNP is associated with better prognosis and better clinical outcomes** [32,34-37]

Roche NT-proBNP

With over 15 years of evidence generation and proven clinical use, you can trust Roche NT-proBNP to support your clinical decision at every stage of care in heart failure [14-15]

- Roche NT-proBNP has clinically validated cutoffs for the diagnosis of heart failure to support clinical interpretation [16-21]
- Roche NT-proBNP has clinically validated interpretation for in-hospital care [24-26]
- Roche NT-proBNP is the only clinically tested NT-proBNP assay in the era of ARNi to support your clinical decision making [32]

How to use and interpret Roche NT-proBNP in your day-to-day practice?

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Patient Case 1

Diagnosis of Heart Failure in non-acute onset

71-year old woman

Medical history: Obesity (BMI: 35 kg / m²), hypertension, diabetes mellitus type 2, hypercholesterolemia, chronic kidney disease (stage II), and chronic anemia.

Current treatment: Losartan 100 mg od, Amlodipine 5 mg bid, Metformin 850 mg bid, Simvastatin 10 mg od, Oral iron supplements.

Key symptoms: She was referred to Cardiology Clinics because of exertional dyspnoea for the last 6 months and nocturnal cough.

Clinical examination: Central obesity. Bilateral rales, ankle swelling, jugular vein congested and hepatomegaly. No fever. No previous history of chest pain.

ECG (Fig 1.1); Chest X-ray (Fig 1.2)

Laboratory test results: Serum Creatinine: 1.6 mg / dL; Urea: 105 mg / dL; GFR: 40 mL / min / 1.73; Sodium: 134 mmol / L; Potassium: 3.8 mmol / L; Haemoglobin: 10.9 g / dL. NT-proBNP: 2,800 pg / mL.

Echocardiogram: Non dilated and moderately hypertrophic left ventricle (14 / 13 mm) with normal systolic function (EF: 59 %). Left atrium moderately dilated (35 mL / m²). Mild mitral regurgitation. Mild pulmonary hypertension (estimated PASP: 37 mmHg). Diastolic dysfunction type I.

Diagnosis: Heart failure with preserved ejection fraction (HFpEF) due to hypertensive heart disease.

According to current ESC HF Guidelines the diagnosis of heart failure should be suspected based on clinical history, physical examination or any abnormality in the ECG. Our patient presents typical signs and symptoms such as breathlessness, ankle swelling and elevated jugular venous pressure.

High levels of natriuretic peptides (NT-proBNP > 125 pg / mL), LVEF ≥ 50 % and suggestive findings on the echocardiogram are required for the diagnosis of HFpEF.

Our patient presented high NT-proBNP levels, concentric left ventricular hypertrophy, dilated left atrium, and diastolic dysfunction. The most probable etiology in this case taking into account the clinical history and findings in the echocardiogram is hypertensive heart disease.

Conclusion: It is a patient with HFpEF. High NT-proBNP concentrations are essential for diagnosis.

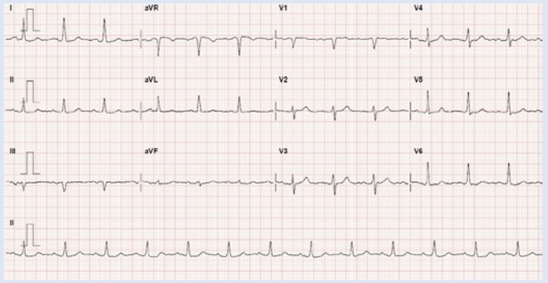


Fig 1.1

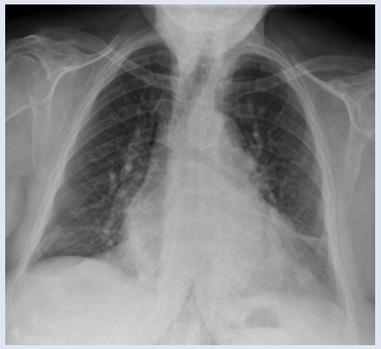


Fig 1.2

Patient Case 2

Diagnosis of Heart Failure in acute onset

43-year old woman

Medical history: Hypertension with no treatment. Metastatic right breast cancer diagnosed 4 years ago, treated with mastectomy, radiotherapy and several chemotherapy treatments including anthracyclines. Currently stable oncologic disease.

Current treatment: Everolimus

Key signs and symptoms: She arrived to the emergency room due to cough for the last 3 days; and in the last 24 h orthopnea with important shortness of breath.

Clinical examination: Tachycardia and tachypnoea, crepitations in both lung bases, no peripheral oedema.

Laboratory test results: CRP: 35 mg / dL; Leukocytes: 13.2 / nL; Serum Creatinine: 1.3 mg / dL; Urea: 85 mg / dL; GFR: 59 mL / min / 1.73; Sodium: 133 mmol / L; Potassium: 4.3 mmol / L; NT-proBNP: 13,200 pg / mL.

ECG (Fig 2.1); Chest X-ray (Fig 2.2)

Echocardiogram: Dilated left ventricle with severe reduction in systolic function (EF: 25 %) due to global hypokinesia. Moderate left atrium dilatation (37 mL / m²). Moderate mitral regurgitation (II / IV). Normal right ventricle. Estimated PASP: 55 mmHg.

Diagnosis: Acute pulmonary edema in a patient with dilated cardiomyopathy secondary to anthracyclines

Initially, this case was diagnosed as bilateral pneumonia in the emergency room, and antibiotic treatment was started. However, the blood test showed very high levels of NT-proBNP and an urgent echocardiogram was performed. The echocardiogram showed a dilated cardiomyopathy with severe ventricular dysfunction.

After support with non-invasive mechanical ventilation and treatment with i.v. furosemide there was clinical improvement and she was admitted to the cardiology ward to complete the study.

Conclusion: The main role of NT-proBNP in the emergency department is to rule out heart failure diagnosis due to its high negative predictive value. However, raised NT-proBNP are indicative of acute decompensated heart failure in patients with dyspnoea, mainly those with very high levels and suggestive symptoms.

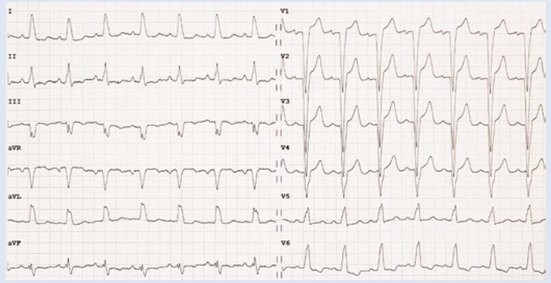


Fig 2.1

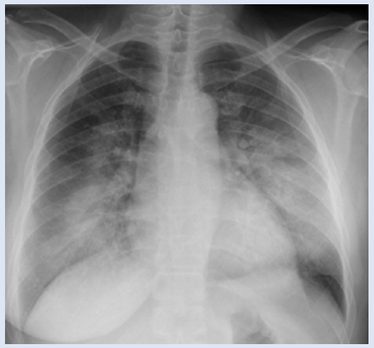


Fig 2.2

Patient Case 3

Heart failure and hospital discharge planning

68-year old man

Medical history: Hypercholesterolemia. TIA in 2011 treated with acenocoumarol. Arrhythmogenic dysplasia with mild-moderate biventricular dysfunction was diagnosed in 2010.

Key signs and symptoms: He was admitted in the cardiology ward because of decompensated heart failure. He did not present syncope or palpitations**.**

Clinical examination: Slight bibasal pulmonary crackles, peripheral oedema, elevated jugular venous pressure, hepatomegaly, and weight gain of 6 kg in 2 weeks.

Laboratory test results (admission): Serum Creatinine: 1.5 mg / dL; Urea; 80 mg / dL; GFR: 45 mL / min / 1.73; Sodium: 132 mmol / L; Potassium: 4 mmol / L; Ferritin: 98; TSat: 11 %; NT-proBNP: 6,800 pg / mL.

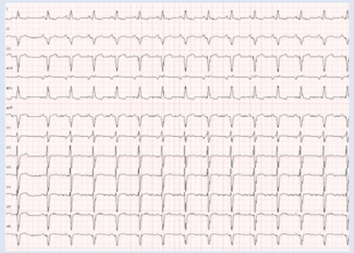
ECG (Fig 3.1); Cardiac MRI (Fig 3.2); NT-proBNP levels (Fig 3.3)

In-hospital evolution: Hospitalization due to acute decompensated heart failure. During admission, he presented a good response to diuretic treatment, medical treatment was adjusted and intravenous iron was administered. Several non-sustained ventricular tachycardia was registered and cardiac MRI showed severely reduced biventricular function. An ICD was implanted.

At the time of assessing discharge, there were still elevated levels of NT-proBNP, but there was a significant reduction (> 30 %) compared to admission blood test. (NT-proBNP at discharge was 1,900 pg / mL).

Conclusion: The NT-proBNP reduction compared to admission values supports the decision of hospital discharge.

A significant reduction (higher than 30 %) is associated with lower re-admission due to heart failure decompensation.



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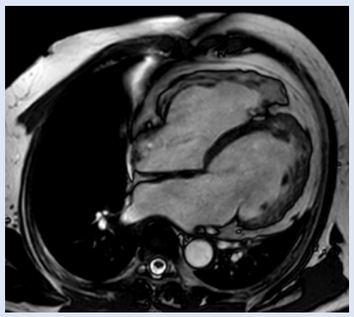

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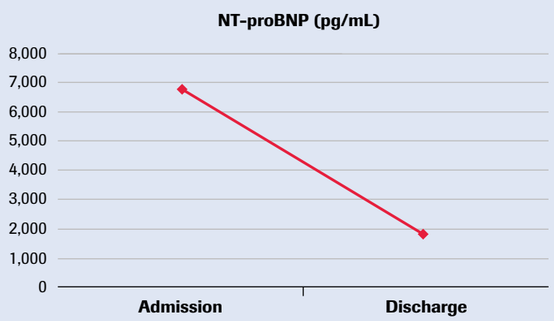


Fig 3.3

Patient Case 4

Heart failure monitoring in the chronic phase

58-year old man

Medical history: 16 years ago left ventricular non-compaction cardiomyopathy was diagnosed. Initial EF was 36 % and coronary angiography showed no coronary lesions. An ICD was implanted after presenting syncope. He is followed in the Heart Failure Clinic. After optimizing medical treatment, LVEF improved and he was in NYHA functional class I.

Key signs and symptoms: In last visit he reported dyspnoea on exertion and functional class II-III. However he did not present orthopnea, paroxysmal nocturnal dyspnoea, ankle swelling or weight gain.

Clinical examination: Mild mitral systolic murmur, normal respiratory auscultation, no oedema, or elevated jugular venous pressure.

Laboratory test results: Serum Creatinine: 1.1 mg / dL; Urea: 80 mg / dL; GFR: 90 mL / min / 1.73; Sodium: 137 mmol / L; Potassium: 4.1 mmol / L; NT-proBNP: 800 pg / mL.

ECG (Fig 4.1); Echocardiogram (Fig 4.2); NTproBNP and LVEF evolution (Fig 4.3)

Diagnosis: Drop in LVEF in patient with left ventricular non-compaction cardiomyopathy. A slow rise in NT-proBNP levels is common in patients with heart failure, which supports the fact that complete stability in heart failure does not exist. A worsening of the NYHA functional class without presenting signs of decompensation with an increase in NT-proBNP levels relative to previous levels may indicate a worsening of LVEF or progression of mitral regurgitation. Our patient presented a progression of functional class with no signs of congestion, however there was an important increase in NT-proBNP levels compared to previous. A new echocardiogram showed a drop in LVEF, from 40 % to 29 %.

Conclusion: The monitoring of NT-proBNP levels in chronic heart failure provides a very useful information for the follow up. We can compare NT-proBNP with previous values for the diagnosis of acute decompensations and it may provide information to detect worsening in LVEF or valvular disease, or ischemia.

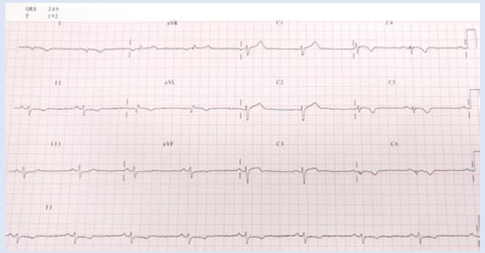
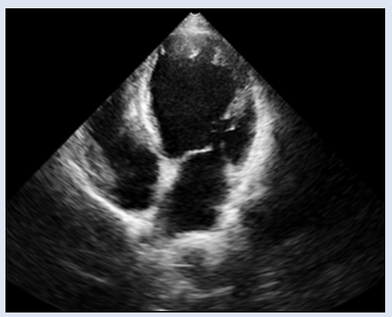


Fig 4.1



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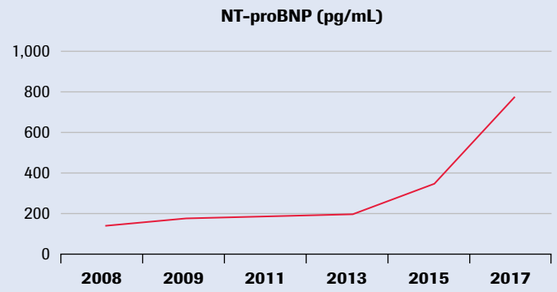

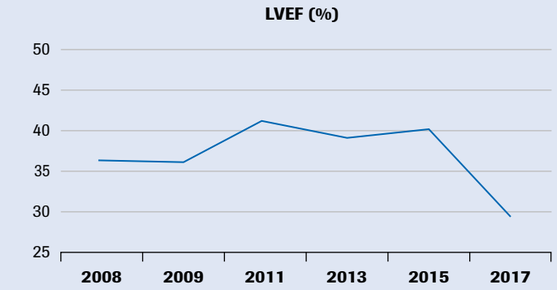

Fig 4.3

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