Original article

Rapid Point-of-Care NT-proBNP Optimal Cut-off Point for Heart Failure Diagnosis in Primary Care

José M. Verdú, Josep Comín-Colet, Mar Domingo, Josep Lupón, Miguel Gómez, Luis Molina, Jose M. Casacuberta, Miguel A. Muñoz, Amparo Mena, and Jordi Bruguera-Cortada

Abstract

Introduction and objectives: Measurement of natriuretic peptides may be recommended prior to echocardiography in patients with suspected heart failure. Cut-off point for heart failure diagnosis in primary care is not well established. We aimed to assess the optimal diagnostic cut-off value of N-terminal pro-B-type natriuretic peptide on a community population attended in primary care.

Methods: Prospective diagnostic accuracy study of a rapid point-of-care N-terminal pro-B-type natriuretic peptide test in a primary healthcare centre. Consecutive patients referred by their general practitioners to echocardiography due to suspected heart failure were included. Clinical history and physical examination based on Framingham criteria, electrocardiogram, chest X-ray, N-terminal pro-B-type natriuretic peptide measurement and echocardiogram were performed. Heart failure diagnosis was made by a cardiologist blinded to N-terminal pro-B-type natriuretic peptide value, using the European Society of Cardiology diagnosis criteria (clinical and echocardiographic data).

Results: Of 220 patients evaluated (65.5% women; median 74 years [interquartile range 67-81]). Heart failure diagnosis was confirmed in 52 patients (23.6%), 16 (30.8%) with left ventricular ejection fraction <50% (39.6 [5.1%]). Median values of N-terminal pro-B-type natriuretic peptide were 715 pg/mL [interquartile range 510.5-1575] and 77.5 pg/mL [interquartile range 58-179.75] for patients with and without heart failure respectively. The best cut-off point was 280 pg/mL, with a receiver operating characteristic curve of 0.94 (95% confidence interval, 0.91-0.97). Six patients with heart failure diagnosis (11.5%) had N-terminal pro-B-type natriuretic peptide values <400 pg/mL. Measurement of natriuretic peptides would avoid 67% of requested echocardiograms.

Conclusions: In a community population attended in primary care, the best cut-off point of N-terminal pro-B-type natriuretic peptide to rule out heart failure was 280 pg/mL. N-terminal pro-B-type natriuretic peptide measurement improve work-out diagnosys and could be cost-effectiveness.

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Resultados: Se evaluó a 220 pacientes (el 65,5% mujeres) con una mediana [intervalo intercuartílico] de edad de 74 [67-81] años. El diagnóstico de insuficiencia cardíaca se confirmó en 52 (23,6%), 16 con fracción de eyeción del ventrículo izquierdo < 50% (39,6 ± 5,1%). Los valores de fracción N-terminal del péptido natriurético tipo B fueron 715 [510,5-1,575] y 77.5 [58-179,75] pg/ml para pacientes con y sin insuficiencia cardíaca respectivamente. El mejor punto de corte fue 280 pg/ml, con un área bajo la curva receiver operating characteristic de 0,94 (intervalo de confianza del 95%, 0,91-0,97). Seis pacientes diagnosticados de insuficiencia cardíaca (11,5%) tuvieron valores de fracción N-terminal del péptido natriurético tipo B < 400 pg/ml. La incorporación de los péptidos habría evitado el 67% de los ecoscardiogramas solicitados.

Conclusions: En una población ambulatoria atendida en atención primaria, el mejor punto de corte de fracción N-terminal del péptido natriurético tipo B para descartar insuficiencia cardíaca fue 280 pg/ml. La determinación de fracción N-terminal del péptido natriurético tipo B mejora los procesos diagnósticos y podría ser coste-efectiva.

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Abbreviations

ECG: electrocardiogram 
HF: heart failure 
LVEF: left ventricular ejection fraction 
NT-proBNP: N-terminal pro-B-type natriuretic peptide 
ROC: receiver operating characteristic

INTRODUCTION

The prevalence of heart failure (HF) and its associated morbidity and mortality has increased exponentially over recent decades. A prompt diagnosis considerably improves the prognosis of HF, but it can be difficult to establish in disease stages showing few symptoms, in which clinical criteria have little specificity. Diagnostic errors are common when the evaluation is based solely on the patient’s signs and symptoms, and in primary care HF is erroneously diagnosed in up to 40% of cases. Furthermore, the initial diagnosis is only confirmed by echocardiography in one third of patients, and more than half the diagnoses of HF are made without evidence of ventricular dysfunction. The most widely used additional objective examination to investigate ventricular function in primary care is Doppler echocardiography. Nonetheless, this valuable test is not accessible to all physicians in our setting and it is often performed after a considerable delay, which further contributes to delaying the final assessment of the clinical picture.

Thus, it is evident that other elements are needed to optimize the diagnostic algorithm of HF, which is based on an appropriate clinical history and physical examination, analyses to rule out triggering factors, and an electrocardiogram (ECG), and thereby to improve the efficiency of echocardiographic study in primary care. Currently, a fast, simple test is available to facilitate the clinical evaluation: determination of natriuretic peptides (B-type natriuretic peptide [BNP] and its N-terminal fraction [NT-proBNP]) in venous blood or urine. These biomarkers enable selection of patients who should undergo a confirmatory echocardiography study and allow reasonable exclusion of the initial suspected HF diagnosis in others.

Natriuretic peptides are hormones with diuretic and vasodilator effects, mainly secreted in the left ventricle as a mechanism to compensate for pressure overload. Concentrations of this biomarker are increased in patients with HF and in other structural heart diseases such as valve disease and atrial fibrillation. Age, deteriorated renal function, and certain conditions such as chronic obstructive lung disease are other causes of elevated natriuretic peptide concentrations. In contrast, treatment with diuretics, beta blockers, and inhibitors of the renin-angiotensin-aldosterone axis decrease the plasma concentrations of these substances.

The cut-off points used to rule out HF have been clearly established in emergency rooms and specialized centers, where natriuretic peptides have shown proven value for screening and diagnosing patients with suspected HF because of their high sensitivity and excellent negative predictive value. Furthermore, the prognostic utility of urinary peptide has been compared to that of plasma determination in patients with acute HF. Nonetheless, there is little available data on the usefulness of natriuretic peptides in primary care in Spain. Few studies have assessed the added value of peptides in diagnosing patients with suspected systolic HF or preserved left ventricular ejection fraction (LVEF) in this setting, despite the fact that the test can be carried out in the physician’s consulting room and the results obtained in less than 15 min. In addition to being advantageous from the diagnostic viewpoint, this biomarker would be cost-effective: unnecessary echocardiography requests could be avoided, thereby reducing cost and delays.

The aim of this study was to evaluate the diagnostic utility of a rapid point-of-care test for plasma NT-proBNP determination as a screening element for detecting systolic or diastolic HF in an ambulatory population seen in primary care, to characterize the optimal cut-off point that will enable reasonable exclusion of HF while significantly increasing the post-test probability of having HF according to the sensitivity, specificity and predictive values for detecting ventricular dysfunction, and to assess the cost effectiveness of this test.

METHODS

Study Design and Population

This is an observational, analytical study evaluating a diagnostic test, performed in two primary care centers in the city of Barcelona. The centers are staffed by 28 general practitioners and have a catchment population of 40 000 inhabitants.

All consecutive patients in whom echocardiography was requested by a primary care physician to investigate suspected HF were invited to participate, regardless of their comorbidities or current medical treatment. All the participating general practitioners received information about the study and specific training in the criteria and diagnostic algorithms used in HF. Eight general practitioners did not request any echocardiographic examination during the study period.

We excluded patients with a previous diagnosis of HF or severe valve disease in the digitized clinical history, those included in a home care program, and those who did not give their consent to participate in the study.
Objective

test
based
on
care
results.
data
repolarization
normal
variation
istics,
N-terminal
echocardiography
referred
X-ray,
criteria
heparinized
examination
procedures
the
cardiologist.
HF
initial
visit,
patients
measured
the
lateral
mitral
ring
(Sa,
Ea,
and
Aa
waves,
E/E
ratio,
deceleration
time,
E/E'
ratio).
The
LVEF
was
measured
in
all
patients,
and
systolic
ventricular
dysfunction
was
declared
as
LVEF<50%. HF
with
preserved
LVEF
was
defined
based
on
normal
or
slightly
abnormal
(≥50%)
LVEF
findings
with
evidence
of
diastolic
dysfunction,
defined
as
abnormal
left
ventricular
relaxation
or
diastolic
rigidity,
according
to
the
diagnostic
decision
proposed
in
the
consensus
statement
of
the
Heart
Failure
and
Echocardiography
Associations
of
the
ESC.12
The
study
met
the
requisites
set
down
in
the
Declaration
of
Helsinki
and
all
patients
gave
written
consent
for
participation.

Statistical Analysis

Categorical
values
are
described
as
percentages
and
continuous
variables
as
the
mean
(standard
deviation)
or
median
[interquartile
range],
depending
on
whether
or
not
distribution
was
normal
(analyzed
with
the
Kolmogorov-Smirnov
test).
Differences
between
the
study
groups
were
analyzed
with
the
chi-
square
test
for
categorical
variables
and
with
the
Student
\( t \)
test
or
Mann-Whitney
\( U \)
test
for
quantitative
variables.
The
sensitivity,
specificity,
predictive
values,
likelihood
ratios
and
ROC
curves
were
calculated
using
the
diagnosis
of
HF
established
by
the
cardiologist
blinded
to
NT-proBNP
results
as
the
reference
standard.
To
determine
which
variables
were
independently
associated
with
NT-proBNP
concentrations,
multivariate
linear
regression
analysis
was
performed
(enter
method)
with
NT-
proBNP
as
the
dependent
variable
and
age,
sex,
ECG,
body
mass
index,
glomerular
filtration
rate,
HF
diagnosis
and
treatment
with
renin-angiotensin-aldosterone
inhibitors,
beta
blockers,
and
loop
diuretics.
SPSS
12.0
software
was
used
for
the
data
analysis.

Comparison With Other Cut-off Points

We
compared
the
cut-off
considered
to
be
optimal
in
our
study
with
other
cut-off
points
commonly
used
in
the
literature,
from
the
guidelines
of
the
ESC13
and
the
National
Institute
for
Health
and
Clinical
Excellence
[NICE]14;
the
cut-off
recommended
by
the
manufacturer
(greater
agreement
in
ambulatory
patients)15;
and
the
triple
cut-off
described
by
Hildebrandt
et
al.16
to
detect
systolic
ventricular
dysfunction
in
primary
care.
To
this
end,
the
sensitivity,
specificity,
and
predictive
values
of
these
proposed
NT-proBNP
cut-offs
were
determined
in
our
population.

RESULTS

The
enrollment
period
was
January
2007
to
June
2009.
A
total
of
221
patients
were
contacted
by
telephone
and
only
1
patient
decided
to
participate.
All
patients
included
went
to
the
initial
visit,
at
which
time
ECG
and
chest
X-ray
were
performed
in
those
who
had
not
undergone
these
studies,
and
echocardiography
was
performed.
Thus,
the
study
included
220
patients
(65.5%
women),
with
a
median
age
of
74
[67–81]
years.
The
demographic,
clinical,
and
treatment-related
values
are
depicted
in
Table
1,
which
shows
a
predominance
of
elderly
persons,
women,
and
patients
with
hypertension.
The
initial
suspected
diagnosis
of
HF
was
confirmed
in
52
patients
(23.6%),
among
whom
16
(30.8%)
had
systolic
ventricular
dysfunction
with
a
mean
LVEF
of
39.6
(5.1)%
and
ventricular
systolic
function
parameters
(fractional
shortening
and
LVEF
calculated
by
the
modified
Simpson
method)
through
the
apical
4-chamber
view,
and
left
ventricular
diastolic
function
parameters
by
the
left
ventricular
filling
curve
and
tissue
Doppler
measured
in
the
lateral
mitral
ring
(Sa,
Ea,
and
Aa
waves,
E/E
ratio,
deceleration
time,
E/E'
ratio).

The
LVEF
was
measured
in
all
patients,
and
systolic
ventricular
dysfunction
was
declared
as
LVEF<50%. HF
with
preserved
LVEF
was
defined
based
on
normal
or
slightly
abnormal
(≥50%)
LVEF
findings
with
evidence
of
diastolic
dysfunction,
defined
as
abnormal
left
ventricular
relaxation
or
diastolic
rigidity,
Table 1
Demographic Characteristics, and Clinical and Treatment Data

<table>
<thead>
<tr>
<th>Total (n=220)</th>
<th>Final diagnosis HF (n=52)</th>
<th>Final diagnosis no HF (n=168)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>73.2±19.2</td>
<td>76.5±10.3</td>
<td>72.2±9.9</td>
<td>.005</td>
</tr>
<tr>
<td>74 (67-81)</td>
<td>79 [71-83.75]</td>
<td>74 [66-80]</td>
<td></td>
</tr>
<tr>
<td><strong>Sex, female</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>144 (65.5)</td>
<td>26 (50)</td>
<td>118 (70.2)</td>
<td>.007</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30.4±4.9</td>
<td>29.6±5.3</td>
<td>30.2±4.8</td>
<td>.188</td>
</tr>
<tr>
<td><strong>Glomerular filtrate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 mL/min</td>
<td>168 (76.4)</td>
<td>30 (57.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>30-60 mL/min</td>
<td>52 (23.6)</td>
<td>22 (42.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Functional class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>24 (10.9)</td>
<td>2 (3.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>II</td>
<td>190 (86.4)</td>
<td>44 (84.6)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>6 (2.7)</td>
<td>6 (11.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>26 (11.8)</td>
<td>8 (4.8)</td>
<td>.362</td>
</tr>
<tr>
<td>IHD</td>
<td>38 (19.3)</td>
<td>14 (20.9)</td>
<td>.035</td>
</tr>
<tr>
<td>Hypertension</td>
<td>190 (85.6)</td>
<td>48 (92.3)</td>
<td>.152</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>80 (36.4)</td>
<td>18 (34.6)</td>
<td>.764</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40 (18.2)</td>
<td>10 (19.2)</td>
<td>.822</td>
</tr>
<tr>
<td>COPD</td>
<td>26 (11.8)</td>
<td>8 (15.3)</td>
<td>.362</td>
</tr>
<tr>
<td>CA due to AF</td>
<td>38 (19.3)</td>
<td>32 (61.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Obesity (BMI&gt;30)</td>
<td>107 (48.6)</td>
<td>21 (40.4)</td>
<td>.173</td>
</tr>
<tr>
<td>Smoker or ex-smoker</td>
<td>62 (28.2)</td>
<td>22 (42.3)</td>
<td>.010</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors or ARB</td>
<td>134 (61.5)</td>
<td>38 (73.1)</td>
<td>.049</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>54 (24.5)</td>
<td>20 (38.5)</td>
<td>.008</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>60 (27.3)</td>
<td>28 (53.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thiazide</td>
<td>60 (27.3)</td>
<td>14 (26.9)</td>
<td>.948</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>6 (2.7)</td>
<td>2 (3.8)</td>
<td>.571</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12 (5.4)</td>
<td>10 (19.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Normal ECG</td>
<td>86 (39.1)</td>
<td>2 (3.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; CA due to AF, complete arrhythmia caused by atrial fibrillation; COPD, chronic obstructive pulmonary disease; HF, heart failure; IHD, ischemic heart disease.

The data express no. (%), median [interquartile range], or mean±standard deviation.

36 (69.2%) had LVEF>50%, meeting the echocardiographic criteria of HF with preserved LVEF. No patient without HF had depressed LVEF. Patients with a final diagnosis of HF showed relatively few symptoms, were of advanced age, and had high comorbidity (an elevated number had a history of hypertension, atrial fibrillation, renal failure, and obesity). Only 2 patients had a strictly normal ECG (both had positive Framingham criteria), and more than three fourths of patients were already receiving diuretic treatment (Table 1).

Median NT-proBNP concentration was 715 [510.5-1575] (290-3000) pg/mL in patients with a diagnosis of HF and 77.5 [58-179.75] (32-1741) pg/mL in those in whom the HF diagnosis was not confirmed.

The ROC curve obtained for the diagnosis of HF was 0.94 (95% confidence interval [95%CI] 0.91-0.97) (Figure). The optimal cut-off point of NT-proBNP to rule out HF was 280 pg/mL. None of the patients with a diagnosis of HF presented values lower than this figure, even though many of them were receiving specific treatment (73.1% angiotensin converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARB], 38.5% beta blockers, and 53.9% loop diuretics).

Twenty patients who had NT-proBNP concentrations>280 pg/mL did not receive a diagnosis of HF.

In our series, NT-proBNP values were significantly higher in men, patients older than 75 years, those with a glomerular filtration rate<60 mL/min, those with abnormal ECG findings, and patients receiving ACE inhibitors or ARB, with beta blockers and with diuretics (Table 2). On multivariate analysis, HF (P<.001), body mass index (P=.039) and glomerular filtration (P<.001) retained statistical significance.

Our cut-off point differs from the values recommended in various clinical practice guidelines (400 pg/mL) and the manufacturer's recommendations (125 pg/mL). Hence, we compared our results with those obtained after applying these NT-proBNP cut-offs to our population. The sensitivity, specificity, and predictive values of our cut-off and the others tested in the individuals in our study are shown in Table 3. In patients with a diagnosis of HF, 6 cases (11.5%) had NT-proBNP values<400 pg/mL (all with atrial fibrillation, receiving ACE inhibitors treatment, and in functional class II) and 57 of those without a diagnosis of HF had NT-proBNP values of >125 pg/mL.

Lastly, incorporation of natriuretic peptides in the diagnostic algorithm of HF led to improvements in the diagnosis (in patients with NT-proBNP>280 pg/mL, the probability of having HF increased from 23.6% pre-test to more than 72% post-test; positive probability of 8.33) and to more efficient use of additional testing. Echocardiographic study would only have been necessary in 72 patients with NT-proBNP>280 pg/mL vs the 220 initial requests, which represents a saving of 67% of the echocardiograms performed.
DISCUSSION

This study shows that HF detection in primary care is difficult and complex, involving a high percentage of suspected cases that are ultimately not confirmed. The percentage of patients who received a final diagnosis of HF (23.6%) in our study is somewhat lower than the rates reported elsewhere in this setting, such as the 25% described by Wright et al.\textsuperscript{17} and the 34% reported by Zaphiriu et al.\textsuperscript{18} Our results are a reflection of the activity in daily clinical practice in primary care, and the diagnosis of HF was made through confirmation by a cardiologist following assessment of the patients’ symptoms and the additional tests performed.

The median NT-proBNP concentrations in patients with and without HF in our study were 715 [510.5-1575] and 77.5 [58-179.75] pg/mL, respectively. These values differ from those reported by Zaphiriu et al.,\textsuperscript{11} who described a median of 1537 [166-21,854] pg/mL in patients with HF and 202 [22-2323] pg/mL in those without HF, and the reported results of Wright et al.,\textsuperscript{17} with medians of 1300 (1450) and 277 (304.5) pg/mL, respectively. We believe that these disparate results are related to differences in the study designs and the populations included.

It is beyond question that a rapid method for NT-proBNP determination to exclude the diagnosis of HF in the physician’s consulting room in 12 min is highly useful. In our study, carried out in an ambulatory population seen in primary care, the best NT-proBNP cut-off value to rule out HF was 280 pg/mL (sensitivity, 1; specificity, 0.88; positive predictive value, 0.72; negative predictive value, 1), with an area under the ROC curve of 0.94 [0.91-0.97]. This performance is even better than the results obtained in studies directed toward diagnosing systolic HF alone in ambulatory populations, such as the reports by Fuat et al.\textsuperscript{19} and Gustafsson et al.,\textsuperscript{20} with cut-off points for excluding HF of 150 pg/mL (sensitivity, 0.94; specificity, 0.40; positive predictive value, 0.48; negative predictive value, 0.92) and 125 pg/mL (sensitivity, 0.97; specificity, 0.46; positive predictive value, 0.15; negative

Table 2

<table>
<thead>
<tr>
<th>N-terminal Pro-B-type Natriuretic Peptide Concentrations and Clinical Variables</th>
<th>Total (n=220)</th>
<th>Final diagnosis HF (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT-proBNP, pg/mL</td>
<td></td>
</tr>
<tr>
<td><strong>HF</strong></td>
<td>715 (510.50-1575.25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>No HF</strong></td>
<td>77.5 (58-179.75)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤75 years</td>
<td>68 (58-294.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>216.5 (89.50-688)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>266.5 (62.25-760.25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Women</td>
<td>92.5 (59-267.50)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>126 (59.50-668)</td>
<td>.262</td>
</tr>
<tr>
<td>≥30</td>
<td>114 (59-317)</td>
<td></td>
</tr>
<tr>
<td><strong>Glomerular filtration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 mL/min</td>
<td>87 (58.25-225.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;60 mL/min</td>
<td>599.5 (183.25-1292.75)</td>
<td></td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>198 (73.75-588.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>68.5 (58-183.75)</td>
<td></td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>201 (65.75-338)</td>
<td>.021</td>
</tr>
<tr>
<td>No</td>
<td>98.5 (59-302.25)</td>
<td></td>
</tr>
<tr>
<td><strong>Loop diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>495.5 (125-760.25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>88.5 (58.25-225.50)</td>
<td></td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>70 (58-155)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abnormal</td>
<td>227.5 (68.25-738)</td>
<td></td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; BMI, body mass index; ECG, electrocardiogram; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
predictive value 0.99) and areas under the ROC curve of 0.81 and 0.87, respectively. Our study required the consensus echocardiographic criteria of diastolic dysfunction published in 2007, which were not applied in previous studies. If we had not used these criteria, the area under the ROC curve would have been 0.79 and the optimal cut-off would have been lower, close to 100 pg/mL, and very similar to that reported in the primary care studies. NT-proBNP determination has proven to be useful and accurate for ruling out the diagnosis of systolic HF, and some authors have even proposed different cut-off points depending on the age of the patient.\textsuperscript{8,16} It was not our aim to seek cut-offs according to age, but instead to find a rapid point-of-care determination that would reasonably exclude the need for additional tests, regardless of the patient’s characteristics. In any case, none of the patients diagnosed with HF presented values below 280 pg/mL independently of their age.

If we had applied other NT-proBNP cut-off points to our population, such as the 400 pg/mL recommended in the ESC and the latest NICE consensus guidelines, 11.5% of final HF diagnoses would have been excluded (false negatives); hence, we believe that the NT-proBNP value to rule out HF should be lower. If, however, we had used the most widely agreed upon cut-off for ambulatory patients (125 pg/mL), there would have been 57 false-positive results instead of the 20 false positives in our study; that is, the false-positive rate would have almost tripled and the negative predictive value would not have changed.

Lastly, the use of natriuretic peptide analysis as a screening element prior to echocardiography in patients with suspected HF attended in primary care can provide support for the initial suspected diagnosis (in our study the pre-test probability of HF was <25% and the post-test probability was close to 75%) and will optimize the decision-making process, by improving accessibility to echocardiography and reducing health costs. In our case, use of the NT-proBNP cut-off of 280 pg/mL to exclude the diagnosis of HF would have avoided 67% of echocardiographic studies. Taking into consideration that the mean cost of an NT-proBNP determination is less than half of the cost of an echocardiogram, we believe that this would be a cost-effective measure that would establish the diagnosis faster. Nonetheless, based on our study, we can only propose this as a hypothesis; further studies designed for this purpose are needed to confirm this idea. Other authors, such as Wright et al.,\textsuperscript{17} have reported improvements in ambulatory diagnosis of HF by incorporation of natriuretic peptides in the decision algorithm (a 21% diagnostic improvement vs 8% in the group without peptide analysis). Fuat et al.\textsuperscript{18} avoided 25% of referrals for additional testing, Goode et al.\textsuperscript{21} avoided 38% of echocardiograms, and Aspromonte et al.\textsuperscript{22} reported a 31% saving. However, natriuretic peptide determination cannot replace echocardiography, which provides data on myocardial morphology and function in addition to confirming the clinically suspected diagnosis of HF.

### Limitations

The main limitation of this study is the fact that the sample could not be stratified by variables such as age, sex, weight, or renal function because of the small number of patients with a final diagnosis of HF. Although the results from recent studies seem to indicate that age would be the only clinically relevant factor for establishing different cut-off points, mainly in systolic HF,\textsuperscript{5,13} we did not find differences in NT-proBNP values according to age in patients diagnosed with HF. Second, the final diagnosis of HF was made by a single cardiologist and the decision was not made by consensus with other experts.

### CONCLUSIONS

The best NT-proBNP cut-off point to exclude HF in an ambulatory population attended in primary care is 280 pg/mL, which showed an area under the ROC curve of 0.94 (95% CI 0.91-0.97). Incorporation of natriuretic peptide determination in primary care improves the diagnostic algorithm of HF, selection of patients needing echocardiographic study, and optimization of healthcare resources, in a setting where a high percentage of initially suspected cases of HF are not confirmed due to difficulties in early stages of the diagnostic process. We believe that the cut-off value obtained and the method used are the most useful for our daily clinical practice.

### ACKNOWLEDGMENTS

The authors would like to thank Aurora Díaz, registered nurse in the Sant Martí de Provençals Primary Care Team, for her generous collaboration in this study.

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### CONFLICTS OF INTEREST

J.M. Verdú participated as a speaker in a congress and in a doctoral course sponsored by Roche Diagnostics. J.M. Verdú, M. Domingo and J. Lupón received honoraria from Roche Diagnostics for their participation in writing other manuscripts for a book.

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**Table 3**

Recommended Diagnostic Cut-off Points Applied to Our Population

<table>
<thead>
<tr>
<th>Group (cut-off point)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Positive probability</th>
<th>Negative probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study (280 pg/mL)</td>
<td>1</td>
<td>0.88</td>
<td>0.72</td>
<td>1</td>
<td>8.33</td>
<td>0</td>
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<tr>
<td>ESC guidelines 2008\textsuperscript{13}</td>
<td></td>
<td></td>
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<tr>
<td>NICE guidelines 2010\textsuperscript{14} (400 pg/mL)</td>
<td>0.88</td>
<td>0.90</td>
<td>0.73</td>
<td>0.96</td>
<td>8.80</td>
<td>0.13</td>
</tr>
<tr>
<td>Manufacturer’s recommendations (Europe) (125 pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;75 years (250 pg/mL)</td>
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</tr>
</tbody>
</table>

ESC, European Society of Cardiology; NICE, National Institute for Health and Clinical Excellence.
REFERENCES