Cost-effectiveness and budget impact analysis of natriuretic peptide testing in the diagnosis of chronic heart failure

Heart failure (HF) is a major reason for hospitalization and represents a huge cost for the Belgian national health care budget. The prognosis for patients with HF is poor, especially when the underlying problem can not be rectified. Uncertainty of diagnosis:

- due to the fact that symptoms of HF are difficult to interpret and
- diagnosis of HF relies on clinical judgement based on a combination of history, physical examination and appropriate investigations: chest X-ray, electrocardiography, echocardiography and blood analysis and delays in confirming diagnosis are major concerns for patients with HF. Inappropriate diagnosis at best leads to patients receiving medication that will not improve their condition but which may indeed harm them.

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Recent literature highlights the high negative predictive value of natriuretic peptides (NPs) in the diagnosis of HF which confirmed their potential value as a 'rule out test' - i.e. a low serum NP level in untreated patients makes HF an unlikely cause for the patient's presentation.

This article focuses on the scientific evidence on the accuracy of NP testing in the differential diagnosis and monitoring during therapy of chronic HF together with the diagnostic accuracy and at its cost-effectiveness as compared to clinical diagnosis.

Scope and primary objective

<table>
<thead>
<tr>
<th>Patients</th>
<th>Adults with dyspnoea and suspected chronic HF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Measurement of serum NPs (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NTproBNP]).</td>
</tr>
<tr>
<td>Comparator</td>
<td>There is no single unique diagnostic test for HF, and diagnosis relies on clinical judgement based on a combination of history, physical examination and appropriate investigations: thoracic echocardiography, electrocardiography and blood analysis.</td>
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<tr>
<td>Outcome</td>
<td>The clinical utility of NP in the differential diagnosis and monitoring of chronic HF together with the diagnostic accuracy and cost-effectiveness as compared to clinical diagnosis.</td>
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</table>
Chronic HF signs and symptoms

Chronic HF is a complex clinical syndrome of symptoms and signs that suggests impairment of the heart as a pump supporting physiological circulation. It is caused by structural or functional abnormalities of the heart.

The symptoms most commonly encountered are breathlessness, fatigue and swelling (fluid retention) in legs, ankles and feet.

Classification HF

The degree of exertion required to elicit symptoms such as breathlessness may be used to grade the severity of symptoms into one of four functional classes (NYHA classes, see Table 1). The functional class tends to deteriorate unevenly over time and the severity of symptoms does not necessarily equate with the severity of the underlying heart problem; mild symptoms may be found in patients with severe damage to the heart, and vice versa.

The common cause of HF is coronary artery disease - with many patients having suffered a myocardial infarction in the past. A history of hypertension is also common, as is atrial fibrillation.

Burden of disease and clinical need

The prevalence (‰/year) of chronic HF in Belgium is 10.6.

The yearly incidence of confirmed HF in the Belgian adult population was estimated to be 194 patients per 100,000 inhabitants.

At diagnosis, most of the patients were classified as NYHA III (50%), 27% as NYHA IV and 20% as NYHA II. Six months after the initial diagnosis, the mortality was 19% and after 12 months it was 26%.

Hence, it can be estimated that in Belgium yearly 15,643 new patients of HF are diagnosed. HF is fatal for more than one quarter of the patients in the first year after the diagnosis.

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**NP assay**

BNP is synthesized as a 108 amino acid pro-hormone. The peptide is named “brain” NP because it was originally isolated from porcine brain extracts, but its primary site of synthesis has been localized to the ventricular myocardium. Upon stretch of stress to the myocyte, the pro-hormone is released as one molecule and enzymatically cleaved in circulation to the 32 amino acid active hormone (BNP) and the inactive 76 amino acid N-terminal portion (NT-proBNP). BNP is quickly removed from circulation by binding to NPR-C receptor and by neutral endopeptidases.

In patients with HF, NPs are released by the heart into the bloodstream. The main stimuli for its secretion are changes in left ventricular wall stretch and volume overload. Its production causes dilatation of the blood vessels which reduces blood pressure and stimulates sodium and water excreti-

on. NP plasma concentrations are therefore raised in patients with HF, and generally the higher the concentration, the more severe the disease (See Table 2).

Table 3 and Table 4 show the findings of the meta-analysis on the diagnostic accuracy of BNP and NT-proBNP compared with the reference standard [NICE, 2010]

**Method**

A literature review was conducted to assess the clinical utility of BNP in the diagnosis and the monitoring of chronic HF. Also, health economic literature was reviewed in order to assess the value for money of the test. Searches were conducted using the PICO and run in the following databases:

- Cochrane Library (Systematic Reviews & Controlled Trials Register)
- NHS Centre for Reviews and Dissemination databases (DARE, HTA, NHS EED)
- Medline via Pubmed.

The clinical evidence was restricted to meta-analysis (MA) or systematic reviews (SRs).

From a health economic perspective, full economic evaluations (cost-effectiveness, cost-utility and cost-benefit analyses), cost-consequence analyses and comparative costing studies that addressed the economic question were included.

One primary cost-minimisation analysis was performed to translate the results found in literature to the Belgian context; from the perspective of the health care payer (Belgian Health Insurance reimbursement).

A model developed by the Belgian KCE draws on the studies from Mueller et al. (2004) and Craig et

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**Table 2: Cut-off values for serum NPs [NICE, 2010]**

<table>
<thead>
<tr>
<th>Level</th>
<th>BNP range</th>
<th>NT-proBNP range</th>
</tr>
</thead>
<tbody>
<tr>
<td>High levels</td>
<td>BNP &gt; 400 pg/ml (116 pmol/litre) or NT-proBNP &gt; 2,000 pg/ml (236 pmol/litre)</td>
<td></td>
</tr>
<tr>
<td>Raised levels</td>
<td>BNP 100-400 pg/ml (29-116 pmol/litre) or NT-proBNP 400-2,000 pg/ml (47-236 pmol/litre)</td>
<td></td>
</tr>
<tr>
<td>Normal levels</td>
<td>BNP &lt; 100 pg/ml (29 pmol/litre) or NT-proBNP &lt; 400 pg/ml (47 pmol/litre)</td>
<td></td>
</tr>
</tbody>
</table>

Cut-off values are age-specific!
Table 3: Diagnostic accuracy of BNP compared to clinical diagnosis

<table>
<thead>
<tr>
<th>N° of Studies</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
<th>Diagnostic OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.93 (0.91-0.95)</td>
<td>0.74 (0.63-0.83)</td>
<td>3.57 (2.44-5.21)</td>
<td>0.09 (0.06-0.13)</td>
<td>39.5 (21.4-72.6)</td>
</tr>
<tr>
<td>N=20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Diagnostic accuracy of NT-proBNP compared to clinical diagnosis

<table>
<thead>
<tr>
<th>N° of Studies</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
<th>Diagnostic OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.93 (0.88-0.96)</td>
<td>0.65 (0.56-0.74)</td>
<td>2.70 (2.12-3.43)</td>
<td>0.11 (0.07-0.18)</td>
<td>24.6 (14.4-42.4)</td>
</tr>
<tr>
<td>N=16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

al. (2005) to estimate the cost effectiveness of BNP testing in patients with symptoms of HF presenting in an acute care setting.

Costs considered in the KCE study include the costs of diagnostic tests (echocardiography and BNP) and the costs of hospital stays. The cost effectiveness of BNP in acute care is assessed by calculating the expected savings through lower number of admissions and a reduction in average length of hospital stay. Only first time patients undergoing diagnosis are taken into account. Calculations do not include costs incurred by false negative results. The lowest price quoted by members of the industry applying to Belgium for 2005 was 18 EUR (Biosite laboratory test). This amount was used in the base case analysis. The daily bed costs per diagnostic category were derived from the reported length of stay and overall cost of hospital stay applying to Belgium. These data concern Belgian government reimbursements for the year 2000.

One-way sensitivity analyses were performed to assess the robustness of the results for variations in “Cost of BNP testing” and “Average Daily Bed Cost”. As BNP is not yet reimbursed, the possible reimbursement rate of this test is uncertain. The average daily bed cost does not necessarily remain constant if the length of stay diminishes, because the first hospitalisation days are generally the most expensive.

**Base case results indicated a cost-saving of 953 EUR per patient. This is a decrease of 34.3% compared to the cost of standard treatment.**

The KCE calculations suggest that NP testing could be cost-saving in an emergency setting provided that negative tests effectively exclude further investigation and treatment for (suspected) HF.

In a primary care setting, KCE calculations do not prove NP testing to be cost-saving. This does not mean that implementing NP testing in primary care should not be considered. The cost per additional true negative result was 13 EUR. It depends on the societal willingness to pay for an added true negative result, and the consequent reassurance for the patient, whether this intervention is considered worth the extra costs.

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An update of this study was done by Hans Hellinckx, under the supervision of Prof. L. Annemans, PhD and Health Economist at the University of Ghent and the Free University of Brussels (VUB).

In order to make a conservative estimate about the impact in the budget for the Federal Institute for Sickness and Invalidity [RIZIV/INAMI] of reimbursing NP, a basic excel cost model was developed.

Results

In the case of applying NP for diagnostic purposes, the model simulates the number of avoided echocardiographies and the number of hospital days avoided (as in the KCE report). We find an estimated saving per patient of 859 EUR.

In the case of applying NP as monitoring tool, the savings are obtained by reducing the number of hospital stays due to more adequate monitoring and adapting the patient management timely. It is assumed that 15% reduction in the number of hospitalisations can be achieved. In that case, more than 4 million EUR can be saved per semester, already taking into account the cost of NP. The total potential saving, the diagnostic and monitoring indication included, amounts to 10.3 million EUR in year 1; 10.5 million EUR in year 2 and 10.7 million EUR in year 3.

Recommendation

The introduction of NP measurement in the nomenclature of reimbursable laboratory examinations should be accompanied by an information campaign on the evidence based use of this test. This should avoid dramatic increases in the use of this test whenever reimbursement would become available.

References


Table 5: The per diem fixed hospital stay cost for APR-DRG 194: HF (2007)(in EUR)

<table>
<thead>
<tr>
<th>SOI</th>
<th>Number of hospital stays</th>
<th>%</th>
<th>AA</th>
<th>LOS</th>
<th>ARA hospital stay (100%)</th>
<th>ARA medication</th>
<th>ARA medical fees</th>
<th>TOTAL ARA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>999</td>
<td>5.2</td>
<td>77</td>
<td>7</td>
<td>2,186.24</td>
<td>81.65</td>
<td>81.65</td>
<td>3,062.09</td>
</tr>
<tr>
<td>Moderate</td>
<td>7,738</td>
<td>40.3</td>
<td>78</td>
<td>10</td>
<td>3,023.45</td>
<td>120.87</td>
<td>120.87</td>
<td>4,091.73</td>
</tr>
<tr>
<td>Major</td>
<td>8,366</td>
<td>43.6</td>
<td>79</td>
<td>14</td>
<td>4,448.23</td>
<td>236.36</td>
<td>236.36</td>
<td>5,974.65</td>
</tr>
<tr>
<td>Extreme</td>
<td>2,078</td>
<td>10.8</td>
<td>79</td>
<td>23</td>
<td>6,986.51</td>
<td>809.42</td>
<td>809.42</td>
<td>10,269.21</td>
</tr>
<tr>
<td>TOTAL</td>
<td>19,181</td>
<td>100.</td>
<td>78</td>
<td>13</td>
<td>4,032.62</td>
<td>243.79</td>
<td>243.79</td>
<td>5,528.60</td>
</tr>
</tbody>
</table>


SOI: Severity Of Illness - AA: Average Age - LOS: Length Of Stay (reimbursed amount) - ARA: Average Reimbursed Amount