Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen

KCE reports vol.24 A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
2005

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Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen

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KCE reports vol. 24 A

Titel :	Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen
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Conflict of interest :	None declared
Disclaimer:	De experts en validator werkten mee aan het wetenschappelijke rapport. De beleidsaanbevelingen vallen onder de volledige verantwoordelijkheid van het KCE.
Layout:	Dimitri Bogaerts, Nadia Bonnouh

Brussel, 23/12/2005

Studie n° 2004-05-2
Domein HTA

MeSH : Heart Failure, Congestive; Natriuretic Peptides; Technology Assessment, Biomedical; Cost and Cost Analysis
NLM classification : WG 370

Taal : Nederlands
Format : Adobe® PDF™ (A4)

Wettelijk depot : D/2005/10.273/34

Elke gedeeltelijke reproductie van dit document is toegestaan mits bronvermelding.
Dit document is beschikbaar van op de website van het Federaal Kenniscentrum voor de Gezondheidszorg.

Hoe refereren aan dit document?
Van Brabandt H, Van den Steen D, Cleemput I. Het gebruik van natriuretische peptides in de diagnostische aanpak van patienten met vermoeden van hartfalen. Brussel : Federaal Kenniscentrum voor de Gezondheidszorg (KCE) ; December 2005. KCE Reports vol. 24A. Ref. D/2005/10.273/34.

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Voorwoord

Hartfalen is een syndroom dat veroorzaakt wordt door een gebrekkige pompfunctie van het hart. Het is het eindstadium van elke hartziekte. De verbeterde behandeling van hartziekten in het acute stadium en de vergrijzing van de bevolking hebben ertoe geleid dat hartfalen meer en meer voorkomt en m.n. een voorname reden tot ziekenhuisopneming geworden is. De ziekte wordt gekenmerkt door kortademigheid en vochtopstapeling in het lichaam. De diagnose is niet altijd eenvoudig en wordt mede bemoeilijkt door het feit dat andere frequent voorkomende aandoeningen bij bejaarden (nierfalen, chronische longziekten) zich min of meer gelijkaardig manifesteren.

Natriuretische peptiden zijn hormonen die door het hart, ook in normale omstandigheden, worden afgescheiden. De bloedspiegel ervan ligt hoger bij patiënten met hartfalen en bovendien is er een relatie met de ernst van het hartfalen. De mogelijkheid om deze stoffen in het bloed te doseren zou dus de vaak moeilijke diagnose van hartfalen mogelijks kunnen vereenvoudigen. Het gebruik van bloedonderzoek is in de medische praktijk gemeengoed geworden. Vaak is het een doeltreffend middel om snel en betrouwbaar tot een diagnose te komen. Soms wordt het – zowel door sommige artsen als door patiënten - evenwel aanzien voor een panacee waarmee elk medisch diagnostisch probleem kan ontmaskerd worden. Het probleem is dat een goede diagnostische test slechts waarde heeft als ze op de juiste manier bij de juiste patiënt wordt gebruikt. Dit rapport onderzoekt voor welke indicaties het doseren van natriuretische peptiden om tot een diagnose van hartfalen te komen wetenschappelijk aangetoond is.

Dit rapport is in die zin vernieuwend dat de doeltreffendheid en doelmatigheid van een diagnostische test geëvalueerd wordt alvorens deze voor terugbetaling in aanmerking te nemen. Dit laat toe om prospectief het gebruik van de test in de praktijk te sturen en m.n. te beperken tot de indicaties waarvoor voldoende wetenschappelijke bewijskracht bestaat. Aanvragers informeren over de juiste plaats van een labo-test in de dagdagelijkse klinische praktijk is een essentiële randvoorwaarde hiertoe. Dit rapport hoopt aan beide doelstellingen te kunnen bijdragen.

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Samenvatting

Inleiding

Natriuretische peptiden (NPs) worden door het hart in de bloedbaan uitgescheiden en vormen in dat opzicht hormonen die door het hart als endocrien orgaan uitgescheiden worden. In normale omstandigheden reguleren deze hormonen de homeostase van de bloedsomloop via hun inwerking op de vaattonus, de diurese en de natriurese. Het is aangetoond dat NP waarden stijgen bij patiënten met hartfalen (HF) en dit evenredig met de klinische ernst van hun aandoening. Deze waarneming voedde de hypothese dat NP waarden in de diagnostiek van HF kunnen worden gebruikt.

HF is een complex klinisch syndroom dat het eindstadium van elke hartziekte vormt. Er is geen unieke diagnostische test voor HF. De diagnose berust hoofdzakelijk op het oordeel van de clinicus, maar door de lage specificiteit van symptomen en de lage sensitiviteit van klinische tekens zijn bijkomende onderzoeken vereist zoals radiografie van de thorax, elektrocardiografie en echocardiografie. Een eenvoudige bloedtest die HF kan diagnosticeren zou daarom zeer welkom zijn. Het is vanuit dit perspectief dat met de bepaling van NPs in de klinische praktijk werd begonnen.

Er zijn minstens vier verschillende NP's. Vooral BNP, "brain natriuretic peptide" en zijn inactieve metaboliet NT-proBNP of "amino-terminal proBNP" werden grondig bestudeerd. [i] Er zijn zowel laboratorium- als ambulante ("point-of-care) tests beschikbaar die voor klinisch gebruik zijn goedgekeurd. Een niet systematische bevraging in België toont aan dat het gebruik van NP tests nogal varieert tussen ziekenhuizen. Vele cardiologen zouden deze test graag routinematig in hun klinische praktijk gebruiken, maar zijn hierin beperkt door de kostprijs. Daarom wordt om de terugbetaling van deze test verzocht.

Voornaamste doelstellingen en scope

Dit HTA rapport betreft het gebruik van NP-meting als diagnosemiddel bij patiënten met acute kortademigheid en waarbij voor de eerste keer HF wordt vermoed op basis van het klinisch onderzoek. Het gebruik van NP meting in de ambulante praktijk of op de spoedgevallendienst wordt toegelicht. Dit HTA rapport slaat uitsluitend op het gebruik van NPs in de diagnose van HF bij patiënten waarbij HF voor de eerste keer wordt vermoed. De potentiële impact van NP tests op patiënten en op de maatschappij wordt belicht. Het rapport bevat ten slotte een aantal aanbevelingen voor een effectief en kosteneffectief gebruik van NP tests.

Methoden

In 2005 zijn er minstens drie uitvoerige "Health Technology Assessment" (HTA) rapporten gepubliceerd in de Angelsaksiche literatuur. Aangezien deze recente HTA's de literatuur bestrijken tot eind 2004 hebben wij onze systematische klinische literatuurstudie beperkt tot studies die na 1 juli 2004 zijn gepubliceerd. De systematische economische literatuurstudie vertrok van studies gepubliceerd na 2000 en verbreedde het bereik van eerdere economische zoekopdrachten. De gevonden studies werden gebruikt om de bestaande HTA rapporten bij te werken en aan te vullen.

De netto kosten en kosteneffectiviteit van NP meting in de acute en de eerstelijnszorg in België werd met behulp van economische modellen geëvalueerd. De toepassing van internationale modellen op de Belgische gezondheidszorg werd bij een aantal deskundigen afgetoetst. Via univariate sensitiviteitsanalyses gingen we de impact na van plausibele veranderingen in onzekere variabelen op de resultaten van het model. Aandachtspunten die nader onderzoek verdienen, werden aangestipt.

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[i] In de tekst verwijst "NP(s)" naar natriuretisch(e) peptide(n), waaronder verstaan wordt BNP EN NT-proBNP. Indien slechts één van deze peptiden is bedoeld, wordt dit aangegeven.

Fabrikanten en vertegenwoordigers van de beroepsvereniging van cardiologen werden voor bijkomende informatie gecontacteerd. Een eerste versie van het rapport werd met een groep van externe deskundigen besproken. De definitieve tekst werd door drie externe validatoren beoordeeld.

Klinische effectiviteit

Tussen normale individuen bestaat een ruime spreiding van NP waarden, afhankelijk van verschillende biologische parameters. NP waarden zijn hoger bij vrouwen dan bij mannen en stijgen voor beide geslachten met de leeftijd. NP waarden variëren ook in functie van de body mass index (BMI). Bij individuen afzonderlijk is eveneens een hoge biologische schommeling van NP-waarden vastgesteld.

Patiënten met HF hebben gemiddeld hogere NP waarden dan patiënten zonder HF. Die waarden weerspiegelen de klinische ernst van HF volgens de functionele klasse van de New York Heart Association (NYHA). Ze zullen eerder dalen tijdens agressieve therapie voor decompensatie. Toch kunnen NP waarden niet goed als streefdoel worden gebruikt om de therapie van individuele patiënten bij te sturen. Vele patiënten die optimale doses medicatie nemen, blijven continu hoge NP waarden behouden. De meeste patiënten in NYHA klasse I, i.e. asymptomatische HF patiënten, vertonen NP waarden die boven de "diagnosedrempel" (blijven) liggen.

NP waarden kunnen verhoogd zijn bij andere aandoeningen dan HF en systolische linkerventrikel disfunctie. Courante hartafwijkingen die hoge NP waarden kunnen veroorzaken zijn linker kamer hypertrofie, klepletsels, acute of chronische ischemie, aritmieën en arteriële hypertensie. Een hoge NP waarde kan ook wijzen op een niet-cardiovasculaire aandoening zoals nierfalen, longembolie of chronisch obstructief longlijden. Al deze ziektebeelden stellen klinische problemen die vaak ook te zien zijn bij patiënten met HF en in de populatie van (bejaarde) patiënten met kortademigheid.

De voornoemde onderzoeksresultaten tonen aan dat NP waarden verhoogd kunnen zijn in zeer verscheiden fysiologische en pathologische omstandigheden. Diverse studies naar de diagnostische precisie van NPs rapporteren verschillende waarden voor sensitiviteit en specificiteit bij gelijke NP drempelwaarden en dit wegens een wisselende samenstelling van de onderzochte populatie met grote verschillen in verdeling naar geslacht en co-morbiditeiten. De resultaten van deze studies werden gecombineerd in een meta-analyse en aan de hand van de drempelwaarden aangegeven door de fabrikanten van de test werd een algemene sensitiviteit van 0,91 en een algemene specificiteit van ongeveer 0,75 berekend. Deze cijfers leiden tot een "aantrekkelijke" negatieve predictieve waarde van 95% tot 99% in een typische populatie patiënten met een diagnostisch probleem van kortademigheid. Wegens de lage specificiteit van de test is zijn positieve predictieve waarde laag bij de populaties die het onderwerp uitmaken van dit HTA rapport. Dat betekent dat het nut van NP meting strikt beperkt is tot de uitsluiting van HF bij patiënten met een recent en nieuw probleem van kortademigheid waarbij klinisch onderzoek en oriënterende tests niet kunnen uitmaken of HF al dan niet de oorzaak is van de kortademigheid.

Er is nog geen algemene consensus over de aangewezen diagnostische drempelwaarden. De NP waarden stijgen met de leeftijd en zijn bij vrouwen hoger dan bij mannen. De huidige richtlijnen stellen een drempelwaarde voor van 100 pg/ml voor BNP, 125 pg/ml voor NT-proBNP voor personen jonger dan 75 jaar en 450 pg/ml NT-proBNP voor oudere patiënten om HF uit te sluiten. Deze cijfers zijn echter niet meer dan een ruwe benadering in afwachting van duidelijke drempelwaarden naar leeftijd en geslacht voor beide NP doseringen.

Voor klinische doeleinden verschilt de precisie van BNP niet van die voor NT-proBNP.

Kosteneffectiviteit

De kosteneffectiviteit van (NT-pro)BNP tests werd geëvalueerd aan de hand van een overzicht van de bestaande economische literatuur en een origineel model dat het gebruik van NP voor de diagnostische uitsluiting van HF in de Belgische spoeddiensten en ambulante zorg simuleert.

Het literatuuroverzicht toont aan dat NP kostenbesparend kan zijn op spoeddiensten als het wordt gebruikt om hartfalen uit te sluiten bij patiënten met kortademigheid. In de ambulante zorg is de mogelijke kostenbesparing ingevolge NP testen onvoldoende aangetoond, hoewel deze niet kan worden uitgesloten. Potentiële kostenbesparingen in het ziekenhuis liggen vooral in de afname van het aantal ziekenhuisopnames en de gemiddelde opnameduur. Kostenbesparingen in de ambulante zorg zijn eerder te vinden in een beperking van het aantal echocardiografieën.

De primaire economische evaluatie geeft aan dat NP tests in de Belgische spoeddiensten kostenbesparend kunnen zijn vanuit het perspectief van de ziekteverzekering (RIZIV/INAMI). Modelresultaten tonen aan dat 34,3% van de behandelingskosten kunnen worden bespaard indien NP tests voor de diagnostische uitsluiting van HF worden gebruikt vergeleken met de standaardverzorging voor vermoedelijke HF patiënten.

In de ambulante zorg echter, liet het model geen besparingen zien voor het gebruik van NP. De totale kostenstijging voor het RIZIV voor de behandeling van dit type patiënten werd geschat op 4,4%. NP bepalingen bleken evenwel samen te gaan met accuratere diagnoses. Of dit laatste de bijkomende kosten waard is, moet aan de beleidsmakers worden overgelaten. Een belangrijke caveat is dat terugbetaling van NP tests in de ambulante zorg kan leiden tot ongepast gebruik van deze test. Dat dreigt de kosten aanzienlijk op te drijven zonder de diagnostiek te verbeteren.

Organisatorische aspecten en Patiëntenperspectief

Studies hebben aangetoond dat, zonder NP tests, bij minder dan de helft van de mensen waarbij de huisarts de diagnose HF heeft gesteld, deze diagnose door verdere tests wordt bevestigd. Vanuit het standpunt van de patiënt is de NP test een eenvoudige en nuttige test op basis waarvan de arts, bij lage NP waarden, HF betrouwbaar kan uitsluiten. Het is voor de patiënt bovendien geruststellend te horen dat hij/zij niet lijdt aan HF. Uitsluiting van HF kan onnodige medicatie en/of verdere tests vermijden, en soms zelfs overbodige ziekenhuisopnames.

In België zijn zowel laboratoriumtests beschikbaar als zogenaamde “point-of-care” (POC) tests, die binnen de 15 minuten resultaat geven. De diagnose van HF door niet gespecialiseerde artsen kan aanzienlijk worden vereenvoudigd door het gebruik van NP plasmawaarden. Deze eenvoud contrasteert met het gebruik van een elektrocardiografie, thoraxradiografie en echocardiografie die een bijzondere vaardigheid vergen in uitvoering en analyse.

Bij kortademige patiënten op de dienst spoedgevallen betekent een laag serumpeil van BNP (100 pg/ml) of NT-proBNP (afhankelijk van de leeftijd: 125 of 450 pg/ml) dat men acuut HF als oorzaak van de kortademigheid kan uitsluiten. In deze gevallen is bijkomende beeldvorming door echocardiografie vanuit diagnostisch standpunt niet meer nodig.

Bij patiënten met hoge NP waarden is verder onderzoek vereist en vervangt de NP meting geen bestaande testen om deze patiënten te evalueren; cardiovasculaire en andere aandoeningen moeten als mogelijke oorzaak van hun klachten worden uitgesloten. Zelfs patiënten waarvan aangenomen wordt dat ze aan HF lijden, moeten een ECG en een echocardiogram ondergaan omdat deze onderzoeken bijkomende informatie geven over de etiologie en uitlokkende factoren van het HF.

Conclusies

De diagnose en behandeling van HF berust op de klinische vaardigheid en het beoordelingsvermogen van de behandelende arts. De bepaling van NP plasmawaarden bovenop de standaardevaluatie levert een nuttige bijdrage tot de diagnose van HF. Op de spoeddiensten zijn de NP tests nuttig om HF uit te sluiten bij patiënten met een atypische presentatie. In de ambulante zorg is NP meting nog niet zo goed bestudeerd. Enkele studies tonen aan dat in de ambulante zorg, waar een te ruime diagnose van HF een aandachtspunt is, NP tests de diagnostiek scherper kunnen stellen. De diagnostische accuratesse kan evenwel in het gedrang komen indien ongepast gebruik door minder ervaren artsen leidt tot buitensporige laboratoriumaanvragen.

Verschillende variabelen zoals leeftijd, geslacht, nierfunctie, hartritme, medicatie en BMI kunnen de interpretatie van de NP plasmawaarden beïnvloeden. Er is nog geen algemene consensus over de drempelwaarden van NP voor diagnostisch gebruik. NP waarden zijn leeftijdsafhankelijk en daarenboven hoger bij vrouwen. De huidige richtlijnen geven een drempelwaarde van 100 pg/ml voor BNP en 125 pg/ml voor NT-proBNP bij patiënten jonger dan 75 jaar en 450 pg/ml NT-proBNP voor oudere patiënten om HF uit te sluiten. Gezien deze beperkingen is een uitgebreide informatiecampagne vereist om te garanderen dat potentiële gebruikers de test zo efficiënt mogelijk aanvragen.

Verder onderzoek

Relevante onderwerpen voor toekomstig onderzoek zijn de kostenraming van verkeerde resultaten (met name vals-negatieven) en de impact van NP tests op het welzijn van de patiënten. Een specifiek kenmerk van de test is dat hij snel HF kan uitsluiten, wat voor de patiënt een belangrijk voordeel kan zijn. Ten slotte moeten mogelijke veranderingen in verstrekkersgedrag als gevolg van de invoering van BNP tests worden geëvalueerd.

Aanbevelingen

Op de spoedafdeling is NP dosering klinisch nuttig voor artsen die patiënten verzorgen met kortademigheid, maar waarvoor na zorgvuldig klinisch onderzoek nog geen duidelijke diagnose kan worden gesteld. Lage NP waarden maken de diagnose van HF weinig waarschijnlijk en vermijden overbodige testen of het instellen van een nutteloze behandeling. Bovendien vermijdt deze aanpak dat sommige patiënten onnodig worden opgenomen en is er een kostenbesparing vergeleken met de standaard diagnostiek, voor zover negatieve tests verder onderzoek en behandeling voor (vermoed) HF daadwerkelijk uitsluiten.

In de ambulante zorg kan NP bepaling nuttig zijn om HF uit te sluiten bij vermoedelijke HF patiënten, wat leidt tot een daling van verkeerd doorverwezen patiënten. NP dosering is hier niet kostenbesparend maar uiteindelijk wel relevant voor de patiënt (vroegtijdige geruststelling, hogere precisie).

Zeer hoge NP waarden maken HF erg waarschijnlijk, terwijl patiënten met tussenwaarden nader onderzoek moeten ondergaan. NP metingen laten echter geen zekere diagnostische conclusies toe, tenzij over afwezigheid van HF.

Er zijn nog veel vragen over het optimaal gebruik van NPs in de diagnostiek van HF, zoals leeftijds- en geslachtsspecifieke drempelwaarden, implicaties van storende factoren, onzekerheid van drempelwaarden, enz.

In het licht van de voorgaande analyse zijn er drie mogelijke modaliteiten om NP bepalingen te financieren:

- Geen terugbetaling wegens onvoldoende duidelijkheid over de toe te passen drempelwaarden. Bovendien bemoeilijkt een gebrek aan epidemiologische gegevens voor België, met name in verband met acute kortademigheid en zijn etiologie, de evaluatie van medische praktijken.
- Terugbetaling op spoeddiensten en geen terugbetaling in de ambulante zorg. Aangezien NP tests op spoeddiensten kostenbeparend blijken, is terugbetaling op spoeddiensten verdedigbaar. In afwachting van verder onderzoek naar de kosteneffectiviteit en voorschrijfgedrag door de verstrekkers in de ambulante zorg, lijkt het redelijk voorlopig geen terugbetaling te voorzien in de eerstelijnszorg. Voor patiënten in de spoeddiensten wordt één enkele NP test per patiënt die zich op een gegeven ogenblik aandient, voorgesteld.
- Terugbetaling in ambulante en acute zorgsector, maar met beperkingen op de frequentie van testen. In dit geval wordt een beperking tot één NP test per jaar per patiënt in de ambulante zorg voorgesteld.

Er is geen bewijs dat de voorspellende waarde van BNP voor klinische doeleinden verschilt van die van NT-proBNP, hoewel het gebruik van BNP beter gedocumenteerd is. Het lijkt dan ook redelijk om beide tests evenveel terug te betalen.

De eventuele invoering van een terugbetaling van NP metingen in de klinische praktijk moet gepaard gaan met een informatiecampagne over het “evidence based” gebruik van deze test.

NP waarden lijken de prognose van patiënten met HF zeer goed te kunnen voorspellen, maar hun nut als instrument om het therapeutisch beleid bij HF te optimaliseren moet nog worden bepaald.

Kernboodschappen

- Hartfalen is een complex klinisch syndroom waarvoor alsnog geen eenduidige diagnostische test is ontwikkeld. De meting van natriuretische peptiden ("NPs", waarmee bedoeld wordt BNP en NT-proBNP) kan bij de diagnose van hartfalen helpen. Dit rapport evalueert het gebruik van NPs in de diagnose van een eerste vermoede hartfalen bij patiënten met kortademigheid in de spoeddiensten en in de ambulante zorg.
- Relevante studies werden geanalyseerd en gebruikt om eerder onderzoek bij te werken en aan te vullen. De kosteneffectiviteit van NP bepaling werd geëvalueerd met behulp van economische modellen.
- NP waarden kunnen verhoogd zijn bij een hele reeks fysiologische en pathologische aandoeningen. Tot dusver is er nog geen consensus over gepaste drempelwaarden. Uit de vakliteratuur blijkt dat NP dosering in de acute zorg kostenbesparend kan zijn door ziekenhuisopnames in aantal en duur te beperken. De kosteneffectiviteit van NP dosering in de eerstelijnszorg is minder goed gedocumenteerd in de vakliteratuur.
- In België kunnen NP tests kosten besparen in spoeddiensten maar niet in de ambulante zorg. De bijkomende kosten in de ambulante zorg gaan wel gepaard met een betere diagnostiek. Het komt er dus op aan te evalueren of men bereid is die bijkomende kosten te dragen voor die betere diagnostiek. Daarnaast moet eveneens rekening worden gehouden met verwachte veranderingen in verstrekkersdrag voor deze test in geval van terugbetaling.
- De NP tests vormen een gebruiksvriendelijk en doeltreffend klinisch instrument om hartfalen als mogelijke diagnose uit te sluiten en patiënten sneller en gerichter te behandelen. Negatieve NP tests maken verder cardiologisch onderzoek overbodig. Positieve NP tests mogen bestaande diagnostische behandelingen niet vervangen.
- De NP tests mogen niet worden terugbetaald zonder beperkingen op de gebruiksfrequentie en eventueel met onderscheid tussen spoeddiensten en ambulante zorg.
- De invoering van NP meting in het Belgische terugbetalingssysteem vergt een uitgebreide informatiecampagne voor potentiële gebruikers van de tests.

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1. INTRODUCTION

This health technology assessment is primarily concerned with the clinical and cost effectiveness of natriuretic peptides as a diagnostic aid for physicians in the initial diagnostic work-up of patients with signs and symptoms suggestive of heart failure. Heart failure is a complex clinical syndrome in which a cardiac abnormality reduces the ability of the heart to pump blood. Symptoms of heart failure typically include breathlessness, fatigue or ankle swelling, but these are often difficult to interpret and diagnosis of heart failure by clinical means alone often is inadequate. Studies show that over 50% of patients diagnosed with suspected heart failure in primary care do not have a diagnosis of heart failure confirmed on further evaluation by a specialist.[1] The latter can make use of additional investigations such as electrocardiography, chest X-ray and echocardiography; sometimes a therapeutic trial is initiated and the resulting clinical outcome is assessed.

The prognosis for patients with heart failure is poor, especially when the underlying problem cannot be rectified. Uncertainty of diagnosis and delays in confirming diagnosis are major concerns for patients with heart failure. Inappropriate diagnosis at best leads to patients receiving medication that will not improve their condition but which may indeed harm them.

In patients with heart failure, natriuretic peptides 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 dilation of the blood vessels which reduces blood pressure and stimulates sodium and water excretion. Natriuretic peptide plasma concentrations are therefore raised in patients with heart failure, and generally the higher the concentration, the more severe the disease. Laboratory and point-of-care assays that measure "brain natriuretic peptide" (BNP) and its inactive metabolite "amino terminal-proBNP" concentrations in the blood are now commercially available.

This HTA report aims at elucidating the scientific support for the diagnostic use of natriuretic peptides in clinical practice, especially for the detection of a cardiac origin in patients with dyspnoea in whom the diagnosis is not readily apparent after clinical evaluation. The use of natriuretic peptide levels for therapeutic monitoring and guiding of therapy in patients treated for heart failure is not considered in this report.

2. PRIMARY OBJECTIVE AND SCOPE

The use of natriuretic peptides in the diagnostic arena has been propagated for different clinical settings:

- As an aid in the diagnosis of HF in patients with symptoms of uncertain cause, i.e. patients with suspected HF.
- Therapeutic monitoring and guiding of therapy in patients treated for HF.
- Risk stratification of patients with HF and other cardiac conditions such as acute coronary syndromes.
- Screening for preclinical disease in asymptomatic subjects.

This report essentially deals with the diagnostic accuracy as compared to expert clinical diagnosis and the cost-effectiveness of NPs in symptomatic patients with suspected HF. We were not concerned in detecting left ventricular systolic dysfunction as such because 20 to 50% of patients with HF have preserved systolic function [2]. The use of NPs in therapeutic monitoring, risk stratification and screening are not considered in this HTA report.

Two levels of care will be considered in the use of NPs in the diagnostic work-up of patients with suspected heart failure:

- The general practitioner setting where the use of natriuretic peptides is discussed in the decision making process whether or not to refer a patient to a cardiologist or a hospital.
- The emergency room setting where its use is evaluated in helping attending specialists to decide whether or not a patient should be admitted to hospital and whether there is need for further investigation and treatment.

3. BACKGROUND

3.1. HEART FAILURE

3.1.1. Definition

Heart failure (HF) is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support a physiological circulation. The syndrome of heart failure is characterised by symptoms such as breathlessness and fatigue and signs such as fluid retention (oedema, rales). There is no single diagnostic test for HF, and diagnosis largely relies on clinical judgement based on a combination of history and physical examination completed with appropriate investigations.[3] Different conditions give rise to HF such as damaged cardiac tissue, malfunctions of heart valves and coronary artery disease (CAD). Among patients under the age of 75 years, myocardial dysfunction is most often due to CAD leading to a predominantly systolic dysfunction. Among elderly patients systolic hypertension and cardiac hypertrophy, as well as cell loss and fibrosis may be more important causes of HF and may predominantly manifest as abnormalities of diastolic function. [4] Diastolic HF is characterised by the impaired ability of the heart to fill with blood whereas in systolic HF the ability to eject blood is impaired. Diastolic HF is diagnosed when symptoms and signs of HF occur in the presence of a preserved left ventricular ejection fraction at rest. Most patients with heart failure and impairment of diastolic function also have some impairment of systolic function.[5]

Some authors use the term HF in asymptomatic patients with systolic cardiac dysfunction but HF is not equivalent to cardiomyopathy or left ventricular dysfunction, the latter terms merely describing possible or structural reasons for the development of HF.[6] Nevertheless, many studies related to patients with HF rely on echocardiographic indices such as left ventricular ejection fraction (EF) to make a final diagnosis of HF. Echocardiography alone cannot diagnose HF, because many patients presenting with HF have a normal or near-normal systolic left ventricular function. HF in these cases is provoked by a diastolic dysfunction of the heart, i.e. the inability of the heart to fill with blood, which is more difficult to demonstrate objectively in clinical practice. The performance of natriuretic peptides as a test for HF has to be compared to standard practice for patients referred for suspected HF, i.e. the diagnosis of the examining cardiologist (or other physician) following the full assessment of the patient, including echocardiography, serves as the gold standard.[7] This view is confirmed by the ESC in its latest update on guidelines for the diagnosis and treatment of chronic HF.[4] It is also in agreement with the different stages of HF as they are defined by the ACC/AHA[6]: patients with structural heart disease but without symptoms of HF are labelled as "at risk for HF" (stages A and B) and not as "HF" (stages C and D).

HF can present itself both acutely and chronically. Acute HF is defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function. It can present itself de novo in a patient without previously known cardiac dysfunction or as an acute decompensation of chronic HF. It is manifested by different distinct clinical conditions such as pulmonary oedema, hypertensive acute HF, cardiogenic shock… [8]

HF can be strictly left sided, giving rise to pulmonary congestion, strictly right sided, resulting in systemic congestion or combined right and left sided. The most common reason of right HF is left HF which is than provoked by increased left ventricular filling pressures, resulting in pulmonary artery hypertension. The latter can also be the consequence of primary pulmonary disease or congenital heart disease, resulting in pure right sided HF.

Because of widely varying definitions, the epidemiology of HF is difficult to interpret. European estimates of the prevalence of HF in the general population range from 0.4 to 2%. The prevalence of HF increases rapidly with age, with a mean age of the HF population being 75 years, the elderly population being nearly 50% female. HF has a poor prognosis. Half of patients carrying a diagnosis of HF will die within 4 years, and in patients with severe HF > 50% will die within a year. [4] The prognosis associated with untreated heart failure is worse than most cancers. Results from a study by Stewart showed that, with the exception of lung cancer, heart failure was associated with a poorer survival rate than myocardial infarction and most common types of cancer.[9] HF is the most frequent cause of hospitalisation among people older than 65 years of age, and these hospitalisations are an important part of the enormous cost of the disease.[10] In the U.S. alone, the economic cost of HF is estimated at 56 billion $ a year, 70% of which is due to hospitalisation.

Key messages

- **There is no single diagnostic test for HF. Diagnosis largely relies on clinical judgement, i.e. on history taking and physical examination.**
- **Ejection fraction calculation alone cannot diagnose HF. Many patients presenting with HF do have a normal or near-normal systolic left ventricular function.**

3.1.2. Symptoms And Signs

Breathlessness, ankle swelling and fatigue are the characteristic symptoms and signs of HF but may be difficult to interpret, particularly in elderly and obese patients. Peripheral oedema, raised venous pressure and hepatomegaly are the characteristic signs of congestion of systemic veins. Peripheral oedema and hepatomegaly have a low positive predictive value. Moreover, peripheral oedema is usually absent in well-treated HF and primary left ventricular systolic dysfunction. The term "congestive heart failure" essentially refers to patients with signs of fluid retention. However, because not all patients have signs of fluid retention at the time of initial or subsequent evaluation, the term "heart failure" is preferred over the older term "congestive heart failure." [6] Although cardiologists attain a high agreement on the presence of an elevated jugular venous pressure, the reproducibility is much lower among non-specialists. When multiple signs of HF are present, including a displaced apex beat, pitting oedema, a raised venous pressure and a third heart sound, in the presence of appropriate symptoms, a clinical diagnosis of HF may be made with some confidence. Because symptoms are non-specific and clinical signs, although specific, are not sensitive, often additional examinations are performed to corroborate the clinical findings.

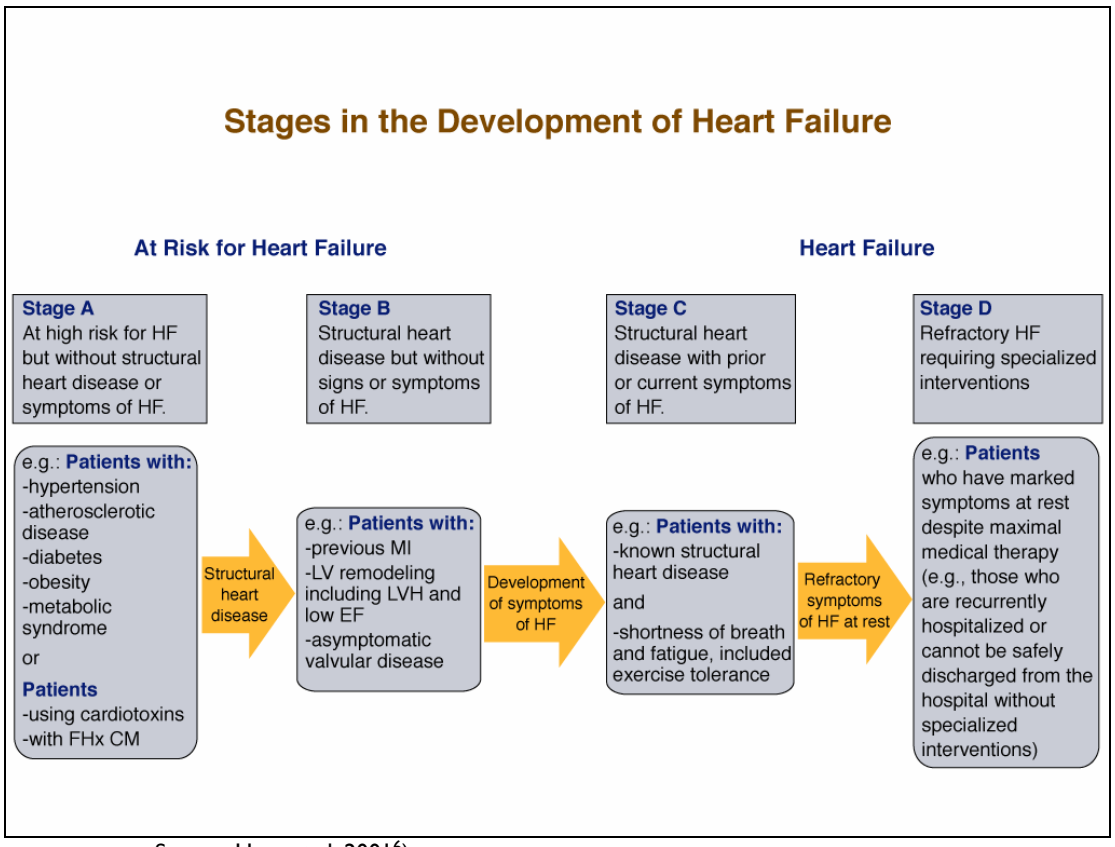
Already in 1928 the New York Heart Association (NYHA) published a functional classification of patients with cardiac disease based on clinical severity and prognosis. Subjective symptoms are used to rank patients according to their functional capacity into four classes as shown in Table 1.

Table 1: NYHA Functional Classification of Patients

NYHA Class	Patient Symptoms
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

This functional classification reflects a subjective assessment by a physician and can change frequently over short periods of time. Moreover, treatments used do not differ significantly across the classes. Therefore, in their 2001 update of the guidelines on HF, the ACC/AHA added a second grading system to the NYHA classification in which both the evolution and the progression of the disease was implied. This staging system (Figure 1) aims to reliably and objectively identify patients in the course of their disease specifying treatments that are uniquely appropriate at each stage of illness. According to this new approach, patients would only be expected to advance from one stage to the next, unless progression of the disease was slowed or stopped by treatment. [6]

Figure 1: ACC/AHA Heart Failure Stages



Source: Hunt et al. 2001[6])

Key Messages

- **Because symptoms are non-specific and clinical signs, although specific, are not sensitive, additional examinations are performed to corroborate clinical findings.**

3.1.3. Diagnostic Investigations

Once a diagnosis of HF has been put forward, based on history taking and clinical examination, appropriate investigations are indicated to confirm the diagnosis and to guide further therapeutic action. Conventionally, electrocardiography (ECG) and chest radiography are the initial tests for diagnosing heart disease in patients with suggestive symptoms. These tests are simple to perform, have only small procedural errors and are inexpensive. However, not only is a certain level of training needed to accurately evaluate the results, but the ability to evaluate also differs greatly between cardiologists and other physicians.

An ECG can be helpful in elucidating the cause of dyspnoea in a patient with suspected HF. The negative predictive value of a normal ECG to exclude left ventricular systolic dysfunction exceeds 90%. Signs of myocardial infarction, conduction abnormalities and arrhythmias are helpful in diagnostic work-up. The HTA report of the NHS on natriuretic peptides[1] studied extensively the use of the ECG in the diagnostic workup of patients with suspected HF. The ECG turned out to have a remarkably high negative predictive value (96 – 99 %), especially in settings with low prevalence rates (5 – 15%). Otherwise, the authors stress that abnormalities on an ECG are linked to a range of cardiac conditions other than HF, including arrhythmias and acute cardiac ischemia. Referral to specialist is appropriate for such conditions. Thus the lower specificity may not be a clinical drawback but rather in accordance with good clinical practice. In a systematic review, Davenport et al[11] reach the same conclusion on the accuracy of the ECG in predicting LVSD as defined by echocardiography: in the majority of the studies reviewed by them, ECG demonstrates a point estimate of sensitivity > 80% while the estimates of specificity were less

good and more heterogeneous, with the majority of studies demonstrating specificity of less than 80%.

A chest X-ray is considered mandatory in the initial evaluation of patients with suspected HF to judge cardiac enlargement, the presence of pulmonary congestion and pleural effusion and to identify abnormalities indicating primary pulmonary disease. However, a high predictive value is only achieved by interpretation of the X-ray in the context of clinical findings and ECG anomalies.

Certain laboratory investigations are recommended as part of a routine diagnostic evaluation of patients with HF because they may reveal the presence of disorders that can lead to or exacerbate HF: complete blood count, serum electrolytes, serum creatinine and thyroid stimulating hormone. In acute exacerbations it might be important to exclude acute myocardial infarction by myocardial biomarkers.[4]

Based on the above mentioned additional investigations, the likelihood of the clinical diagnosis of HF can be increased. Next, objective evidence of cardiac dysfunction (systolic and/or diastolic) by echocardiography is to be sought. Echocardiography not only helps in objectifying cardiac dysfunction, it also gives additional mechanistic information on the underlying heart disease which ultimately led to HF. Sometimes, echocardiography as well as ECG can reveal cardiac anomalies that are amenable to correction which can even result in "curing" HF. Echocardiography provides information on chamber dimensions and geometry, diffuse or focal systolic dysfunction, pericardial disease and valvular malformations. Left ventricular ejection fraction serves as a measure of systolic function. Cardiac Doppler is used to evaluate evidence of diastolic dysfunction, valvular dysfunction and to estimate pulmonary pressures. EF measurements are not optimal reproducible. Even using cutting-edge techniques of myocardial imaging, such as contrast echocardiography and cardiac magnetic resonance imaging, there can be a substantial difference in the EF between these studies in an individual patient.

Patients not amenable to echocardiography can be evaluated by means of radionuclide angiography. The use of this modality is not routinely recommended. Invasive investigation is generally not required to establish the presence of HF but may be important in elucidating the underlying cause.

The aforementioned difficulties, i.e. the importance of clinical skills in diagnosing HF and the absence of a gold standard, have increased the interest in the natriuretic peptides (NPs) as a diagnostic aid in this widespread clinical syndrome. Plasma concentrations of certain NPs, especially BNP and NT-proBNP, are helpful in the diagnosis of HF. It is the aim of this report to elucidate the evidence supporting the efficiency of this diagnostic test in patients with HF.

Key messages

- **ECG and chest radiography are the initial tests for confirming heart disease in patients with symptoms suggestive of HF. However the ability to evaluate the results greatly differs between cardiologists and other physicians.**
- **ECG and echocardiography, besides helping in diagnosing HF, provide additional information needed in the treatment of HF patients.**

3.2. NATRIURETIC PEPTIDES

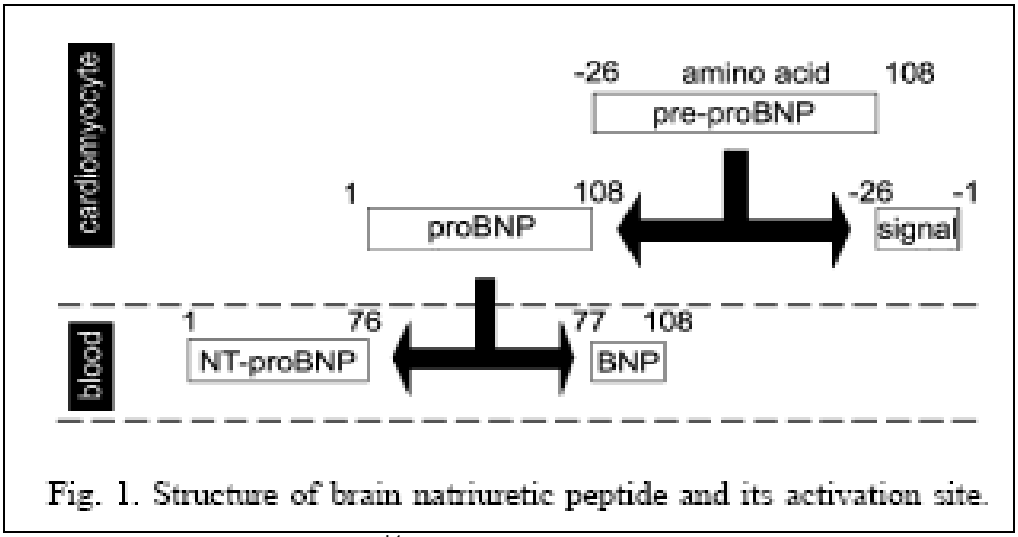
3.2.1. Physiology And Pathophysiology

The concept of the heart as an endocrine gland was first advanced in 1956 when Kisch and colleagues reported the presence of secretary granules in the atria of guinea pigs. That same year, Henry et al reported that balloon stretching of left atrium produced increased urinary flow in dogs. However, it was not until the landmark study of de Bold et al in 1981 that the existence of a substance of cardiac origin with systemic actions was proven. Subsequent isolation and purification revealed that a new peptide, called atrial natriuretic peptide (ANP), was responsible for these effects. An explosion of research stimulated by these observations has led to the discovery of a family of structurally similar but genetically distinct peptide hormones of cardiac

and endothelial cell origin including besides ANP, brain (B-type) (BNP) natriuretic peptide (1988) and C-type (CNP) natriuretic peptide (1990). More recently, with dendroaspis natriuretic peptide (DNP) a fourth member of the natriuretic peptide system (NPS) emerged. Since de Bold's seminal study, the NPS has been proven to be a key hormonal system critical to blood pressure homeostasis. Several data demonstrate that the NPS plays an important role in normal cardiovascular homeostasis and that it should not be thought of as a compensatory mechanism that comes into play only in response to circulatory or cardiac derangement. The NPS produces vasodilatation, diuresis and natriuresis and it reduces sympathetic tone and has an inhibitory effect on the renin-angiotensin-aldosteron system. Growing evidence supports the role of this system as a compensatory neurohumoral system which in contrast to other compensatory systems such as the renin-angiotensin-aldosterone and sympathetic nervous systems, functions to retard rather than promote the progression of heart failure. In patients with HF the average BNP and NT-proBNP levels are significantly higher compared to patients with no HF.

BNP is synthesized as a 108 amino acid pro-hormone. The peptide is named "brain" natriuretic peptide because it was originally isolated from porcine brain extracts,[12] but its primary site of synthesis has been localized to the ventricular myocardium.[13] Upon stretch or 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 72 amino acid N-terminal portion (NT-proBNP) (Figure 2). BNP is quickly removed from circulation by binding to NPR-C receptor and by neutral endopeptidases, while the half-life of N-BNP is considerably longer and levels are higher.

Figure 2: Structure of BNP and its activation site



Source: Vanderheyden et al. 2004[14]

With the recognition that ANP levels were elevated in patients with HF, interest in the potential for measurement of natriuretic peptide levels in the diagnosis and management of cardiovascular disease began to emerge. One of the earliest studies examined the potential for ANP or N-ANP to detect preclinical or asymptomatic systolic dysfunction and reported that N-ANP had promise for detection of preclinical systolic dysfunction. Subsequently discovery of BNP and assay systems to measure it led to speculation that it may be a better marker for ventricular dysfunction. A study by Yamamoto et al.[15] reported that BNP was superior to ANP and N-ANP in the detection of systolic dysfunction, ventricular hypertrophy, diastolic dysfunction, and elevated filling pressures. While a few studies in patients with suspected HF followed, it was not until development of a commercially available assay system that interest in the use of BNP for the diagnosis of HF entered the mainstream of clinical investigation.[16].

Key messages

- **The NPS plays an important role in normal cardiovascular homeostasis. It should not be thought of as a compensatory mechanism that comes into play only in response to circulatory or cardiac derangement.**
- **In patients with HF, the average BNP and NT-proBNP levels are significantly higher compared to patients with no HF (without renal failure or an acute coronary syndrome).**

3.2.2. Natriuretic Peptide Assays

In Belgium, BNP assays are marketed for laboratory settings (Bayer, Abbott, Biosite) and for point-of-care (POC) testing (Biosite). An assay for NT-proBNP is available (Roche Diagnostics, Dade-Behring) in both settings. In 1993 the first commercial assay for BNP was introduced by Shionogi. It is a one-step immunoradiometric assay (IRMA) that requires approximately 20 hours. Most of the early clinical and basic research studies utilized the Shionogi method. In February 2003 Bayer Diagnostics released the ADVIA Centaur Assay which uses the same antibodies as the original Shionogi Shiono-RIA BNP manual assay. A rapid point-of-care test for determination of BNP concentrations in human plasma was introduced in 2000 by Biosite Inc, the Biosite Triage BNP test. The time from the application of sample until the result is reported is about 15 minutes. The bulk of recent clinical studies have used this assay system. The method uses a kit that resembles a blood glucose meter but a venipuncture rather than a finger prick is needed to provide an adequate blood sample.[17] In November 2002, Roche Diagnostics received FDA clearance to market the Elecsys proBNP Assay.

Whether measurement of NT-proBNP is equivalent, superior or inferior to measurement of BNP for diagnosing the cause of dyspnoea is uncertain. Limited evidence suggests that both assays appear to have comparable diagnostic accuracy and have their own advantages and disadvantages.[18] There is some concern that more of NT-proBNP is cleared via renal excretion and thus that levels may be more influenced by renal dysfunction but extensive studies comparing BNP and NT-proBNP in renal disease are lacking. The inter- and intra-assay variabilities of the NT-proBNP assay are less than for the BNP Biosite Triage BNP test.[16] In the PRIDE study, NT-proBNP measurements were performed with the Roche Elecsys assay. This assay has a < 0.001% cross-reactivity with bioactive BNP and in the PRIDE study, had an interassay coefficient of variation of < 1%. In the same study, BNP measurements were performed with the Bayer Advia assay. This assay demonstrated an interassay coefficient of variation of < 3.0%.[19]

Some characteristics of the different assays are represented in Table 2 which has partly been retrieved from the NHS HTA report.[1] Cut-offs used in the diagnosis of HF are discussed later in the text.

Table 2: Characteristics of Natriuretic Peptide Assays

CHARACTERISTICS	BNP	NT-proBNP
LABORATORY SETTING	BAYER-ADVIA Centaur ABBOTT-AxSYM BIOSITE	ROCHE-Elecsys DADE-BEHRING
POINT OF CARE	BIOSITE-Triage	DADE BEHRING: Stratus CS pBNP
Hormonally active	Yes	No
Half life	22 min	120 min
Clearance mechanism	Neutral endopeptidase clearance receptors	Renal clearance
Increases with aging	+	+++
Cut-offs for diagnosis of chronic heart failure[18, 1 20, 21]	100 pg/ml	Men: 100 pg/ml Women: 150 pg/ml Age > 75 yr: 450 pg/ml.
ASSAYS IN QUOTED 2005 PRIMARY STUDIES		
UK Natriuretic Peptide Study[7]	Biosite	Roche
PRIDE[22]	Bayer (in subgroup analyses)	Roche
BASEL[10]	Biosite	-

Key messages

- **BNP and NT-proBNP assays are available for both laboratory setting and POC testing.**
- **Whether measurement of NT-proBNP is equivalent, superior or inferior to measurement of BNP for diagnosing the cause of dyspnoea is uncertain.**

3.2.3. Normal values of BNP and NT-proBNP

Originally, levels of natriuretic peptides were most often reported in SI units (pmol/l), but increasingly pg/ml is used. To convert from pmol/l to pg/ml, levels have to be multiplied by 3.45 for BNP and by 8.5 for NT-ProBNP.[23]

In a study by Redfield et al[24] a normal subset of 767 subjects was identified which were in sinus rhythm and without cardiovascular, renal or pulmonary disease or diabetes, on no cardiovascular medication and with normal systolic, diastolic and valvular function. The distribution of BNP in the normal subgroup by age and gender is shown in Table 3. Adjusting for age, BNP was higher in women than men and increased with age within each gender. Plasma BNP was 32% higher in women than men (confidence interval = 15% to 51%, $p < 0.001$) by Shionogi assay and 80% higher by Biosite assay (CI = 50% to 116%, $p < 0.001$).

Table 3: Plasma BNP by age and gender in normal subjects

Table 1. Plasma BNP (Biosite [BNP-B] and Shionogi [BNP-S] Assays) by Age and Gender in Normal Subjects

Gender BNP	Age 45–54 n	Age 45–54 Median (25th, 75th)	Age 55–64 n	Age 55–64 Median (25th, 75th)	Age 65–74 n	Age 65–74 Median (25th, 75th)	Age 75–83 n	Age 75–83 Median (25th, 75th)
Women								
Biosite	180	18 (10, 32)	135	27 (15, 43)	56	29 (19, 52)	17	67 (28, 89)
Shionogi	194	28 (13, 55)	141	32 (18, 68)	59	45 (20, 111)	18	58 (26, 172)
Men								
Biosite	181	7 (3, 13)	111	11 (5, 20)	40	18 (7, 37)	2	21 (17, 24)
Shionogi	193	17 (9, 34)	118	31 (14, 49)	42	28 (10, 58)	2	38 (31, 44)

The median 25th and 75th percentiles are shown.
BNP = brain natriuretic peptide.

Source: Redfield et al. 2002[24]

Hess et al studied the reference interval determination for NT-proBNP in healthy blood donors using an immunoassay (Elecsys proBNP, Roche Diagnostics).[25] NT-proBNP clustered in all blood donors below the age of 50 years but significant differences in NT-proBNP levels were shown between the age group between 40 and 50 and between 50 and 60 as well as between 60 and 69 (see Table 4). Based on the assumption that individuals below the age of 50 years had a low prevalence of cardiac disease, the 97.5th percentile was determined and found to be 84 pg/ml in males and 146 pg/ml in females, respectively, and designated upper limit of normal.

Table 4: NT-proBNP levels in healthy subjects according to age and gender

Age and gender classified NT-proBNP levels (pg/ml) in apparently healthy blood donors (N=1980)

Age group	Age 18–29 years, median: 25 years			Age 30–39 years, median: 35 years			Age 40–49 years, median: 44 years			Age 50–59 years, median: 54 years			Age 60–69 years, median: 62 years		
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female
N	492	268	224	573	375	198	461	314	147	296	202	94	158	125	33
Min	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Median	20	20	37	22	20	37	21	20	50	36	25	61	46	43	68
97.5th	112	65	130	119	88	132	128	95	169	185	172	249	303	278	303
Max	196	108	196	211	211	190	534	534	392	865	865	287	960	960	303

Source: Hess et al. 2005[25]

The mechanism of age-related changes in BNP levels is unclear. The study of Redfield et al[24] rigorously assessed diastolic function and excluded subjects with even "age-related" diastolic dysfunction. Thus, diastolic dysfunction would not appear to be an explanation for the association of age and natriuretic peptide levels. Alterations in renal clearance, production, secretion, or metabolism may occur with age and alter natriuretic peptide levels. Similarly, the reason for higher natriuretic peptide levels in women is unclear, although the study of Redfield et al suggested that oestrogen status may play a role as older women on hormone replacement levels had higher BNP levels than those not on hormone replacement therapy.[16]

The plasma levels of BNP and NT-proBNP vary depending on the assay method employed and the nature of the control population.[4] The definition of 'abnormal' varies widely in both BNP and NT-proBNP studies and ranges between the equivalent of 5 pmol/L and 49 pmol/L (median 16 pmol/l = 55.2 pg/ml) for BNP studies and the equivalent of 5 pmol/L and 250 pmol/l (median 31 pmol/l = 263.5 pg/ml) for NT-proBNP studies. This variation is likely to be a reflection of the wide spectrum of patients encompassed by individual studies (including an explicit distinction made between males and females in some studies) and a desire on behalf of researchers to optimise test performance in a given population.[11]

Apart from age and sex, NPs are sensitive to other biological parameters, such as haemoglobin and weight. In 2004, Wang et al[26] reported the results of the relations between NP and body mass index (BMI) in 3389 Framingham Study participants without HF. Obese and overweight individuals had considerably lower plasma natriuretic peptide levels than individuals with a normal BMI, a finding that could not be attributed to underlying differences in cardiovascular risk factors

or cardiac structure between obese and non-obese subjects. The validity of this observation was supported by its consistency across both BNP and N-ANP, in both sexes, and in separate analyses focusing on low NP values. In women, an abdominal pattern of obesity additionally predicted lower NP levels, even after adjustment for BMI.

Finally it should be noticed that there is a high biologic variability of NPs: among healthy volunteers it is at least 25% and possibly higher, even up to 100%. [27]

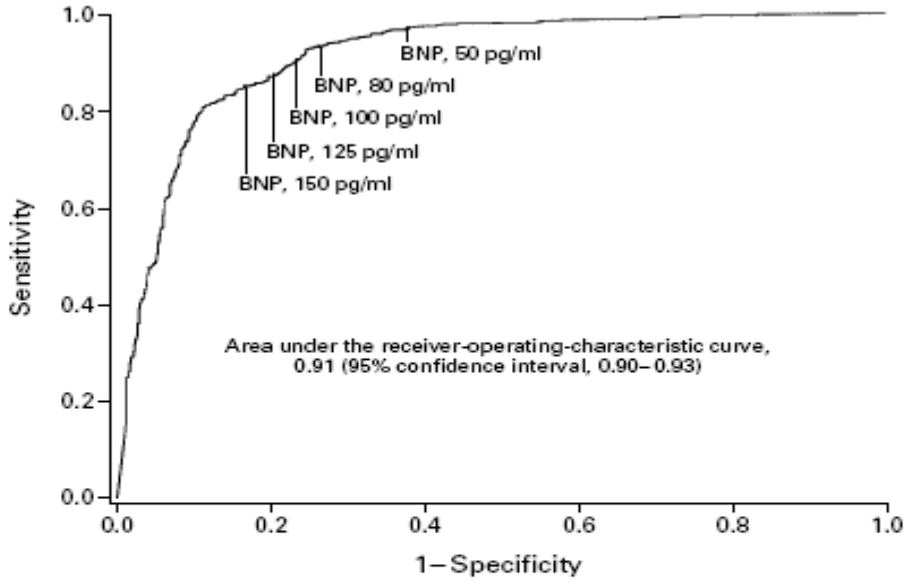
Key messages

- **NP levels are higher in women than in men and increase with age within each gender.**
- **There is a high biologic variability of NPs: in healthy volunteers it is at least 25% and possibly higher, even up to 100%.**
- **Apart from age and sex, NP levels are sensitive to other biological parameters, such as haemoglobin and BMI.**
- **These elements should be taken into account in the interprtation of the NP results.**

3.2.4. Natriuretic peptide values in LVSD and overt HF

Serum BNP levels have been shown to increase in patients with HF. In the Breathing Not Properly Study, Maisel et al [28] obtained the following receiver-operating-characteristic (ROC) curve (Figure 3) for various cut-off levels of BNP in differentiating between dyspnoea due to HF and dyspnoea due to other causes. Their optimal cut-off point for making the diagnosis of HF was 100 pg/ml.

Figure 3: ROC curve for various cut-off levels of BNP

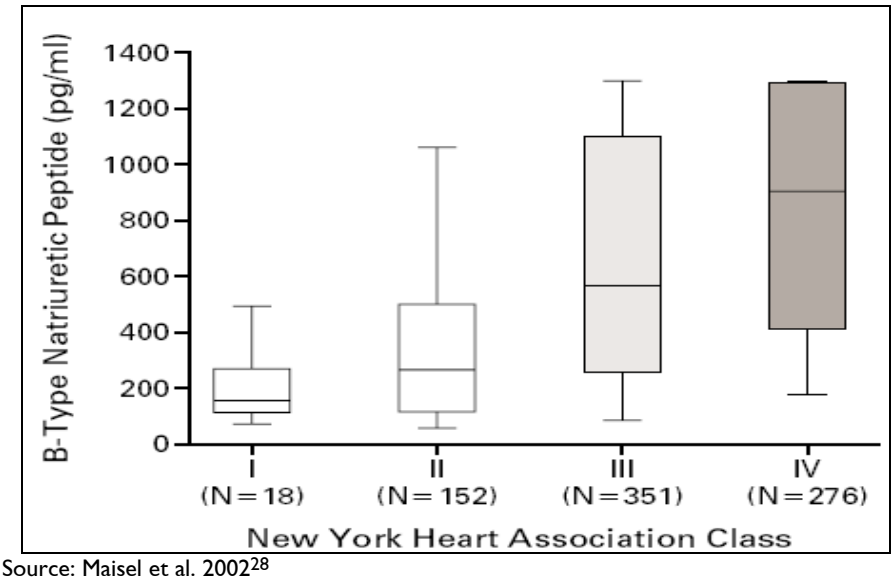


BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent confidence interval)				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

Source: Maisel et al. 2002[28]

NPs levels parallel the clinical severity of HF as assessed by NYHA class in broad populations. They are higher in hospitalized patients and tend to decrease during aggressive therapy for decompensation. However for the time being, it is not clear whether BNP levels can be used effectively as targets for adjustment of therapy in individual patients. Many patients taking optimal doses of medications continue to show markedly elevated levels of BNP.[6] Figure 4 depicts box-plots from the Breathing Not Properly study showing median levels of BNP among patients in each of the four NYHA classifications. BNP values differed significantly as a function of the severity of HF. It can be inferred from the figure that most patients in NYHA class I, i.e. HF patients rendered asymptomatic, still show BNP levels above the "diagnostic level" of 100 pg/ml. Their mean BNP level was 244 ± 286 pg/ml.

Figure 4: Boxplots of BNP levels according to NYHA class (Breathing not Properly study)



Source: Maisel et al. 2002[28]

For NT-proBNP, in a study of the use of NP in the diagnosis of HF, Wright et al[29] obtained a ROC curve with an area under de curve of 0.85. Sensitivity and specificity were maximized at a cut-off of 100 pmol/l (= 850 pg/ml).

In the UK natriuretic peptide study, plasma BNP concentrations were available for 301 patients, and NTproBNP in 302 patients. The correlation between the plasma concentrations of both peptides was very high (r =0.92). BNP was higher in patients with a confirmed diagnosis of HF (median and 90% range 285 [29–1300] pg/ml) compared with the other patients (51 [7–350] pg/ml). A similar difference was found for NTproBNP (1537 [166–21 854] pg/ml compared with 202 [22–2323] pg/ml.[7]

The cut-off value suggested by the manufacturer for use in the detection of CHF is 100 pg/ml for the BNP POC assay and for the Bayer laboratory-based BNP assay in those aged 55 years or older. In Europe the suggested cut-off values for NT-proBNP are 100 pg/ml for men and 150 pg/ml for women, but 125 pg/ml for both genders in the United States.[18] NT-proBNP levels are more affected by age than BNP levels. The current recommendation from Roche suggests that the appropriate cut-off for HF detection is 125 pg/ml below the age of 75 years and increases at the age of 75 to 450 pg/ml.

Key messages

- **Serum BNP levels have been shown to parallel the clinical severity of HF as assessed by NYHA class in broad populations.**
- **Asymptomatic patients with cardiac dysfunction, (NYHA class I) have higher NP levels than patients with other reasons of dyspnoea.**
- **Differences in suggested cut-off values illustrate the current uncertainty regarding the optimal use of BNP testing.**

3.2.5. Natriuretic peptide values in conditions other than HF

Common cardiac abnormalities that may cause elevated NP levels include left ventricular hypertrophy, valvular heart disease acute or chronic ischemia, arrhythmias and hypertension. A high BNP may also signify non-cardiac disease such as renal dysfunction, pulmonary embolism and chronic obstructive pulmonary disease. The underlying mechanism of NP elevation in these conditions might at least partly be the result of an increased cardiac wall stretch. In renal failure, an impaired clearance of the peptide also plays an additional role. Moreover, high levels of NP might reflect both sub-clinical and clinically overt structural heart disease which is overwhelmingly prevalent in these patients.[27] The mutual influence of HF and renal function is not yet fully clarified.[30] It has been suggested to use a higher cut-off rule-out value of BNP in patients with renal disease (200-225 pg/ml instead of 100 pg/ml) and suspected HF.[31] In a subgroup analysis of the BASEL study, the mean BNP-level in patients with a non-cardiac cause of dyspnoea and renal dysfunction was nearly 300 pg/ml.[31]

In the PRIDE-study, the most common cause of an elevated NT-proBNP in the absence of acute CHF was non-cardiac dyspnoea in a subject with a history of CHF. In these subjects, NT-proBNP levels exceeded the diagnostic thresholds for acute CHF in 57% patients.[27]

Baggish et al[27] reported the association between elevated BNP levels and mortality among patients with hospitalized with shock resulting from various aetiologies. They demonstrated that elevated NP levels were potently predictive of adverse outcomes but totally unrelated to filling pressures. The authors suggest that, similar to the situation observed with elevations of serum troponin T in critically ill patients, elevations of BNP might be consequent to subtle alterations in myocardial structure and function resulting from cytokine-mediated injury, as well as direct toxic effects of medications such as catecholamine infusions used in the intensive-care setting.

Key messages

- **Cardiac abnormalities other than HF that may cause elevated NP levels including left ventricular hypertrophy, valvular heart disease, cardiac ischemia, arrhythmias and hypertension.**
- **A high BNP may also signify non-cardiac disease such as renal dysfunction, pulmonary embolism and chronic obstructive pulmonary disease.**

4. CLINICAL EFFECTIVENESS

4.1. METHODOLOGY

An initial hand-search was performed in August 2005 aimed at identifying recent high-level evidence on the diagnostic use of natriuretic peptides such as HTAs and systematic reviews. We found three HTA reports: (1) a report from Alberta Heritage Foundation For Medical Research[18], originally published in July 2004 and updated in January 2005, (2) a NHS Quality Improvement Scotland HTA report.[1] published in May 2005 and (3) a HTA Report on the use of BNP for the diagnosis and management of HF by ICSI, released in August 2005.[17] A SR on the prognostic value of BNP was published in March 2005 by Doust et al [32]. In October 2004, the same authors had published a SR on the diagnostic accuracy of natriuretic peptide for HF.[33] Januzzi et al performed a SR on the value of NT-proBNP, an abstract of which was presented in a poster session at the ACC annual meeting of March 2005. The paper is reportedly accepted for publication in the European Heart Journal but only an abstract of a poster session presented is available so far. [34]

Due to a limitation of the allocated time, we decided to limit our systematic search to the literature published from July, 1 2004 on, because recently published HTAs had covered the literature until the end of 2004. A first search was performed in August 2005 and it was repeated at the end of October 2005. We limited our selection to systematic reviews, HTA reports and randomized trials, the latter limited to those in which the reference test was a clinical diagnosis of HF. We searched papers in the CRD database, Medline, Embase (keywords: "heart failure" and "natriuretic peptides") and in the Cochrane Library. We used the same MeSH and text word terms for the Medline search as those described in the papers by Doust et al. Details of it are given in Appendix 1. Only papers which were not included in one of the aforementioned HTA reports were used to update the results of the latter. The methodological quality of the studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist.[35] In addition to a literature search in scientific literature databases, different stakeholders, including manufacturers and professional associations, were contacted for additional information. External experts in the field of HF and natriuretic peptides were consulted.

The hierarchy of the evidence levels of diagnostic efficacy as described by Fryback and Thornbury were used in this report.[36] Details of it are described in Appendix 2. We ended with the relevant recent literature data presented in Table 5

Table 5: Relevant clinical literature

	STUDY	SHORTHAND TITLE	DIAGNOSTIC EVIDENCE LEVEL
HTA REPORTS			
1	Alberta Heritage Foundation[18]	BNP for diagnosing congestive HF	
2	NHS Scotland[1]	Natriuretic peptides in the investigation of HF	
3	ICSI[17]	BNP for diagnosis and management of CHF	
SYSTEMATIC REVIEWS			
4	Doust[32]	BNP prognostic use	NA
5	Davenport[11]	Diagnostic value to identify LVSD	2
6	Wang[37]	Dyspnoeic patient in ED	3
PRIMARY LITERATURE			
7	Zaphiriou[7]	UK Natriuretic Peptide study	2
8	Januzzi[22]	PRIDE study	2
9	Mueller[38]	BASEL Elderly subgroup analysis	5
10	Mueller[31]	BASEL Kidney disease	5

4.2. LITERATURE REVIEW

First, we summarize the results of the HTA reports, then we discuss the recent systematic reviews and finally, we describe more extensively the 2005 primary literature, the results of which are than compared with antecedent evidence and included in a general summary.

4.2.1. HTA Reports

ALBERTA HERITAGE FOUNDATION HTA REPORT[18]

This report focuses on the scientific evidence on the accuracy of both BNP and NT-proBNP to differentiate acute dyspnoea caused by HF from other conditions. It is labelled as a "TechNote", i.e. "a brief report, prepared on an urgent basis, which draw on limited review and analysis of relevant literature". It specifically addresses the use of NPs in patients presenting with dyspnoea and only those studies in which the diagnostic accuracy of NPs was assessed against clinical judgement as the standard reference test were considered.

The majority of the studies included found that average BNP or NT-proBNP levels were significantly higher in patients with HF compared to patients with no HF. In these studies, patients were without renal failure, acute myocardial infarction or unstable angina. NP levels were correlated with the clinical severity of HF and inversely correlated with left ventricular ejection fraction.

The SR by Cardarelli et al[39] which was the only SR retained in this HTA report, showed that a BNP level of 80 pg/ml had sensitivities ranging from 93% to 98% in diagnosing CHF in symptomatic patients, and NPVs ranging from 92% to 98%, demonstrating the ability of BNP to rule out CHF.

The authors conclude that the NP test might be a useful addition to the diagnosis of HF in the primary care setting where over-diagnosis of HF is common, enabling (well-informed) GPs to correctly rule-out CHF. In the ED population, in conjunction with other clinical information, rapid BNP measurement is useful in diagnosing or ruling out CHF. The diagnostic value of echocardiography with Doppler analysis appears to be superior to the NP test for confirming HF.

It still seems to be early to judge the relative clinical value of the BNP versus NT-proBNP assays for diagnosing the cause of dyspnoea. The optimal BNP cut-off values, either for establishing the diagnosis of HF or for ruling out HF, remain to be determined.

NHS HEALTH TECHNOLOGY ASSESSMENT REPORT 6[1]

This HTA report takes the NICE recommendations on chronic HF, published in 2003,[3] as a starting point. In these guidelines, it is recommended that health professionals should seek to exclude a diagnosis of HF through the use of an ECG and/or BNP or NT-proBNP where available. If one or both are abnormal, echocardiography and referral to a specialist should be done. This HTA was undertaken to establish the place of BNP in the diagnosis of HF in Scotland. More specifically it investigated whether or not a normal BNP or NT-proBNP result should be used for patients with signs and symptoms of possible HF, in the primary care setting to inform the decision to refer a patient to a specialist or in the ED to inform decisions around treatment and placement of patients. Clinicians in primary and secondary care are assumed to use an ECG for such patients and hence the use of ECG represents an important aspect in this HTA. An economic model of the primary care setting compared the clinical and cost effectiveness of the current diagnostic pathway (physical examination and an ECG, followed by referral if there is clinical suspicion of HF) with (1) specialist aided ECG interpretation and (2) BNP testing, before deciding to refer a patient with suspected HF to a specialist.

Data from different studies were combined using a meta-analysis approach. For BNP in diagnosing HF with a cut-off of 100 pg/ml, a pooled sensitivity of 0.91 (95% CI: 0.90 – 0.93) and a pooled specificity of 0.73 (0.71 – 0.75) was calculated with a pooled diagnostic odds ratio of 36 (17-74). For NT-proBNP, the corresponding figures were 0.91 (0.88 – 0.93), 0.76 (0.75 – 0.77) and 40 (18 – 88). The resulting estimated NPVs were similar for BNP and NT-proBNP, depending on a pre-test prevalence of 5, 15, 25 or 50%: 99, 98, 96 and 89%.

The conclusions of this report can be summarized as follows. A cardiologist report of an abnormal ECG and BNP tests have similar sensitivities but the latter have higher specificity. There is very little published data on how accurately GPs interpret ECGs. There is no evidence that the accuracy of BNP differs from that of NT-proBNP. However, more studies have been conducted using BNP, and behaviour in concomitant disease and in the elderly is better characterised with BNP.

The accuracy of NPs is greatest in severe disease. The accuracy is poorer in patients who are receiving therapy for HF.

GPs who do not record ECGs in their own practice should adopt BNP-tests when deciding which patients to refer for further assessment for HF. The test result should be used to rule-out a possible diagnosis of HF. Physicians in the ED should use BNP tests, in conjunction with other clinical information, for patients in whom there is genuine diagnostic uncertainty after standard evaluation, and no timely access to echocardiography. The test result should be used to rule-out HF. There is evidence that the availability of rapid BNP results in admission units, in addition to the standard initial clinical assessment, may improve the evaluation and treatment of patients. This could reduce the length of stay and total treatment costs compared with current practice.

INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT HTA REPORT.[17]

The scope in this report is limited to BNP only and does not consider NT-proBNP, "since BNP has been the most well-studied of the NP". As far as BNP measurement in the evaluation of patients with suspected HF is considered, the conclusion of this HTA is as follows. BNP measurements are useful as an adjunct to other clinical tools for differentiating HF from other causes of dyspnoea presenting in the emergency department or urgent care setting. In particular, the diagnosis of HF is highly unlikely in patients with normal BNP levels. Care should be taken when measuring BNP within 2 to 4 hours after the onset of acute symptoms as false negatives may occur.

4.2.2. Systematic Reviews

We retrieved four SRs on NP, published in 2005. We considered two of them being not relevant for the current report. The SR by Doust et al[32] studied the use of BNP in predicting death and cardiac events in patients with HF, which was beyond the scope of our analysis. The SR by Davenport et al[11] studied the diagnostic accuracy of natriuretic peptides in de diagnosis of left ventricular systolic dysfunction. As discussed earlier, our survey was limited to studies which specifically included patients with HF presenting with dyspnoea, irrespective of left ventricular function. The SR by Januzzi is not yet published in detail and hence we were not able to fully assess its possible contribution to our HTA.

In October 2005, a SR was published by Wang et al.[37] It is a comprehensive study which assesses the usefulness of history, symptoms and signs along with routine diagnostic studies (chest radiograph, ECG and BNP) to differentiate HF from other causes of dyspnoea in the ED. The authors notice that a high initial clinical suspicion of HF alone (LR 4.4) had a greater positive LR than a composite of (high clinical suspicion or BNP >100 pg/ml or both), which had a combined positive LR of 3.1. They conclude that BNP may not contribute much more in patients for whom the initial clinical suspicion of HF was already very high. However, in patients for whom the initial clinical suspicion of HF was not very high, BNP at a threshold value of 100 pg/ml was useful, especially for excluding heart failure in this group of patients. Hence, to apply these results correctly, it is necessary that clinicians first quantify and acknowledge their clinical suspicion (eg, formulate a pre-test probability). In this review, no individual feature was sufficiently powerful in isolation to rule heart failure in or out and an overall clinical impression based on all available information was best. The authors conclude that, if the appropriate constellation of findings with high LRs for HF is present, that may be sufficient to warrant empirical treatment without further urgent investigations. Conversely, if the clinical suspicion of heart failure is very low (e.g. pulmonary disease), the physician should investigate and treat other causes of dyspnoea.

4.2.3. Primary Literature

According to our predefined limits, three primary papers qualified for inclusion in this review. A summary of the details of these studies are summarized in Table 6. A more comprehensive table can be found in Appendix 3.

Table 6: Overview of Primary Clinical Literature

STUDY	SET	REFERENCE	INDEX TEST	CUT-OFF	PPV	NPV
UK Natriuretic Peptide Study	ED	cardiologist (history, clin, echo , X-ray)	BNP; proBNP	BNP: 100; proBNP: 125 pg/ml	proBNP 0,44 BNP 0,59	proBNP 0,97 BNP 0,87
PRIDE Study	ED	cardiologist (id., clinical data up to 60 days)	proBNP	proBNP: 300 pg/ml	0,62	0,99
BASEL Study: Elderly and Renal failure subgroups	ED	NA	BNP	BNP: 100 pg/ml	NA	NA

UK Natriuretic Peptide Study.[7]

This study has already been implemented in the NHS Quality Improvement Scotland HTA report. It was not yet published at that moment. The main objective of the study was to determine the diagnostic accuracy of both BNP and NTproBNP in patients with symptoms suggestive of HF referred by their GPs to rapid access HF clinics. 306 patients were included. HF was diagnosed by

the cardiologist if there was at least one symptom of HF (shortness of breath, fatigue, leg oedema) at rest or on exertion and objective evidence of cardiac dysfunction on assessment including echocardiography. The diagnosing physicians were blind to the BNP and NTproBNP results. The diagnosis of heart failure was confirmed in 104 (34%) patients. At the manufacturers recommended decision cut-points, NTproBNP provided a higher NPV (0.97) than BNP (0.87), but at lower PPV (0.44 versus 0.59). The authors used a range of decision cut-points to obtain different sensitivities and specificities as shown in Table 7. The sensitivity value obtained in this trial is is lower compared to other studies that showed an overall sensitivity estimate of > 90%.

Table 7: Diagnostic Utility of NP testing

Table 3
Diagnostic utility of ECG and plasma NTproBNP and BNP at a range of decision cut-points

Peptide	Sensitivity	Specificity	PPV	NPV
Manufacturer recommended cut points				
NTproBNP ≥ 125 pg/ml	0.98	0.35	0.44	0.97
BNP ≥ 100 pg/ml	0.79	0.72	0.59	0.87
Other cut-points				
NTproBNP ≥ 166 pg/ml	0.96	0.43	0.46	0.96
BNP ≥ 65 pg/ml	0.87	0.57	0.51	0.90
BNP ≥ 30 pg/ml	0.95	0.35	0.43	0.93
ECG				
Abnormal	0.81	0.60	0.51	0.86

PPV positive predictive value; NPV negative predictive value; LR+ positive likelihood ratio; LR − negative likelihood ratio.

Source: Zaphirou et al. 2005[7]

They confirm the value of the measurement of plasma BNP or NTproBNP as a rule-out test for HF in patients referred by GPs to rapid access diagnostic clinics. It is interesting to note that at the manufacturers' recommended cut-offs, the BNP (but not the NT-proBNP) assay has a slightly poorer sensitivity than ECG. As the cut-off level is reduced, sensitivity improves but specificity declines. This suggests that in patients corresponding to the population studied, a low cut-off for Biosite BNP (30 pg/ml) is needed to retain high sensitivity. At this cut-off level, a NPV of 0.93 is obtained.

In the NHS Quality Improvement Scotland HTA report, an interesting exercise is done by calculating the benefit of NP testing from the population studied by Zaphiriou. This analysis (Table 8) shows how referral patterns would be altered for 1000 patients currently referred for rapid-access echocardiography as in the Zaphiriou paper, assuming a true prevalence in this group of 25.2% (that is, the GP specificity for diagnosis of heart failure is 0.252).

Table 8: Benefits of NP Testing

Patient sub-group	Number of patients
No BNP	
Referred – not heart failure	747
Referred – heart failure	252
NT-proBNP >125 pg/ml	
Avoided referrals – not heart failure	261
Missed referrals with heart failure	5
BNP – 100 pg/ml	
Avoided referrals – not heart failure	538
Missed referrals with heart failure	53
BNP – 30 pg/ml	
Avoided referrals – not heart failure	261
Missed referrals with heart failure	13
ECG	
Avoided referrals – not heart failure	448
Missed referrals with heart failure	48

Source: Craig et al. 2005[1]

This table suggests that 1000 NT-proBNP tests at the manufacturer's recommended cut-off could yield a saving of 261 referrals for further assessment and echocardiography.

PRIDE study.[22]

In this prospective trial 600 patients who presented in the ED with dyspnoea were studied. The primary end point of the study was a comparison of NT-proBNP results with the clinical assessment of the managing physician for identifying acute CHF. The diagnosis of the managing physician was based upon standard clinical assessment in the ED, including ECG and X-ray but not echocardiography. He was asked to estimate (on a scale from 0% to 100%) the likelihood that acute HF was the cause of the patient's dyspnoea. Reference diagnosis was provided by a study cardiologist who used all available data from presentation through a 60-day review, without knowledge of the NT-proBNP testing.

Using the estimates of the attending physicians, receiver-operating characteristic curves that compared the sensitivity and specificity of NT-proBNP results with those of clinician-estimated likelihood for diagnosis of acute CHF were drawn. NTproBNP alone was superior to clinician-estimated likelihood of CHF alone (area under the curve 0.94 vs 0.90). Adding the results of NT-proBNP to those of clinician estimation for the presence of acute CHF improved the sensitivity and specificity further, with an area under the curve of 0.96.

An age-independent NT-proBNP cut-off point of <300 pg/ml was optimal for ruling out acute CHF, with a negative predictive value of 99%. Specificity was less good and ranged from 68% to 86% depending on an accepted cut-off value ranging from 300 pg/ml to 1000 pg/ml. Accordingly, PPV ranged from 62 to 78%. To optimize the performance of the test in ruling in HF, the authors suggest age-dependent cut-off points, depicted in Table 9.

Table 9: Optimal Cutpoints Depending on Age

TABLE 2 Optimal NT-proBNP Cutpoints for Ruling In and Ruling Out Acute Congestive Heart Failure (CHF)*

	Optimal Cutpoint (pg/ml)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
Rule-in cutpoints						
All patients (n = 599)	900	90	85	76	94	87
<50 yrs old (n = 144)	450	93	95	67	99	95
≥50 yrs old (n = 455)	900	91	80	77	92	85
Rule-out cutpoint						
All patients (n = 599)	300	99	68	62	99	83

*NT-proBNP testing was of value to identify and exclude acute CHF with high accuracy. In the PRIDE study, the optimal rule-in strategy using NT-proBNP was an age-stratified approach with 2 cutpoints, whereas a single cutpoint of 300 pg/ml was of value for excluding the diagnosis.

Source: Januzzi et al. 2005[22]

At the ACC annual meeting of March 2005, these authors presented the results of a review on the value of NT-proBNP for the evaluation of acute HF. Based on these, in order to increase specificity, they proposed an extra age-dependent cut-off point for ruling in HF at 1800 pg/ml for ages above 75 years, resulting in a specificity of 0.72 and a sensitivity of 0.85.[34 27]

During the months following the index paper, several subgroup analyses have been published on the PRIDE –study. In one of these,[19] presents data on the ejection fraction of the HF-patients included in the trial. The overall relationship between natriuretic peptides and EF was rather weak. Half of the patients had an EF of > 50% and hence suffered from diastolic HF. Levels of both NT-proBNP and BNP (as measured by the Bayer Advia assay) were significantly lower in patients with diastolic HF. In contrast to NT-proBNP however, BNP was false negative in up to 20% of patients with diastolic HF. The authors conclude that NT-proBNP might be superior to BNP for the evaluation of suspected acute HF in patients with preserved EF. Sakhuja et al[40] studied the diagnostic value of a combination of an elevated NT-proBNP and a prolonged QRS complex in diagnosing LVSD in the PRIDE population. The combination of an elevated NT-pro-BNP level plus a wide QRS-complex was associated with 100% sensitivity and 71% specificity for a decreased LVSD. The results of this study however are less important in the current report because they concentrate on LVSD whereas our interest is focused at clinical HF. Krauser et al[41] studied the effect of BMI on NP in the HF patients from the PRIDE cohort. When adjusted for relevant covariates, compared with normal counterparts, overweight and obese patients with

acute HF had lower circulating NT-proBNP and BNP levels. NT-proBNP fell below the diagnostic cut-off for CHF less often than BNP in these patients. The authors conclude that, when used as a diagnostic tool to identify HF in such patients, both markers may have reduced sensitivity.

BASEL STUDY[38]

The B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) Study is a prospective, randomized, controlled, single-blind study conducted in the emergency department of the University Hospital in Basel, Switzerland.[10] In the index study, which was published in 2004, of 452 patients who presented to the emergency department with acute dyspnoea, 225 were randomly assigned to a diagnostic strategy involving the measurement of BNP levels with the use of a rapid bedside assay, and 227 were assessed in a standard manner. The time to discharge and the total cost of treatment were the primary end points. The use of BNP levels in conjunction with other clinical information reduced the rate of hospital admission by 10 percentage points, the median length of stay by three days, and the mean total cost of treatment by about 1800 $. The rates of readmission and mortality within 30 days after discharge were similar in the two groups.

The mean age of the patients in this study was 70 years. Elderly people however represent the major part of patients with HF. They are characterised by specific features that might compromise the validity of the results of studies in which younger subjects with HF were included: elderly patients have more co-morbidity, they have poorer renal function and they more often have diastolic HF. In order to evaluate whether the original results of the BASEL study were valid in the elderly part of the cohort, the authors published a subgroup analysis of their data on patients older than 70 years. The mean age of these patients was 80 years. As in the original trial identical BNP cut-off levels were used to separate HF from other causes of dyspnoea. In patients with a BNP level below 100 pg/ml, HF was considered unlikely. In patients with a BNP above 500 pg/ml, HF was considered likely and therapy for HF was initiated. For BNP levels in-between the protocol recommended further diagnostic testing. The usefulness of BNP determination found in the BASEL trial was confirmed in this sub-study: the median time to discharge was reduced by 2 days, total treatment cost was 2000 $ less and in addition, a significant reduction in 30-day mortality was observed.

A second subgroup analysis was published on patients with renal failure,[31] i.e. patients with a calculated glomerular filtration rate less than 60 ml/min/1.73m at presentation and a serum creatinine of less than 2.8 mg% (as patients with severe renal disease had been excluded in the index BASEL study). The same BNP cut-off values as in the original cohort were used. In contrast to patients without kidney disease, in those with kidney disease the use of BNP did not significantly improve outcome. This can be explained by the fact that the same cut-off values for BNP were used in renal failure patients as in the unselected cohort. The mean BNP-level in patients with a non-cardiac cause of dyspnoea and renal dysfunction was nearly 300 pg/ml. This is three times the cut-off value used for exclusion of HF. Accordingly, only very few patients with kidney disease and non-cardiac causes of acute dyspnoea will present with BNP levels below 100 pg/ml and can accordingly be diagnosed as not having HF. As the high NPV for HF is seen as the most important feature of BNP testing, the failure to significantly improve the management of patients with renal failure with the currently approved cut-off values seems logical. Data from the Breathing not Properly Multinational study indicate that 225 pg/ml may be the best cut-off point for these patients.[31]

We attributed the BASEL study and its subgroup analyses an evidence level 5 because it was a randomised trial of a diagnostic technology that focused on patient outcome, i.e. the impact of BNP level on the outcome in terms of mortality of (elderly) patients presenting with acute dyspnoea. We decided not to allocate a level 6 because the time horizon of 30 days was considered to be too short to allow an estimation of the impact on society.

4.2.4. Up To Date Literature Summary

Use of BNP in primary care setting

Two studies assessed the use of a NP test in patients presenting at the GP's office with dyspnoea and/or peripheral oedema. In a RCT, Wright et al[29] found that NT-proBNP measurement (> 850 pg/ml) improved the diagnostic accuracy of HF by 21% (from 49% diagnoses correct to 70%

correct) compared to an improvement by 8% in a control group without the NT-proBNP measurement. The resulting increase of diagnostic accuracy of 13% allows the calculation of a number needed tot diagnose of seven. The measurement of NT pro-BNP in 7 patients with a provisional diagnosis of HF is needed to re-characterize one patient correctly. This study shows that NT pro-BNP measurement significantly improves the diagnostic accuracy of HF by GPs.

Nielsen et al.[42] evaluated the utility of NT-proBNP for the detection and exclusion of HF in a patient population seen in GP with symptoms of dyspnoea for at least two weeks. The authors suggest that for patients aged 50 years and older, HF could be ruled out with a high probability if the NT-proBNP level did not exceed 94 pg/ml in men and 145 pg/ml in women.

We could not retrieve diagnostic studies that specifically studied BNP in HF in general practice. The UK natriuretic peptide study[7] considers patients sent to rapid access clinics by GPs, but it does not evaluate how NPs change diagnostic performance of GPs. The role of the GP in this study is limited in defining the index population studied.

From a GP's perspective, current evidence from the literature can be summarized as follows: NPs can be a useful addition in the diagnosis of dyspnoea in patients with suspected HF, enabling GPs to correctly rule-out HF. Evidence is relatively weak and is obtained from only two studies. More research is needed to firmly state that the wide availability of NP assays in primary care will lead to a decrease of referrals of patients intitially suspected of suffering HF. The usefulness of NP measurement in general practice will heavily depend on selection of patients by GPs. Therefore, information and education of GPs on the appropriate indications and limitations of NP testing is mandatory.

Use of BNP in emergency care setting.

The highest evidence in this setting, up to 2004, was from the Breathing Not Properly multinational study[28] involving 1586 patients. ED physicians, blinded to the results of the BNP test, provided an estimate of the probability of the presence of CHF on a visual analogue scale. Two independent cardiologists, blinded to both the BNP results and the ED physician's diagnosis, determined the final diagnosis based on the review of all relevant clinical information. The area under the ROC curve for various cut-off levels of BNP in differentiating between dyspnoea due to HF and dyspnoea due to other causes was 0.91. At a cut-off of 100 pg/ml sensitivity was 90% and specificity 76%. PPV was 79% and NPV was 89%. In a subgroup analysis[43] it was suggested that adding the BNP test to clinical judgment would enhance accuracy from 74% to 81% in determining the correct diagnosis (HF versus no HF). According to the authors, clinicians should probably use a low cut-off if the main goal is to exclude the possibility of HF (rule-out).

The PRIDE study, published in 2005,[22] was similar in design to the Breathing Not Properly Multinational study, but studied the utility of NT-proBNP in the ED to rule-out acute HF. An age-independent NT-proBNP cut-off point of <300 pg/ml was optimal for ruling out acute CHF, with a negative predictive value of 99%. In order to increase specificity in this setting, and to be able to use BNP as a rule-in test, Januzzi et al, in a yet unpublished study,[34] propose to make use of age-dependent cut-off values for NT-proBNP: < 50 years old, 450 pg/ml, 50-75 years: 900 pg/ml and > 75 years: 1800 pg/ml. This algorithm has yet to be validated. The figures are in accordance with those obtained by Wright et al[29] in a GP based study in patients with a mean age of 70 years where sensitivity and specificity were maximized at a cut-off of 850 pg/ml.

The UK Natriuretic Peptide Study confirms previous suggestions that BNP measurement is especially useful in ruling out HF. From the results of this study and estimating a prevalence of 25% in the GP setting, it has been calculated in the NHS HTA report that the number of patients to test in order to prevent one referral for specialist examination is four (261/1000).

The BASEL study is the only trial that has investigated the therapeutic impact and the effect on patient outcome of NPs in patients with suspected HF admitted to the ED. The study suggests that the use of NP in these patients can lead to a shorter hospital stay and a lower cost of treatment. Approximately one third of the cost-savings associated with the use of BNP measurement was achieved because the result led to an alternative diagnosis, one that did not require hospitalization. This effect is consistent with the high NPV of a low level of BNP with respect to the diagnosis of HF. It is not yet fully known how the remaining two thirds of the observed cost-savings in the BASEL Study resulted from the detection of an elevated level of BNP in the ED.[44]

Key messages

- In patients with HF, the average NP levels are higher compared to patients without HF.
- NP measurements are useful as an adjunct to other clinical tools for differentiating HF from other causes of dyspnoea.
- It is particularly useful to correctly ruling-out HF in patients in which there is genuine clinical doubt about the origin of the dyspnoea. In primary care a number needed to diagnose of 7 is needed to re-characterize one patient correctly after notification of the NP level. A calculation in the ED setting suggested that of 4 patients being tested with NT-proBNP, one referral for further examination could possibly be avoided.
- NPs are unlikely to be useful as a rule-in test for HF. Problems arise with the sex- and age dependency of NP levels, and the influence of obesity, renal function, haemoglobin and co-morbidities which influence NP levels, apart from HF as such. Cut-off levels that take into account all these variables have yet to be defined.
- The accuracy of B-type natriuretic peptides is poorer in patients who are receiving therapy for HF.
- There is no evidence that for clinical purposes the accuracy of BNP differs from that of NT-proBNP.
- There is evidence that the availability of rapid BNP results in the ED, in addition to the standard initial clinical assessment, may improve the evaluation and treatment of patients

5. ECONOMIC EVALUATION

5.1. REVIEW OF ECONOMIC STUDIES

5.1.1. Methods

Economic studies were searched using the search filter from Chuck ([45]), which we adapted to include economic studies about NT-proBNP. Our search strategy, including databases and filters, is presented in the Appendix 4.

The search results were limited to references published after 2000. Abstracts of retrieved entries were screened. References were excluded from further analysis for various reasons. Obviously, the absence of (substantial) cost analysis in the study design was an important reason. In addition, studies assessing patient populations that were not relevant for our purposes (diabetes patients or renal patients, asymptomatic patients, etc) were excluded from further analysis. Likewise, the use of peptides for other purposes than patient diagnosis (hormonal drug treatment, screening of the general population, etc) was not taken into consideration.

Fifteen unique references were retained for further analysis. One study, which had not yet been referenced in the searched databases due to its recent publication date, was added.[45]. All 16 full text documents were then analysed. The perusal of available full text documents allowed researchers to narrow relevant publications down to 4 ([46, 10, 45, 1]). Evidence tables on these publications are available in Appendix 6 to Appendix 9. The following section summarizes the main findings.

Key messages

- **The literature review produced 16 full text documents for further analysis.**
- **4 relevant publications were eventually selected.**

5.1.2. Results

All studies retained for this review were cost-minimisation analyses. It is assumed that final (clinical) outcomes of patients diagnosed with BNP or without BNP would not differ. The major potential benefit of BNP is considered to be the cost-savings generated by the procedure.

Two studies relied on observational data to estimate the cost-savings with BNP [10 46] and two studies based their calculations on a model [1 45]. Two studies looked at the use of BNP in an acute care setting [10, 45], one at both acute and primary care [1] and one at primary care only [46].

Acute care setting

Mueller et al. 2004 [10] conducted a prospective RCT in 452 patients with acute dyspnoea presenting in an emergency department. A standard diagnostic protocol (history, physical, ECG, pulse oximetry, blood test, chest radiography and ECHO) was followed for the control group. The BNP-group concerned patients who followed a clinical protocol including BNP testing. BNP testing was used as a rule out tool for heart failure for patients with BNP levels below 100pg per millilitre. Patients with levels between 100pg and 500pg per millilitre were submitted to "clinical judgement and possible further diagnostic testing". With patients testing above the 500 pg threshold "heart failure was considered the most likely diagnosis". As a result, it is not univocally clear whether BNP testing is used solely as a rule out tool or also as a rule-in test and hence as a substitute for other diagnostic tests such as echocardiography. Endpoints taken into consideration were time to discharge, time to (appropriate) treatment and total cost of treatment as approximated by hospital charges. The study indicates that the BNP-group benefited from a shorter time to treatment, a shorter time to discharge and less need for hospitalization, resulting in a lower overall cost of treatment. Researchers concluded that BNP testing was cost-saving ($5410 compared to $7264 for control group, (two-sided) 5% significant difference (t-test)). No sensitivity analysis, however, was performed in order to assess the robustness of this

finding. As hospital charges for one particular institution were used to approximate real overall costs, assessing the sensitivity of the results for various "hospital bill effects" seems necessary.

Chuck et al. 2005 [45] present a cost estimation of BNP for the diagnosis of heart failure applying to the Canadian province of Alberta. The report's objective was to estimate costs over a one year period of a Point-of-Care BNP assay from a payer's perspective. The BNP test is used to rule out congestive heart failure from other pulmonary conditions in acute care in patients suffering from acute dyspnoea. Several cost scenarios (drawing on published medical outcome data and mostly on provincial cost data) are considered, differentiating patient cohorts by age and sex. The distinction made between an urban and rural setting is of little relevance to Belgium. The importance of factors like sex and age (corresponding to different BNP cut-off values in the model) is illustrated in this model. Furthermore, the model emphasizes the importance of substitution of echocardiography by preliminary (rule-out) BNP-testing as a necessary condition to render the introduction of BNP cost-saving. The report concludes that "compared to standard protocols, BNP testing in one year could considerably reduce total costs." This overall effect would be more important in urban settings and in populations with a high prevalence of congestive heart failure (i.e. older populations). It should be noted, however, that the model indicated that relative gains are more important in low prevalence populations (as these run a higher risk of false-positives undergoing an echocardiography otherwise).

Craig et al. 2005 [1] deal with the cost-effectiveness of diagnostic BNP testing for suspected heart failure patients in their HTA report. The cost analysis of BNP in acute care is based on the results of Mueller et al. 2004 and adapted to Scottish cost data. Two types of costs were taken into account: cost for a single BNP test and average cost per day in hospital. Savings were achieved through lower admission rates and diminished times to discharge. The potential cost-saving of adopting rapid BNP testing as a standard rule-out tool in an acute care setting was estimated at £430 per patient (21,77% drop in treatment costs).

Primary care setting

Craig et al. 2005 [1] also dealt with the cost-effectiveness of diagnostic BNP testing for suspected heart failure patients in primary care. The potential economic effects of BNP testing were assessed in a cost model, calculating the cost differences in the entire diagnostic process (including costs following a false-positive and false-negative result) but not treatment or follow-up. The results of this model prove to be sensitive to a wide range of variables as demonstrated by univariate sensitivity analyses. Consequently, authors diffidently conclude "that using B-type natriuretic peptide tests in primary care could be cost-saving if the specificity of the tests GPs currently use to refer patients for echocardiography is less than 50%."

Sim et al. 2003 [46] investigated the use of BNP in decisions about patient referral to further echocardiographic examination. The study focused on patients with breathlessness visiting their GP. If referral was needed, the patient went to an open access echocardiography service for testing. An observational within group comparison among 83 patients (all receiving both echocardiography and BNP) was performed in order to assess the possible value of BNP testing. Costs were assessed from the treating service's perspective, limiting the analyzed cost items to echocardiographies and BNP tests. Net savings of BNP testing as a rule-out tool to avoid unnecessary echocardiographies were calculated. The authors conclude that "there would be a net saving of £964.20 without compromising the diagnostic accuracy." This net saving (21,5% reduction in costs) leads to the conclusion that BNP measurement appears to have a significant economic benefit for the selection of patients for echocardiography. Savings from differences in hospitalization admissions and length of stay were not included. This is an important limitation of this study.

5.1.3. Discussion

From the literature review we can conclude that BNP could be cost-saving if applied as a means to rule out heart failure in suspected (dyspnoeic) patients in both acute and primary care settings. Potential cost-savings can primarily be obtained from reducing the number of other diagnostic interventions and the number of days spent in hospital. These beneficial cost outcomes are at a par with potential patient benefits such as reduced time to appropriate treatment and reduced time to hospital discharge.

Critical in all studies is the assumption that other diagnostic interventions such as echocardiography are no longer performed in patients who test negative on a preliminary BNP test. Therefore, supplier behaviour is the key in assuring the cost-effectiveness of BNP testing as an addition to current practice [45].

Various questions remain with regard to the comparability of existing BNP assays (e.g. the cost overview of various BNP test in published literature, see Appendix 5) and the impact of age, sex and co-morbidities on the (cost-)effectiveness of this technology. Chuck et al. demonstrated how allowing for some of these factors in their analysis rendered results more robust.

Further elements to be taken into consideration are the estimation of costs related to false results (false-negatives in particular) and the potential benefit patients enjoy from establishing a rapid and correct negative diagnosis. None of the economic studies looked at cost-effectiveness or cost-utility in terms of cost-per-life year gained or cost per quality adjusted life year gained. This is related to the absence of clinical studies comparing final outcomes such as survival between diagnosis with or without BNP.

Key messages

- **Findings in the literature tentatively indicate that BNP and Nt-proBNP are cost-saving as a rule-out diagnostic procedure for suspected heart failure patients in an emergency setting; in primary care, the cost-saving nature of NPs assays is less strongly documented, but should not be dismissed.**
- **Essential questions regarding diagnostic properties and long term outcomes remain unanswered.**

5.2. PRIMARY ECONOMIC EVALUATION

We performed two primary cost-minimisation analyses to translate the results found in literature to the Belgian context. The use of BNP in the acute care setting and the primary care setting is examined. Both analyses are performed from the perspective of the health care payer (Belgian Health Insurance reimbursement)

5.2.1. Acute care setting

Model Design

The model for Belgium draws on the studies from Mueller et al. (2004) and Craig et al. (2005) to estimate the cost effectiveness of BNP testing in patients with symptoms of heart failure presenting in an acute care setting. Costs considered 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 numbers 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.

Sources for data

Clinical data

Data with regard to hospital admission and median length of stay were based on Mueller et al. (2004). For two hypothetical cohorts of 100 suspected patients these parameters are presented in Table 10.

Table 10: Clinical Parameters based on Mueller et al. 2005

		BNP Group	Control Group
Number of patients	Total	100	100
	Admitted	75	85
Median time to discharge (days)		8	11

Final discharge diagnoses for patients are summarized in Table 11. A significant difference in the prevalence of pulmonary diseases was found between the BNP Group and Control Group. The authors put forward that "this finding corresponds well with a recent observation that exacerbation of chronic obstructive pulmonary disease frequently escapes recognition in the emergency department […] and may well have gone unrecognized as the cause of acute dyspnoea in a considerable number of patients in the control group."

Table 11: Final Discharge Diagnosis as indicated by Mueller et al. 2005

		BNP Group	Control Group
Number of patients	Total	100	100
	Admitted	75	85
Heart Failure		45	51
Exacerbation of Pulmonary Disease		23	11
2 Combined Causes (Heart Failure and Exacerbation of Pulmonary Disease)		5	4
Undefined Cause		2	19

Economic data

The lowest price quoted by members of the industry applying to Belgium for 2005 was 18€ (Biosite laboratory test). This amount will be used in the base case analysis. The daily bed costs per diagnostic category (Table 12) are derived from the reported length of stay ([47], [48]) and overall cost of hospital stay ([48]) applying to Belgium. These data concern Belgian government reimbursements for the year 2000.

Table 12: Derived Daily Cost applying to Belgian hospitals

Diagnostic Category	Average Length of Stay (days)	Overall Cost for Hospital Stay (€)	Derived Average Daily Cost (€)
All Causes	8,2	3.164,70	385,94
Chronic Obstructive Pulmonary Diseases	13	4.121,18	317,01
Heart Failure	15	4.410,49	294,03

Based on Table 11 and Table 12 average daily bed costs for the BNP Group and the Control Group were calculated. It is assumed that patients for whom the final discharge diagnosis could not be established were treated throughout their hospital stay as symptomatic heart failure patients. Hospital stays for patients diagnosed with both heart failure and a pulmonary condition are assumed to correspond to a mean daily cost, defined as the arithmetic average of average

daily bed costs for heart failure and pulmonary diseases. Consequently, 66% ((45+2+2,5)/75) and 85% ((51+19+2)/85) of hospital stays for the BNP Group and Control Group respectively are assigned to the category of "Heart Failure". The remainder of hospital stays is assigned to the category of "Pulmonary Diseases" for both groups. As a result the weighted average daily cost is 301,85€ for the BNP Group and 297,55€ for the Control group.

Sensitivity analyses

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. Theoretically, if shorter hospital stays would generate no savings at all, the rise in average daily cost would be 37,5% (11 days/8days% - 1%).

Cost formula

The difference in cost per patient between a BNP and a control group patient equals:

$\Delta[(Admissions_{BNP} * (DBC_{BNP} * LOS_{BNP}) + Patients_{BNP} * BNP\ Test\ Cost))/Patients_{BNP}, (\#Admissions_{CONTROL} * DBC_{CONTROL} * LOS_{CONTROL})/Patients_{CONTROL}]$

With:

"DBC": daily bed cost

"LOS": length of stay

Subscripts "BNP" / "CONTROL": applying to patients in the BNP/Control Group

Results

Base case analysis

Base case results (see Table 13) indicate a cost-saving of 953€ per patient. This is a decrease of 34,3% compared to the cost of standard treatment.

Table 13: Base case results for the Acute Care Model

		BNP Group	Control Group
Number of patients	Total	100	100
	Admitted	75	85
Length of Stay (days)		8	11
Cost of BNP testing (€)		18	
Average Daily Bed Cost (€)		301,85	297,55
Cost per Patient (€)		1.829,10	2.782,09

Sensitivity analyses

Setting "Cost of BNP testing" at 12,17€ and 40,54€ led to a respective drop in savings percentages from 34,5% to 33,4%. (elasticity of -0,01). These input figures are based on reimbursement levels for Japan and the USA ("national medicare limit") as indicated in the Appendix 5: Cost/price of BNP in different countries. The modelling results appear to be robust to changes in the reimbursement of BNP.

Assuming that the "Average Daily Bed Cost" for the BNP Group rises with 37,5%, brings the savings percentage down from 34,3% to 9,8% (elasticity of -4,8). This reflects the strong impact of assumed daily bed costs on the modelling results.

Assumptions and limitations

In this model we assumed that the number of admissions and hospital days in the BNP group and the control group in Belgium are as those found in the study by Mueller et al. 2004. However, the results of this study may have been influenced by patient related factors and health care system related factors. There may be differences in demographic and medical traits between the analysed patients and Belgian patients. Furthermore, the reimbursement system and hospital financing regulation may be different, which may have an impact on clinical practice. The observed discrepancy between the average length of stay applying to Belgium and the data reported by Mueller et al. 2004 illustrates this problem.

Daily bed costs for Belgium are derived by dividing total costs for hospital stays by corresponding average lengths of stay according to applying broad diagnostic categories. An important remark should be made. Given the presumed shorter hospital stay for the BNP protocol, the average length of stay for "heart failure" may actually diminish if BNP would be implemented. This would imply a higher average daily cost if the overall hospital costs for "obstructive pulmonary" decreases less than proportionally with the average length of stay. This is likely to be the case, due to fixed costs associated with hospitalisation and due to the fact that the first days in hospital are generally more expensive than later days. The costs of hospitalisation may hence not necessarily go down at a constant rate, as assumed in our base-case model.

The constituent cost averages of daily bed costs are assumed to be equal for the BNP group and the Control Group. In practice, however, the cost for the BNP group could be lower, as there may be a substitution effect in diagnostic interventions. For example, BNP negative patients will not need an echocardiography. Properly correcting for these effects would require insight into the proportion of heart failure and pulmonary disease patients among suspected patients. Furthermore, a detailed and exhaustive overview of cost items per type of hospital stay (BNP group versus Control group) is needed on a day-to-day basis. As these data were lacking, we could not correct the average daily bed cost for the BNP group. This implies that in our model there is a one to one relationship between the costs for hospital stays and the number of hospital days. Furthermore, the marginal cost for each added day a patient spends in hospital is considered to be constant.

The model was limited to the estimation of cost-savings in a period of the first 30 days following admission, as in the study by Mueller et al. No assessment of long term effects was performed.

Discussion

Our analysis indicates that the use of BNP testing in an acute care setting could be cost-saving. However, given the assumptions underlying the estimation of the average daily bed costs applying to Belgium, the base case results should be interpreted with due reserve. This conclusion is corroborated by the sensitivity analyses.

Further prospective research is necessary to reach definitive conclusions about the cost effectiveness of BNP testing in acute care. Research should include a detailed description of cost items, comparing patients undergoing clinical assessment respectively with and without BNP testing. Cost analysis should take day-to-day cost item overviews into account, clearly distinguishing various cost categories (e.g. overheads, labour, consumables) so that the marginal cost for added days in hospital can be evaluated in detail. Longer follow-up of patients is essential in order to assess the impact of false negative BNP findings on long term costs and outcomes.

Key messages

- **Base case analyses indicate that BNP testing is cost-saving in acute care.**
- **However, the estimation of more refined "average daily bed costs" requires a substantial effort in further research.**

5.2.2. Primary care setting

Model Design

A general framework is developed to assess the use of BNP testing as a diagnostic rule out tool in primary care, based on previous work by Craig et al. 2005. Relevant diagnostic protocols are shown in Figure 5 and related cost drivers are shown in Table 14. This analysis focuses exclusively on diagnostic interventions for suspected heart failure patients in primary care. Costs of subsequent treatment (ensuing hospital stays) are not taken into account, neither are costs incurred by further diagnosis to establish the nature of conditions other than heart failure. It is assumed that negative BNP tests exclude subsequent interventions by cardiologists (including echocardiographic testing). As a consequence, savings may be obtained from substitution among diagnostic interventions and from fewer referrals to a specialist. Current diagnostic protocols in primary care are assumed to differ only from the BNP protocol with regard to the use of BNP testing and its effect on the number of referrals and the use of echocardiography.

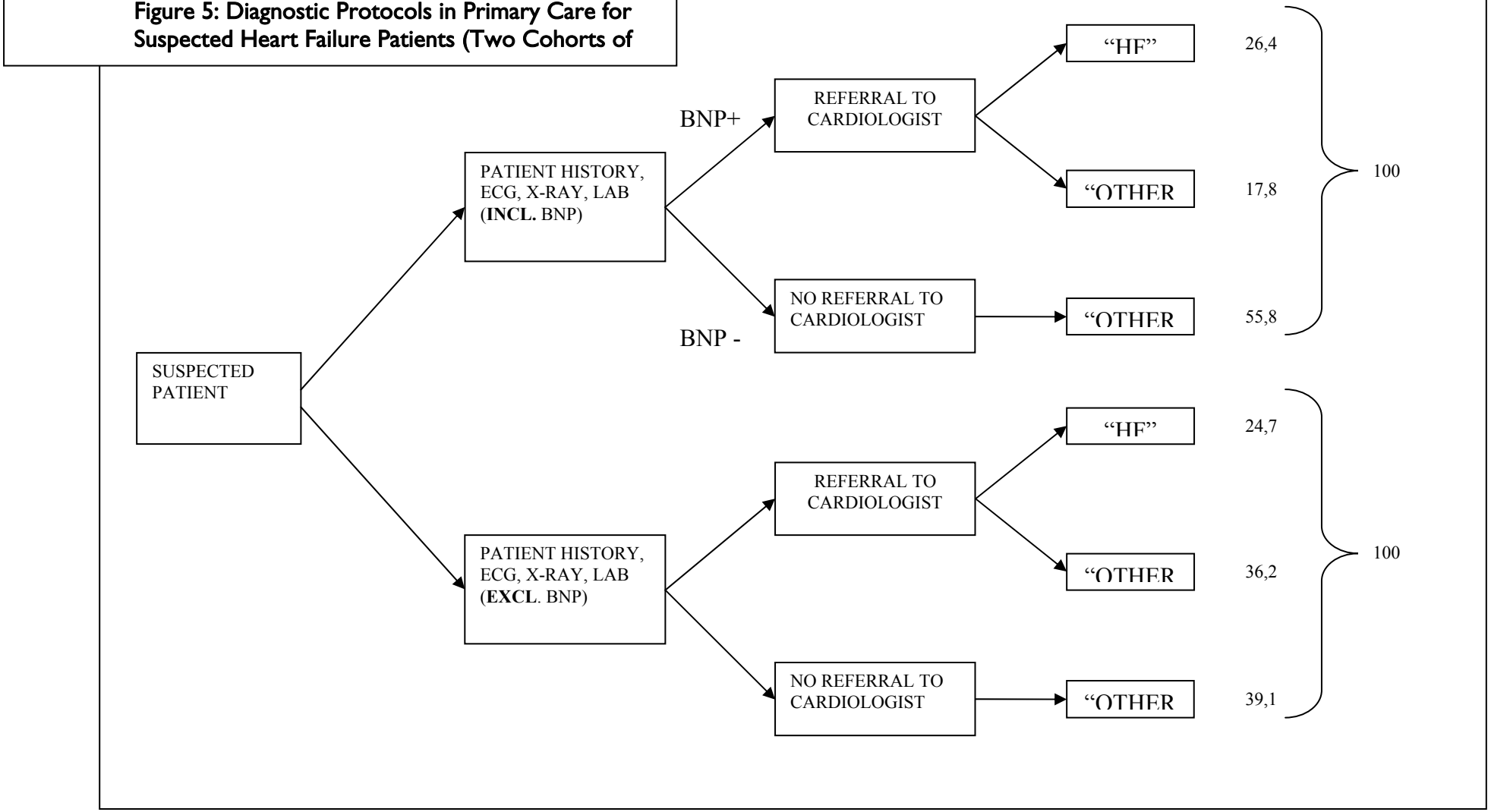
Possible savings would be realised through a reduction in the number of visits to a cardiologist and the number of diagnostic interventions by cardiologists. Only first time patients undergoing diagnosis are taken into account. Abstraction is made of costs incurred by false negative test results.

The incremental cost-effectiveness of BNP testing was examined by calculating the incremental cost per additional correctly diagnosed patient in primary care. In particular, the added cost per true negative was reported as this measure reflects the performance of BNP as a rule out test.

Table 14: Relevant diagnostic cost drivers

Cost Items	Clinical Protocols				Labour (incl. fees)	Equipment		
	Current		BNP rule out			Consumables	Fixed Costs	
	No Referral	Referral	No Referral (BNP-)	Referral (BNP+)			Annual Machine Life	Overheads
1st ECG	X	X	X	X	X	X	X	X
CHEST X-RAY	X	X	X	X	X	X	X	X
LAB (excl. BNP)	X	X	X	X	X	X	X	X
BNP TESTING			**X**	**X**	X	X	X	X
ECHO		**X**		**X**	X	X	X	X
2nd ECG		**X**		**X**	X	X	X	X

Figure 5: Diagnostic Protocols in Primary Care for Suspected Heart Failure Patients (Two Cohorts of



Sources for Data

Clinical Data

Data on incidence and prevalence of heart failure vary considerably "as there is no gold standard for the diagnosis of heart failure and there has been much variation in the diagnostic criteria used in previous studies" [49]. No specific study on the epidemiologic background of heart failure among Belgian patients was found. Therefore, it is not possible to estimate the overall cost effects for the Belgian population. Derived effects will be calculated on a per patient basis.

In the outpatient setting, "many investigators have found that there are 3 referrals of suspected heart failure per true case" [50]. Cowie et al. (1997) found a prevalence of heart failure of 29% among newly suspected heart failure patients. We used this figure, together with combined pooled sensitivities and specificities for BNP- and NT-proBNP testing from Craig et al. (2005). An overview can be found in Table 15. For our two hypothetical cohorts of 100 patients in each "arm" of the model, this resulted in the patient numbers mentioned in Figure 5.

Table 15: Diagnostic Parameters Applying to Primary Care

Intervention	Sensitivity	Specificity
BNP test (95% CI)	91% (90%-93%)	75% (74%-76%)
GP-read ECG	85%	49%

Economic Data

A price of 18€ for a BNP test was imputed in the model (Biosite laboratory test, see Appendix 5). This amount will be applied in base-case calculations as a value for the supposed health care reimbursement. A cardiologist consultation fee[a] is 30,6€, of which 19,97€ is reimbursed. Reimbursement of Echocardiography is currently 59,84€ according to the Belgian reimbursement scheme[b] ([51]). Supposing interventions by cardiologists entail additional cost for the reimbursement of an ECG[c], a total cost of 92,97€ for every cardiologist's intervention is assumed (December 1st 2005 as a reference date).

Cost Formula

The cost difference per suspected heart failure patient between the algorithm with BNP and the algorithm without BNP equals:

$$\Delta[(BNP_{-} * Cost_{BNP} + BNP_{+} * (Cost_{BNP} + Cost_{cardiol})) / \#Patients_{susp} ,$$

$$(\#Referred\ Patients * Cost_{cardiol}) / \#Patients_{susp}]$$

with:

Subscripts "- / + " indicating negative/positive BNP test result

Subscripts "cardiol" referring to costs by cardiologist interventions

Subscripts "susp" referring to suspected patients

Subscripts "BNP" referring to costs by BNP testing

[a] Reimbursement corresponding to RIZIV-INAMI nomenclature code 102594 "consultation by an accredited cardiologist"

[b] Reimbursement corresponding to RIZIV-INAMI nomenclature code 469814, "full transthorax echographic cardiac overview"

[c] This amount includes a reimbursement of 13,16 € (RIZIV-INAMI nomenclature number 475075).

Assumptions and limitations

The analysis focuses exclusively on costs generated by diagnostic protocols in primary care. It is assumed patients of both protocol groups undergo a homogeneous set of diagnostic interventions prior to being respectively BNP tested (BNP protocol) or referred by the GP (non-BNP protocol). Patients who tested BNP negative are supposed not to be referred for further cardiologic examinations. Costs due to possible differences in treatment times and waiting times were not taking into account. Cardiologist interventions are assumed to include an echocardiography. Abstraction was made of costs incurred by false negative test results. Cost drivers are therefore limited to the number of BNP tests and cardiologist interventions performed on newly suspected heart failure patients undergoing first time diagnosis.

Differences in travel costs, patient benefits from swift diagnostic exclusion, etc. were not included. The reimbursement for BNP testing is set at a supposed maximum level, covering the market price of 18€. This is the lowest price we obtained from the industry. Higher prices may prevail, which will reduce the potential cost-savings.

It is assumed that the patient population undergoing the diagnostic protocols are similar. Implicitly baseline simulations therefore do not take the possible impact of the BNP protocol on supplier behaviour into account. The reimbursement of BNP as a diagnostic intervention may, however, incite suppliers to test a wider population of patients due to the user-friendliness of BNP testing, financial motives, etc.

Sensitivity analyses

Sensitivity analyses were performed on the economic input variables (the reimbursement rate of BNP tests) and epidemiologic and diagnostic parameters (prevalence of heart failure, sensitivity and specificity of ECG in primary care).

Results

Base Case Results

Table 16 summarizes the estimated overall costs of both diagnostic algorithms for the hypothetical cohorts of 100 patients in each arm. The incremental cost of BNP is 2,47€ per suspected heart failure patient (i.e. a 4,4% rise in costs).

Table 16: Base Case Results Diagnostic Protocols: overall costs (€)

Protocol	BNP tested	Cardiologist Intervention	Total
BNP Group	1800	4109	5909
Non-BNP Group	0	5662	5662

Table 17 summarizes the marginal costs for each added true negative and each added correct diagnostic outcome. The introduction of diagnostic BNP testing does not result into overall cost-savings as compared with the baseline diagnostic protocol. Diagnostic accuracy, however, is better for the BNP group. The incremental cost per true negative result is 13€. The incremental cost per correct test result is 12€.

Table 17: Base Case Results Diagnostic Protocols: cost effectiveness

Protocol	Aggregate Cost	True-Negative Results	Added Cost/True-Negative	Correct Results	Added Cost/Correct Result
BNP Group	5.909 €	53,3		79,7	
Non-BNP Group	5.662 €	34,8	13 €	59,5	12 €

Sensitivity analyses

Economic variables

Setting the reimbursement for a single BNP test at 12,17€ (lower limit) or 40,54€ (upper limit) led to a rise in the incremental cost per suspected heart failure patient from respectively -3,36€ (incremental saving) to 25,02€. These reimbursement boundaries are based on the reimbursement levels for Japan and the USA ("national medicare limit") as indicated in the Appendix 5: Cost/price of BNP in different countries. With a sufficiently low reimbursement level, BNP diagnostic protocols would become both cost-saving and clinically more effective from a healthcare payer's perspective.

Epidemiologic and diagnostic parameters

Following Craig et al. 2005 a prevalence rate of 48% for both protocol groups was assumed in all calculations (Table 18).

Table 18: Sensitivity Analysis for Overall Prevalence

Protocol	Aggregate Cost	True-Positive Results	Added Cost/True-Positive	Correct Results	Added Cost/Correct Result
BNP Group	7.068 €	43,7		82,7	
Non-BNP Group	6.266 €	40,9	285 €	66,4	49 €

Applying the upper boundary values of the reported confidence intervals as an optimistic approximation of diagnostic BNP test parameters resulted into the outcomes reported in Table 19.

Table 19: Sensitivity Analysis for BNP diagnostic parameters

Protocol	Aggregate Cost	True-Negative Results	Added Cost/True-Negative	Correct Results	Added Cost/Correct Result
BNP Group	5.892 €	54,0		80,9	
Non-BNP Group	5.662 €	34,8	12 €	59,5	11 €

Assuming sensitivity and specificity of the Non-BNP diagnostic protocol drop to 50% and 25%, i.e. supposing GPs' are less competent in interpreting ECG results, leads to the results presented in Table 20. If this situation applies, the BNP protocol would be cost-saving and would improve diagnostic outcomes, i.e. BNP dominates current practice.

Table 20: Sensitivity Analysis for ECG diagnostic parameters

Protocol	Aggregate Cost	True-Negative Results	Correct Results
BNP Group	5.838 €	54,0	80,4
Non-BNP Group	6.299 €	17,8	32,3

Assuming a separate prevalence rate for the BNP protocol group of 20% leads to costs and effects as summarized in Table 21 and

Table 22. This simulation corresponds to a situation where supplier behaviour would alter due to organisational changes and more tests would be performed in general (ease of BNP testing, financial incentives, etc). In this hypothetical situation the BNP protocol at first would appear to be a cost-saving rule-out strategy. Taken the number of (true) positives into account, however, it becomes apparent that overall costs would rise considerably without enhancing the final diagnostic outcome for high risk patients.

Table 23 illustrates this by presenting the changes in positive and negative predictive values for the BNP test for the considered heart failure prevalences.

Table 21: Sensitivity Analysis for Varying Group Prevalences

Protocol	Aggregate Cost	True Positives	Added Cost/Positive
BNP Group 2 (20% prev)	5.351 €	18,2	294,0 €
Non-BNP Group (29% prev)	5.662 €	24,65	229,7 €

Table 22: Sensitivity Analysis for Varying (BNP) Group Prevalences

Protocol	Aggregate Cost	Positives	Added Cost/Positive
BNP Group 1 (29% prev)	5.909 €	44,2	133,7
BNP Group 2 (20% prev)	5.351	38,2	140,1

Table 23: Predictive Values for BNP Group Prevalences

Predictive Value	BNP (29% prevalence)	BNP (20% prevalence)
PPV	0,60	0,48
NPV	0,95	0,97

The model outcomes are fairly robust for changes in epidemiologic and diagnostic parameters. A remarkable finding with considerable policy implications is the possible impact of changes in supplier behaviour.

Discussion

Our analysis suggests that adopting diagnostic BNP testing for suspected heart failure patients in primary care is not a univocally preferable approach in comparison to a standard diagnostic protocol. Improvements in clinical outcome for patients incur additional costs for healthcare insurers.

This finding differs from conclusions by Craig et al. 2005. This discrepancy can be explained by several factors. Firstly, higher relative[d] costs for cardiologist interventions compared to BNP testing are taken into account by our analysis. Secondly, the number and type of considered cost drivers vary between both studies. Thirdly, no follow-up of false negative test results is taken into consideration by our model. Furthermore, the implicit cost perspective is societal: Craig et al. 2005 include costs for patient travel time and waiting times. This reflects unfavourably on costs related to echocardiography as waiting times, lasting over several months, should be accounted for when modelling outcomes applying to the NHS. Therefore, our analysis did not adopt the approach developed by Craig et al. 2005 to account for the follow-up of false negative results[e].

The analysis further emphasized the key importance of supplier behaviour. If proper medical scrutiny is not respected or enforced, BNP testing may considerably raise current overall diagnostic costs. The literature review did not yield publications assessing the impact of supplier behaviour.

Further research should cover the cost impact of organisational factors applying specifically to Belgium, a thorough assessment of the long term repercussions related to false negative results and possible changes in supplier behaviour.

Key messages

- **BNP testing in primary care is not an unambiguously recommended approach from a cost-effectiveness point of view.**
- **Further research should be dedicated to organisational issues, supplier behaviour and long term follow-up of patients.**

[d] A threshold ratio of 16,7% applies to the relative cost of BNP testing and cardiologists' interventions: below this value, the BNP protocol becomes cost-saving in our model. Craig et al. 2005 assumed 30,7€ for BNP testing and 159,14€ for costs related to taking an echocardiography.

[e] Given the baseline scenario, when the cost for treating a false negative patient under the BNP protocol remains below an amount equal to approximately 1,7 times the cost for treating a false negative in the standard protocol minus 95€, the BNP protocol is a dominant strategy, i.e. both cost-saving and diagnostically superior.

6. PATIENT ISSUES

From a patient's point of view, BNP testing represents a simple non-invasive test, only requiring a blood sample being taken. The POC test requires a venipuncture as well, rather than a finger prick to provide an adequate blood sample.

Although BNP testing on its own cannot be used to diagnose HF (rule-in), it is useful to rule out this diagnosis. Patients with dyspnoea showing a normal BNP level are very unlikely to suffer from HF which can be reassuring. Studies have shown that only about half of the people diagnosed with HF by their GP have the condition confirmed by further tests.[1] On the other hand, HF is a serious condition with a poor prognosis and hence, from a patient's perspective, it is very desirable to be informed at an early stage that one is not bearing this dreadful diagnosis. Timely excluding HF can avoid the patient not only being scared but also being prescribed unnecessary and sometimes even harmful medication. Correctly excluding HF by their GP can avoid the need for these often elderly people to travel to hospital for further testing.

The ability to cope with an illness for a patient, is affected by the attitude of the healthcare professional and his willingness to spend time explaining the condition.[1] A negative BNP test allows the GP to firmly exclude HF, a positive test will accelerate the decision process for seeking further advice. A BNP test gives the GP more certainty over a diagnosis in a patient with dyspnoea, which in turn will give the patient more confidence in the GP.

When a GP finds a positive BNP test in a patient with dyspnoea, further investigations are mandatory to correctly define and treat the underlying disease, the latter not necessarily being of cardiac origin.

For patients presenting at the ED with dyspnoea, ruling out HF enables doctors to focus on other possible causes of the patient's problem and to identify the appropriate treatment sooner. Moreover, in some cases a hospital admission will be avoided. On the other hand, correctly diagnosing HF early results in sooner initiating treatment and earlier identifying the underlying (cardiac) cause which may lead to sooner and even better recovery.

The most often cited cut-off values make BNP tests very sensitive resulting in a high NPV, i.e. few false negatives. So far, no studies have been published that consider the fate of the latter patients. The fact that a low BNP level implicates a good prognosis might nevertheless be reassuring. In a retrospective cross-sectional analysis, it was found that symptomatic patients with known and treated HF, demonstrating a plasma BNP level within the normal diagnostic range (i.e. < 100 pg/ml), were more likely to be younger, to be female, to have non-ischemic pathogenesis and to have a better preserved cardiac and renal function and were less likely to have atrial fibrillation.[52]

Key messages

- **Correctly ruling out HF can be reassuring for patients. It can eliminate further inappropriate testing and prescription of unnecessary and sometimes even harmful medication.**
- **BNP testing can allow GPs to prevent their patients being sent to hospital and in patients presenting at the ED, it can be a crucial aid to decide whether or not he/she should be admitted to hospital.**

7. ORGANISATIONAL ISSUES

This chapter outlines some of the organisational issues that could arise from providing BNP testing services in the acute sector and in primary care. The relevant literature from the clinical and cost-effectiveness searches was used, in addition to information from manufacturers and the expert group. A systematic literature search on the organisation of BNP testing services was undertaken. The economic search filter previously used by researchers was adapted to focus on relevant MeSH terms. The search strategy and searched databases are presented in Appendix 10. Six unique studies were selected for closer examination but none of the studies turned out to be relevant. Grey literature was searched using the Google search engine with various relevant entry keywords, but this search failed to produce relevant findings.

Both laboratory and point-of-care (POC) assays are available in Belgium. This POC test cannot be compared to the POC blood glucose testing because a venous blood sample is still needed instead of the more easy finger prick. The BNP result can be available within 15 minutes. Laboratory based tests take a similar time to process but samples need to be transported to the laboratory and procedures have to be implemented to report the results urgently. Within the Belgian legal framework, it would be allowed for quantitative POC testing to be executed and reimbursed outside a clinical laboratory. The question remains however whether the time gain outweighs the financial implications for adopting the test-kit and the better technical and organisational skills of clinical laboratories.

The accuracy of the diagnosis of HF by physicians, other than those specialized in cardiology, is improved markedly by the use of blood BNP concentrations in patients with heart disease [53] because it only requires a venous blood sample, which can be obtained at an outpatient clinic, and the results can be evaluated numerically. In contrast, evaluation of the findings from ECG and chest radiography requires training, and with echocardiography, a high level of skill is required, both for performing the examination and for the results. Thus, blood BNP measurement can be expected to be very useful for the detection of heart disease by general practitioners and physicians not specialized in cardiology. [54]

In the PRIDE study,[22] a ROC curve was constructed from the sensitivity and specificity of the attending physician estimated likelihood of HF, based on clinical examination, ECG and chest X-ray. An area-under-the-curve (AUC) of 0.90 was obtained, compared to an AUC of 0.94 for the sensitivity and specificity of NT-proBNP results. Adding the results of NT-proBNP to those of clinician estimation for the presence of acute CHF the sensitivity and specificity were further improved, with an AUC of 0.96. This is illustrated in Table 24.

Table 24: BNP Values by Varying Age and Gender

Table 1. Plasma BNP (Biosite [BNP-B] and Shionogi [BNP-S] Assays) by Age and Gender in Normal Subjects

	Age 45–54		Age 55–64		Age 65–74		Age 75–83	
Gender BNP	n	Median (25th, 75th)	n	Median (25th, 75th)	n	Median (25th, 75th)	n	Median (25th, 75th)
Women								
Biosite	180	18 (10, 32)	135	27 (15, 43)	56	29 (19, 52)	17	67 (28, 89)
Shionogi	194	28 (13, 55)	141	32 (18, 68)	59	45 (20, 111)	18	58 (26, 172)
Men								
Biosite	181	7 (3, 13)	111	11 (5, 20)	40	18 (7, 37)	2	21 (17, 24)
Shionogi	193	17 (9, 34)	118	31 (14, 49)	42	28 (10, 58)	2	38 (31, 44)

The median 25th and 75th percentiles are shown.
BNP = brain natriuretic peptide.

Source: Januzzi et al. 2005[22]

In this study, NT-proBNP is superior to standard clinical assessment but the combined use of clinical judgement and NT-proBNP is superior to either diagnostic modality alone. These results indicate that laboratory testing for NPs should not supplant clinical acumen.

In patients presenting with dyspnoea in the ED, a low serum level of BNP (100 pg/ml) or NT-proBNP (depending on age: 125 or 450 pg/ml), can be used to exclude acute HF as the origin of the dyspnoea. In these cases, additional cardiac imaging by means of echocardiography can be considered as futile in the diagnostic work-up of acute dyspnoea.

Symptomatic patients with known HF who present themselves to the ED can have normal or near normal NP levels but repeating an echocardiogram, mostly to confirm previous findings will only rarely be useful.

In patients in whom NP levels are high, further assessment is required and the NP measurement does not replace any current test to evaluate these patients and both cardiac and non-cardiac reasons are to be excluded as a possible aetiology of the complaints. Even in patients who are considered as having HF, an ECG and echocardiogram has to be performed because these examinations provide additional information on the aetiology and contributing factors to the HF problem (rhythm disturbances, ventricular hypertrophy, valvular lesions, …).

From an organisational point of view, standardization of the cut-off levels to be used is of utmost importance. Although there is not yet a universal agreement on cut-offs, currently a value of 100 pg/ml for BNP and 125/450 for NT-proBNP is most often used in clinical practice to rule-out HF in untreated patients.[55, 1] Some authors have proposed to use a higher BNP cut-off of 400 pg/ml or an age dependent NTpro-BNP level of 450 through 1800 pg/ml [34] in order to confirm a diagnosis of HF (rule-in) but evidently any increase in the threshold value increases the false negative rate.

It is not yet clear whether the use of NP testing will result in cost-savings from one perspective or another but it can enable patient needs to be met more rapidly. An unknown element in predicting possible cost-savings is the effect of reimbursement of the test on the number of requests by different groups of physicians. It is important to inform both GPs and specialists on the value and the use of the new laboratory examination simultaneously with its introduction into the nomenclature of reimbursed laboratory examinations. NP measurements should only be used in conjunction with other clinical information in patients in which there is genuine diagnostic uncertainty after standard evaluation. It should be clearly stated that for the time being, NPs can only be used to rule-out HF. The safe and relatively low cut-off level presented above should be proposed in order to minimize falsely ruling out HF. Finding levels above these cut-offs does not allow to make any conclusion on the origin of the patients condition.

Introducing a new laboratory examination and providing support and training in using it, might constitute an appropriate moment to reconsider the clinical indications of other laboratory exams that are obsolete, redundant or outmoded but nevertheless frequently used in daily practice.

Key messages

- **Both laboratory based and POC tests provide a NP test result within 15 minutes.**
- **NP testing does not replace history taking or clinical examination. The test is only useful in patients in which there is genuine doubt on the existence of HF.**
- **NP testing offers a simple and useful tool in the care of patients presenting with dyspnoea obviating access to more demanding techniques such as ECG and echocardiography.**
- **Training of physicians in interpreting the results of NP testing is imperative in order to make use of the test correctly.**

8. GENERAL CONCLUSIONS

The diagnosis and treatment of HF heavily relies on the scholarship, skills and judgement of practicing physicians. There is no single diagnostic test for HF. Most therapies of HF are guided by reproducing the treatment strategies used in clinical trials without a means of demonstrating a prognostic benefit in individual patients.[55] Hence, it comes as no surprise that physicians are enthusiastically welcoming NP measurement as a means that can help to overcome these limitations, providing them an easy-to-use intermediate endpoint, similar to the measurement of blood pressure or cholesterol.

Plasma NP measurement has been established as a helpful aid in the diagnosis of HF. It is best used as a rule-out test for suspected cases of new HF in breathless patients. This has best been documented in the emergency department setting. It can be expected to be particularly helpful to improve the diagnostic performance of non-cardiologists that are less skilled in clinical examination and electrocardiography such as ED physicians. The performance of the test in primary care is less well documented. It can be useful in ruling-out HF in this setting too, provided GPs are well informed on the indications and limitations of the test and make use of them accordingly.

A cut-off level of 100 pg/ml for BNP or 125 pg/ml for NT-proBNP (450 pg/ml in patients aged > 75 years) identifies patients who are unlikely to have acutely decompensated HF or acute worsening chronic HF. These cut-offs are relatively crude and need further refinement in the future. The symptoms of patients in whom HF has been excluded might be due to pulmonary disease, general internal conditions (anaemia, thyroid dysfunction,…), muskuloskeletal problems, obesity, lack of training, psychosomatic illness, … Some of these conditions are benign and hence, it can be reassuring to a patient to be informed his or her complaints are due to one of these. A normal test cannot completely exclude cardiac disease but a normal or low concentration in an untreated patient makes HF unlikely as the cause of symptoms. Nevertheless, values in the normal range are associated with an excellent prognosis. An NP measurement showing a level above these cut-off points on the other hand, can be associated both with acutely decompensated HF or a variety of other cardiac or non-cardiac conditions.

Overenthusiastic use of the test should be avoided. Although a lot of excellent studies on the topic have been done, many questions and uncertainties for a routine use of NP remain unanswered. Several confounders, including age, sex, renal function, cardiac rhythm, drug therapy and BMI have to be taken into account in the interpretation of NP results. NP measurements should not be used routinely in all patients presenting with dyspnoea. They should only be used in conjunction with other clinical information in patients in which there is genuine diagnostic uncertainty after standard evaluation. Most studies have been done in patients with new onset HF who were not yet treated with diuretics, ACE-inhibitors or beta-blockers. Higher cut-off levels might be applied in chronic HF patients to rule-out an acute exacerbation of HF although so far, the NP levels to use in these cases have not been well established. These limitations and caveats make clear that, from an organisational point of view, training of physicians in interpreting the results of NP testing is imperative in order to make use of the test correctly. Attention should also go to differences in the application of NP measurement between acute and primary care.

Patients with dyspnoea in which HF has been excluded by NP measurement in addition to clinical examination do not need further cardiac testing such as echocardiography. NP levels above the approved cut-offs cannot be used to differentiate diagnosis. Both cardiac and non-cardiac disease will have to be considered. This means that in these cases, NP measurement comes on top of other standard investigations. Both electrocardiography and echocardiography will be needed because they offer additional relevant information. Sometimes, echocardiography as well as ECG can reveal cardiac anomalies that are amenable to correction which can result in “curing” HF.

From a patient’s perspective, the introduction of NPs as a diagnostic tool can be especially rewarding when a diagnosis of HF can be excluded based on the NP result. It is reassuring to be informed timely that one has no HF. Moreover additional tests, referrals and sometimes a hospital admission might be avoided.

9. RECOMMENDATIONS

9.1. APPLICATION

The measurement of natriuretic peptides[f] is useful as a rule-out test of heart failure (HF) in patients presenting with recent onset dyspnoea in primary care and in the emergency department. Our 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, our 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€. 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.

Finding a low[g] NP level in a patient with dyspnoea renders acute HF very unlikely as the origin of the dyspnoea. It obviates the need for a GP to refer the patient to a cardiologist or to order additional cardiac tests including echocardiography. In the emergency department, a low NP level can avoid inappropriate cardiac testing or the initiation of a useless treatment. Moreover, it can prevent unnecessary admissions of some patients.

The positive predictive value for HF is not robust. This is because NP levels are dependent on several biological parameters in normal subjects (age, sex, weight, etc.) and because they can be elevated in a series of other medical conditions. Very high values of NP make HF likely but patients showing intermediate values need further exploratory investigations and no firm diagnostic conclusions can be put forward solely based on the increased NP level.

NP measurement has been most thoroughly studied in the acute care setting in patients with new onset dyspnoea. Although NP levels have been shown to parallel the clinical severity of HF and prognosis of patients in broad populations, it cannot yet be assumed that they can be used effectively as targets for adjustment of therapy in individual patients.

9.2. FINANCING

In light of the preceding analysis, three options are suggested for financing NP testing in patients with new onset dyspnoea:

- no reimbursement,
- restricted reimbursement in primary an acute care,
- restricted reimbursement in acute care and no reimbursement in primary care.

As the scientific debate on the appropriateness of cut-off levels and confounder influences is yet unsettled, policy makers could consider not reimbursing NP testing. Moreover, the lack of epidemiologic data applying to Belgium, particularly with regard to acute dyspnoea and its aetiology, would complicate the evaluation of medical practices.

Secondly, policy makers could contemplate the reimbursement of NP measurement with defined limitations on the frequency of testing per patient in primary and acute care settings. The frequency of testing could be limited to once in a lifetime or to once a year per patient in order to take into account new intercurrent cardiac events that can give rise to HF. In primary care, a once per year testing should be sufficient. It is unlikely that a patient will develop HF within a year following a negative NP test in the absence of an intercurrent cardiac event. In addition, given the additional cost associated with NP testing in primary care, it is reasonable to limit the number of tests per patient in order to maintain economic feasibility. The risk associated with reimbursement of NP testing in primary care is that there will be a rapid increase in the inappropriate use of this test. This threatens to raise costs in a considerable way and bears no guarantees of enhancing diagnostic outcomes for high-risk populations. Our sensitivity analysis confirms this. For acute care, a limit of one NP

[f] Natriuretic peptide(s) = NP(s), denoting BNP AND NT-proBNP.
[g] "Low" as defined in the general conclusions: below a cut-off level of 100 pg/ml for BNP or 125 pg/ml for NT-proBNP (450 pg/ml in patients aged > 75 years)

test per patient presenting at a given moment in the emergency department could be suggested. NP testing at time of possible admission allows to identify and/or exclude acute HF in the ED setting and is superior to standard clinical assessment. In addition, the combination of NT-proBNP testing plus standard clinical assessment appears to be superior to either diagnostic modality alone. However, the predictive value of the test as determined by up-to-date studies might no longer be applicable if the test is applied to new populations of patients in which both a very low (screening) or very high prevalence of HF (chronic HF patients) can become manifest.

A final option would be to reimburse restricted (cf. supra) NP testing in acute care, but to as yet renege on the reimbursement of NP testing in primary care. In the absence of solid evidence supporting the cost-effectiveness of NP testing in primary care and given the uncertainty on supplier behaviour, it would appear logical to defer any decision on NP measurement in primary care in anticipation of further research.

There is no evidence that for clinical purposes the predictive value of BNP differs from that of NT-proBNP, although the use of BNP is better documented. Therefore, an equal reimbursement rate for both tests seems reasonable.

Consideration of reimbursement for BNP or NT-proBNP might be good occasion to reconsider the indications and reimbursement of a number of obsolete, redundant or outmoded laboratory examinations still frequently requested in EDs or primary care for patients with dyspnoea. In 2006, the KCE will perform an evaluation of routine laboratory tests.

9.3. TRAINING

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.

NP levels appear to be strong predictors for adverse outcomes in patients with HF but their utility in terms of improving patient outcome as a tool to optimize management of HF has yet to be defined. This aspect represents a potentially useful application of NPs, on which especially cardiologists are keen. More studies are needed however to clarify the clinical utility of serial NP testing.

10. VALIDATION

The methodology applied in the report throughout chapters I-VIII was assessed by three external validators. Their main comments concerned the necessity:

- to clearly distinguish the report's scope, NP measurement for diagnostic purposes, from other possible applications of NP measurement such as prognosis and in particular clinical monitoring,
- to stress relevant differences in the application of NP measurement in acute and primary care,
- to present policy makers with practical recommendations on the implementation of NP measurement, especially regarding appropriate NP cut-off levels.

All of the above points were taken into consideration in the final version of our report. We presumed we were not able, based on current available literature, to make more specific recommendations on cut-off levels than those described in Table 2. Both 2005 reported HTAs[1], [18] emphasize that the optimal NP cut-off values and how these are affected by age, sex and co-morbidities, remain to be determined.

11. ANNEXES

11.1. APPENDIX 1

MEDLINE SEARCH CLINICAL EFFECTIVENESS

Medline was searched via PubMed in August 2005. This search was repeated on October, 27, 2005.

(1) The following search terms were introduced for "Heart Failure":

"Heart Failure, Congestive"[MeSH] OR heart failure OR "Ventricular Function"[MeSH] OR cardiac failure OR ventricular dysfunction OR ventricular systolic dysfunction OR ventricular diastolic dysfunction OR cardiac dysfunction OR cardiac function OR cardiac overload OR systolic dysfunction OR diastolic dysfunction OR myocard* dysfunction OR cardiac insufficiency OR heart insufficiency OR CHF OR CCF OR HF OR LVSD

(2) The following search terms were introduced for "Natriuretic Peptides":

natriuretic peptide[MeSH] OR atrial natriuretic factor OR natriuretic peptide brain OR natriuretic peptide* OR BNP OR ANP OR natiuretic peptide*

Searches for (1) and (2) were combined ("AND") and limited to the following:

Publication date from 2004/07/01

English

Humans

Randomized Controlled Trial OR Meta-Analysis OR Review [Publication Type]

This resulted in 117 papers. The methodological quality of the studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist.[35]. Further on, we limited our selection to papers in which the reference test was a clinical diagnosis of HF. In this way, 16 of the 117 papers were selected. Only papers which were not included in one of the initial 2005-HTA reports were used to update the results of the latter.

11.2. APPENDIX 2

EVIDENCE LEVELS OF DIAGNOSTIC STUDIES

Fryback and Thornbury described a hierarchy of diagnostic efficacy, which is used as the basis of this report.[36]

Efficacy is defined as the probability of benefit from a medical technology to individuals in a defined population under ideal conditions of use. In other words: can the diagnostic test work? This is not the same as effectiveness, which assesses the test's ability to work in the real world: does it work in clinical practice? Finally, in efficiency the test's financial implications are considered: is it worth it?

The model is characterized by a change in perceived goals. It is hierarchical: on one extreme are endpoints describing only the technical performance of the test, on the other extreme are endpoints pertaining to the value of the diagnostic technology to society. If a test performs poorly at one level, it is unlikely to perform well at a higher level. The reverse, however, is not true: increases in the technical performance of a test will not necessarily guarantee improvement at a higher level, for example effect on patient outcome.

A diagnostic test does not necessarily have to demonstrate effectiveness at each level before it can be used in clinical practice, but the possible gain and remaining uncertainty on the test's efficacy is clearly presented by this approach.

11.2.1. Level 1: technical efficacy

The technical efficacy of a test refers to the ability to produce usable information. The test's feasibility and operator dependence refer to in what circumstances and by whom the test can be performed. The analytical sensitivity is the ability to detect small quantities of the measured component. This should be distinguished from the diagnostic sensitivity, the ability of a test to detect disease. The precision or reproducibility of results is the ability to obtain the same test results on repeated testing or observations. It is influenced by analytical variability and observer interpretation. Analytical variability consists of inaccuracy and imprecision. Inaccuracy implies systematic error, such as calibration error. Imprecision implies random error. Agreement between two continuous test methods can be expressed in a regression analysis or Bland & Altman plots. A correlation coefficient does not provide information on agreement. The agreement between two observers (interobserver) or the same observer on different occasions (intraobserver) can be expressed with a kappa statistic. It is often assumed that the technical efficacy does no longer need to be evaluated once a test is being used in clinical practice.

11.2.2. Level 2: diagnostic accuracy

This level refers to the test's ability to detect or exclude disease in patients compared with a criterion standard or reference test. Test characteristics are sensitivity, specificity, predictive values, likelihood ratios and ROC curves. Sensitivity and specificity are the most widely used outcome measures, but are sensitive to spectrum bias. Spectrum bias may occur when the study population has a different clinical spectrum (more advanced cases, for instance) than the population in whom the test is to be applied. If sensitivity is determined in seriously diseased subjects and specificity in clearly healthy subjects, both will be grossly overestimated relative to practical situations where diseased and healthy subjects cannot be clinically distinguished in advance. This design has been called "inappropriate case-control design" in the pilot assessments. Predictive values, with the positive predictive value being the proportion of patients with a positive test result that actually has the disease and the negative predictive value the proportion of patients with a negative test result that does not have the disease, are dependent on disease prevalence in the study sample. For example, in a situation where disease prevalence is very low, say 1%, the negative predictive value of the test will be easily over 95% as already 99% of the population do not have the disease. Prevalence and the setting in which patients were recruited should be noted to reflect on this. The likelihood ratios show how a test result alters the pre-test probability into a post-test probability, using Bayesian reasoning. The pre-test probability depends on the prevalence of the target condition and the results of previous tests, for example history,

clinical examination, imaging or laboratory tests. Another outcome measure which is sometimes used, is the number needed to diagnose, analogous to the number needed to treat in intervention studies. However, using this measure it is assumed that diagnostic testing is always done to rule in a target condition, to diagnose the target condition, while in clinical practice tests are also used to rule out a target condition. Finally, test accuracy can be illustrated using an ROC curve. The ROC curve graphs test sensitivity versus 1-specificity for various cut-off points. The area under the curve provides a summary measure of the test performance. It also allows comparison of two different tests by testing the two areas under the curve or by testing partial areas under the curve in which the test is most useful. Clearly, the first level of diagnostic efficacy, technical efficacy, contributes to the diagnostic accuracy. But it also becomes apparent that there may be a point beyond which improvement in technical performance no longer improves diagnostic accuracy. Assuming therefore that diagnostic accuracy can be estimated on the basis of technical accuracy studies is not correct.

11.2.3. Level 3: diagnostic thinking

This level of diagnostic efficacy is concerned with assessment of the effect of test information on diagnostic reasoning and disease categorization. Studies on diagnostic thinking serve as a proxy for estimating the effect of a test on patient care. PatientsÊ outcome can not be influenced by the diagnostic technology unless the physician is led to do something different than would have been done without the test information. Using the likelihood ratio and calculating the post-test probability, this change in diagnostic thinking can be computed. However, the pre-test probability of a disease is not always available in clinical practice and depends not only on setting, but also on patient characteristics and other selection processes, such as referral and the results or previous tests. Clinicians who wish to apply the Bayesian properties of diagnostic tests require accurate estimates of the pre-test probability of target disorders in their area and setting. These estimates can come from five sources personal experience, population prevalence figures, practice databases, the publication that described the test or one of a growing number of primary studies of pre-test probability in different settings. An alternative are studies that empirically test the change in the physician's subjective assessment on the probability of disease. In these studies, physicians are asked to estimate the probability of disease before knowing the test result, and estimating it again after the test result has been disclosed. Efficacious tests are those that significantly increase or lower pre-test probabilities assumed by the physician or computed by likelihood ratios using Bayesian reasoning. One major difficulty with this level of diagnostic efficacy is that it is not always known what post-test probability of disease should be used as a threshold. Which probability of disease is low enough to exclude disease, which is high enough to treat the patient? These thresholds will differ according to the target condition and the treatments that are available.

11.2.4. Level 4: therapeutic impact

The most efficacious tests at this level are those that lead to the institution of a new management strategy. Studies can assess this empirically by comparing the intended management before the test result is known with that after the test result has been disclosed. In what proportion of patients did the information change the intended management? In some cases, management changes are considered not only in the patient himself, but also in other persons, for example prophylactic measures in case of an infectious outbreak. These prospective case-series, however, can be subject to bias such as selection bias. The lack of a concurrent control group may lead to confounding, as there is no information on those patients not enrolled in the study and therefore not receiving the new technology. These considerations underscore the need for randomized controlled trials. But, in he absence of RCTs they do play an important role as an intermediate.

11.2.5. Level 5: patient outcome

The ultimate goal of health care is to improve patient outcome. For diagnostic tests that are expensive, dangerous or widely used, knowledge about patient outcome efficacy seems particularly important. It is at this level that expected harm, such as burden, pain, risk, can be weighed directly against its expected benefit, such as improving life expectancy, quality of

life, disease related morbidity, etc. The randomized controlled trial is the study design the least prone to bias to estimate these risks and benefit. However, it is not always feasible to perform an RCT for ethical, financial or other reasons. In those cases, case-series collected before and after the introduction of a new test technology or case-control studies may provide some of the answers. A methodological difficulty with this level is that the independent contribution of test technology to patient outcomes may be small in the context of all the other influences and therefore very large sample sizes may be required. But, in spite of these difficulties, RCTs on diagnostic tests are feasible. Various designs are possible, according to the specific research question. Some tests, however, will never be able to prove a change in "objective" patient outcomes such as mortality or morbidity, simply because there is no treatment available at this moment that has an impact on these outcomes. This is the case in for example dementia or Amyotrophic Lateral Sclerosis (ALS). A diagnostic test will therefore never produce a difference in mortality, but may improve quality of life measures by giving the patient (and the carer) an affirmative diagnosis and providing an explanation for the signs and symptoms the patient experiences.

11.2.6. Level 6: cost-effectiveness analysis

This level goes beyond the individual risks and benefits, but assesses whether the cost for use of a given test is acceptable for society. Is the price for the positive effect on patient outcome worthwhile? Resources can not be allocated twice; money spent on one technology can not be spent on another. Cost-effectiveness studies compute a cost per unit of output. Any of the measures of the previous levels can be used as input, for example cost per surgery avoided, cost per appropriately treated patient, cost per life year gained or cost per quality adjusted life year gained. Final outcomes, such as life years gained or QALYs gained, are preferred over intermediate outcomes in economic evaluations, as they allow comparisons across a broader range of health interventions, e.g. diagnostic and therapeutic interventions. Because data on these outcomes and costs of the diagnostic and subsequent therapeutic paths are not routinely available from observations, modelling becomes inevitable to examine the cost-effectiveness of diagnostic tests. The validity of the model input parameters is crucial for the credibility of the model. The values of all input variables must be based on solid evidence obtained from literature or observations. Sensitivity analyses can illustrate the robustness of the conclusions, by demonstrating the sensitivity of the results to changes in the values of remaining uncertain input parameters. Cost-effectiveness models can only upgrade the level of evidence if level 5 evidence was available on the outcomes used in the model (be it life years gained or procedures avoided) and if this evidence was actually used in the model.

11.3. APPENDIX 3: OVERVIEW OF RECENT PRIMARY CLINICAL STUDIES

STUDY	SETTING	n	med. age	PREV.	QUALITY LEVEL (1-6)	REFERENCE TEST	INDEX TEST	CUT-OFF	SENS	SPEC	PPV	NPV
UK Natriuretic Peptide Study - ZAPHIRIOU[7]	patients with suspected HF (new), referred from primary care	306	74	34%	2	cardiologist (history, clinical, echo , X-ray)	BNP: Biosite; proBNP: Elecsys Roche	BNP:100 pg/ml; proBNP: 125 pg/ml;	proBNP 0,98 BNP 0,79	proBNP 0,35 BNP 0,72	proBNP 0,44 BNP 0,59	proBNP 0,97 BNP 0,87
								BNP: 30 pg/ml	0,95	0,35	0,43	0,93
PRIDE Study - JANUZZI[22]	patients with dyspnoea presenting in ED	600	HF 72,8 noHF 56,9	35%	2	study cardiologist, knowing all clinical data except proBNP, up to 60 days after admission;	proBNP: Elecsys Roche	proBNP: 300 pg/ml (rule out)	0,99	0,68	0,62	0,99
BASEL Study: subgroup analysis in elderly - MUELLER[38]	elderly patients (> 70 yr) admitted to ED because of acute dyspnoea	269	80 plm 6	54%	5	NA	BNP: Biosite	rule out: BNP > 100 pg/ml rule in: BNP > 500 pg/ml	NA	NA	NA	NA
BASEL Substudy: renal failure vs no renal failure - MUELLER[31]	patients with GFR < 60 ml/min/1,73 sq m but creatinin < 2,8 mg%	240 with vs 212 w/o	76 vs 65	65% vs 28%	5	NA	BNP: Biosite	rule out: BNP > 100 pg/ml rule in: BNP > 500 pg/ml	NA	NA	NA	NA

11.4. APPENDIX 4: SEARCH STRATEGY FOR ECONOMIC LITERATURE

Date of Search	Database	Platform/URL	Search Terms	Limitations	# hits
November 10th, 2005	PubMed	www.pubmed.gov	(CHF or congestive heart failure or heart failure or HF or left ventrical dysfunction or ventrical dysfunction * or ventric* dysfunction* or "shortness of breath" or acute dyspnea) AND ((natriuretic peptide, brain OR b-type natriuretic peptide or b type natriuretic or natriuretic peptide, b type or type b natriuretic peptide type b or natriuretic peptide, type b or BNP) or (pro-bnp or probnp or nt-pro-bnp or nt-probnp or ntprobnp)) AND (expenditure* or health care expenditure* or cost*)	NA*	41
	Embase	Licensed product Embase		NA	30
	EBM Reviews: Cochrane DSR, ACP Journal Club, DARE, CCTR	Licensed Product CEBAM (OVID-screen)	(health care expenditures.mp. or exp "health care cost"/ or expenditure$ or cost$) AND (natriuretic peptide, brain or b-type natriuretic peptide or b type natriuretic peptide or natriuretic peptide type b or natriuretic peptide, type b or ((BNP and "b type") or (BNP and "type b) OR (BNP AND B-type") or (BNP and "B Type") or (pro-bnp or probnp or nt-pro-bnp or nt-probnp or ntprobnp))) AND (acute dyspnea or dyspnoea or (shortness adj breath) or (CHF or congestive heart failure or heart failure or HF or left ventric$ dysfunction$))	NA	107
	British Nursing Index (BNI)				
	Cumulative Index to Nursing and Allied Health Literature CINHAL				
	OVID MEDLINE ® OVID MEDLINE In-Process and Other None Indexed Citations				
	EBSCO EJS		(natriuretic or peptide or BNP or pro-bnp or probnp or nt-pro-bnp or nt-probnp or ntprobnp) AND (expenditure or cost)	Article Titles	18
	CRD (DARE, NHS EED, HTA)	www.york.ac.uk	Brain natriuretic peptide* OR BNP OR (pro-bnp or probnp or nt-pro-bnp or nt-probnp or ntprobnp)	NA	11
*"NA": no (other than default) limitations apply					

11.5. APPENDIX 5: COST/PRICE OF BNP IN DIFFERENT COUNTRIES

Reference[h]	Country	Cost/Price Item	Indicated Cost/Price	in €
Sim et al. 2003 ([46])	UK (Wales)	"Standard Costing Package by Data Tree International (including labour cost)"	£6.62	9,74
Ogawa et al.2002 ([54])	Japan	BHI reimbursement	Y1.700	12,17
AdvaMed 2004 ([56])	USA	"a BNP test"	"about $15"	12,82
Biosite bvba/sprl ([57])	Belgium	Lab test	18 €	18 €
Kleckner 2004 ([58])	USA	BNP measurement	$25	21,37
Strategic Analysis 2002 ([59])	Finland	"triage BNP test for congestive heart failure (CHF); 15-min TAT, with blood; in ER"	$27	23,08
Fisher Scientific 2005 ([60])	USA	"Triage* BNP Test, Automated Test for Congestive Heart Failure, Triage BNP for Beckman Coulter Immunioassay Systems, 100 test"	$29	24,79
Biosite bvba/sprl ([57])	Belgium	Point-of-Care	25 €	25 €
Heidenreich et al. 2004 ([61])	USA	Average Cost of Biosite and Bayer test (including technician costs)	$32	27,35
Russel, 2003 ([50])	UK	Assumed Cost for individual test	£20	29,41
Round Table, Young, 2004 ([62])	USA	"suggested list price of BNP assays"	"around $35"	29,91
KCE 2005 ([63])	Belgium	Invoiced charges to patients in Belgium as indicated to KCE by 1 member of industry	€25-€30	25-30
Fisher Scientific 2005 ([60])	USA	"triage BNP Test, pack of 25"	$36	30,77
Craig et al. 2005 ([1])	Uk (Scotland)	BNP lab test (covering transport, lab, staff time and communication with patient)	£21	30,88
Chuck et al. 2005 ([45])	Canada (Alberta)	BNP (labour & supplies)	$40	34,19
yandle, 2004 ([64])	New Zealand	"a single clinical measurement of plasma BNP"	NZ$50-60,7	29,41-35,71
SBU 2005 ([65])	Sweden	"Taking a (blood) sample and analyzing BNP"	SEK 200-350	20,92-36,61
Mueller et al. 2004 ()	Switzerland	Reimbursement in Switzerland	$47	40,17
Round Table, Young,	USA	"medicare reimbursement limit for BNP testing"	"approximately $47"	40,17

[h] Cost/price data were retrieved from literature (search performed November 10th 2005)

Reference[h]	Country	Cost/Price Item	Indicated Cost/Price	in €
2004 ([62])				
Biosite 2005 ([57])	USA	"national medicare fee limit"	$47,43	40,54
ICSI 2005 ([66])	USA	"Performing Biosite Triage BNP bedside test"	"about $50"	42,74
Morimoto et al. 2003 ([67])	USA	BNP measurement (per 3 months); Cost applying to "a university hospital in the US"	$67 (range 33-100)	57,26 (range 28,21-85,47)
ICSI 2005 ([66])	USA	"some laboratory-based BNP assays, used for specialized testing"	"may cost up to $165"	141,03

11.6. APPENDIX 6: ECONOMIC EVALUATION SUMMARY SHEET: SIM ET AL.

Author	Sim et al. 2003 ([46])
Country	UK
Design	Within Group Comparative Cost Minimisation Analysis (observational set-up)
Perspective	Not formally stated, but clearly the analysis is presented from the treating (echocardiography) service
Time window	1 year (between 1997 and 1998)
Interventions	ECHO vs. (blood) BNP rule-out + ECHO
Population	Patients suffering from breathlessness, excluding patients showing heart murmur (N = 83, age range 37-87years)
Assumptions	BNP test is performed once Negative BNP test not followed by ECHO (assumption of "rule out") Assumed total of 1400 echocardiography studies per machine life year.
Data source for costs	Costs for ECHO based on published articles (covering machine cost and depreciation) Costs for BNP based on standard laboratory package.
Cost items included	ECHO: machine costs, consumables, overhead and staff cost. BNP: fixed and variable costs per test, no additional costs assumed for taking blood samples
Data source for outcomes	Prevalence of LVSD based on primary research for this study
Discounting	Depreciation rate for Echocardiography machines set at 5%, Annual cost of invested money included. No valuation of long term health outcomes
Costs	Diagnostic costs for Echocardiography and BNP
Outcomes	Diagnosis of LVSD
Cost-effectiveness	Net saving of £964.20 without compromising diagnostic accuracy (cut-off value for BNP set at 19pg/ml), ie net savings of 21,5% compared to baseline situation where all patients receive ECHO. Net saving of £1288,2 for 20pg threshold (causing 1 extra false-negative compared to 19pg threshold).
Sensitivity analysis	Cost per ECHO as performed only by technician. Applying BNP threshold of 19pg/ml and 20pg/ml Results appear robust for univariate analyses, though no allowance was made for extra false-negatives
Conclusions	Applying BNP+ECHO protocol is cost-effective for patients with breathlessness.
Remarks	Cost perspective is very limited (ECHO versus BNP-ECHO, not taking into account following hospital stay…)

11.7. APPENDIX 7: ECONOMIC EVALUATION SUMMARY SHEET: MUELLER ET AL.

Author	Mueller et al. 2004 ([10])
Country	Switzerland
Design	RCT (no stratification)
Perspective	(Implicitly) societal
Time window	Trial + 1 month follow-up after discharge
Interventions	All patients: history, physical, ECG, pulse oximetry, blood test, chest radiography (blood) BNP group vs. Control Group
Population	665 adults with acute dyspnoea in ED, 452 randomized into BNP group (225) and control group (227) without stratification.
Assumptions	Hospital charges assumed to reflect real cost.
Data source for costs	Hospital charges BNP: applying Swiss reimbursement level at the time
Cost items included	All Patients: history, physical, ECG pulse oximetry, blood test, chest radiography. BNP group: Biosite Triage POC Assay Control Group: "standard" clinical protocol
Data source for outcomes	Primary research
Discounting	NA
Costs	Cost of treatment (hospital charges for stay).
Outcomes	Median time to discharge and median time to (appropriate) treatment.
Cost-effectiveness	BNP testing reduces total cost of treatment by 26%. Total mean cost of treatment: $5.410 for BNP group vs. $7.264 for control group. Median time to discharge: 8 days for BNP group and 11 days for control group.
Sensitivity analysis	NA Would be interesting to analyze "hospital bill effect".
Conclusions	Rapid measurement of BNP in the ED improves the care of patients with acute dyspnoea and thereby reduces time to discharge and total cost of treatment.
Remarks	Break-up of BNP cost not mentioned, no validation of robustness. Follow-up too short to allow for cost analysis of false-negatives.

11.8. APPENDIX 8: ECONOMIC EVALUATION SUMMARY SHEET: CRAIG ET AL.

Author	Craig et al. 2005 ([1])
Country	UK (Scotland)
Design	HTA Report comprising cost minimisation analysis CE in acute care is assessed by applying published findings to the Scottish situation CE in primary care is assessed by means of a cost model
Perspective	Implicitly societal (Scottish perspective)
Time window	NA
Interventions	Acute Care: standard clinical protocol (control group) vs. clinical protocol including BNP Primary Care: BNP used as a rule out tool compared to standard practice
Population	Suspected (symptomatic) patients both in acute and primary care setting
Assumptions	Acute Care: Applying findings from published literature on Scottish patient population Primary Care: Costs limited to diagnostic part, Assumption that GPs reading ECGs have an accuracy level equivalent to consultant-read studies and an ECG-machine. Added cost of false negatives = 2 additional GP visits.
Data source for costs	Acute care setting: 1 RCT (Mueller et al. 2004) and Scottish daily bed costs Primary Care: Economic Model: data provided by manufacturers of BNP assays. Staff costs, costs of patient travel taken from previous reports.
Cost items included	Laboratory and reagent cost of BNP tests; additional costs of consultant-led ECG service; cost managing false-negative patients; cost of ECHO and 2 months of diuretics for false-positive patients
Data source for outcomes	CE in acute care: published data in RCT (Mueller et al. 2004) and Scottish Health Statistics (ISD Scotland) CE in primary care: combined data based on meta-analysis
Discounting	NA
Costs	CE in acute care: total hospital charges CE in primary care: marginal cost for correct diagnosis following BNP
Outcomes	CE in acute care: mean time to (appropriate) treatment and discharge CE in primary care: correct diagnosis
Cost-effectiveness	CE in acute care: BNP testing proved cost-effective as an added rule out test to clinical protocol. CE in primary care: Base Case showed BNP to be cost-effective, though model results are not robust.
Sensitivity analysis	Univariate analyses for 8 variables (costs, epidemiology, clinical effectiveness) Results for primary care model are sensitive to variation in service delivery and patient numbers.
Conclusions	There is evidence that in the emergency setting rapid BNP results can improve the evaluation and treatment of patients with heart failure compared with current practice, thereby reducing length of stay and total treatment costs. The economic model suggests that using B-type natriuretic peptide test in primary care could be cost-saving if the specificity of the tests GDP currently use to refer patients for echo is less than 50%.
Remarks	Authors stress the need for further research into clinical relevance of data pertaining to the Scottish situation

11.9. APPENDIX 9: ECONOMIC EVALUATION SUMMARY SHEET: CHUCK ET AL.

Author	Chuck et al. 2005 ([45])
Country	Canada (province of Alberta)
Design	Cost minimisation models, comparing cost for BNP with standard clinical protocols after Cost Minimization was applied.
Perspective	Payer's perspective
Time window	One year period
Interventions	BNP vs. ECHO
Population	Patients in Alberta's EDs with acute dyspnoea, but without acute myocardial infarction, renal dysfunction or unstable angina. Stratification into cohorts based on age and sex.
Assumptions	Model probabilities were obtained from available literature. Diagnostic properties of tests are based on previous reports. Cost attribution: Only dyspnoeic patients where presence of CHF is uncertain are tested; Diagnostic procedure is administered once, Reduction in hospitalization days is observed in urban settings only; ECHO is unavailable in rural settings. Cut-off values for BNP testing varying according age and gender profile of cohorts.
Data source for costs	Cost data were primarily based on provincial data. Cost factors for which little information was available, were estimated through expert consultation and from otherwise available data.
Cost items included	Standard diagnostic protocols (History, Physical, ECG & Chest X-ray) BNP / ECHO Ensuing number of hospital days.
Data source for outcomes	Model probabilities were obtained from available literature. Diagnostic properties of tests are based on previous reports.
Discounting	NA
Costs	Savings for ECHOs not performed after rule out by BNP Savings for reduction in number of hospital days after BNP testing.
Outcomes	Correct diagnosis. Number of hospital Days.
Cost-effectiveness	Base Case results indicate BNP testing to be cost-effective for all age-sex cohorts in both settings (rural-urban). However, results are sensitive to assumptions regarding reduction of number of ECHOs and hospital days.
Sensitivity analysis	Univariate sensitivity analyses for 8 variables. Results proved to be robust. It should be noted the model comprises 5 scenarios for varying cohorts and thus already takes result sensitivity into account by design.
Conclusions	Depending on whether BNP testing can effectively reduce number of ECHOs and number of hospitalization days, the cost impact of BNP testing will be beneficial. Furthermore, the size of the effect varies according to different age cohorts among patients.
Remarks	Distinction made between rural and urban setting is not relevant for Belgian health services.

11.10. APPENDIX 10: SEARCH STRATEGY FOR LITERATURE ON ORGANISATIONAL ISSUES

Date of Search	Database	Platform/URL	Search Terms	Limitations	# hits
November 10th, 2005	PubMed	www.pubmed.gov	(CHF or HF or congestive heart failure or heart failure or left ventrical dysfunction or ventrical dysfunction * or ventric* dysfunction* or "shortness of breath" or acute dyspnea) AND ((natriuretic peptide, brain OR b-type natriuretic peptide or b type natriuretic or natriuretic peptide, b type or type b natriuretic peptide type b or natriuretic peptide, type b or BNP) or (pro-bnp or probnp or nt-pro-bnp or nt-probnp or ntprobnp)) AND (organisation* or reimbursement or health insurance or financ*)	NA*	0
	Embase	Licensed product Embase		NA	0
	EBM Reviews: Cochrane DSR, ACP Journal Club, DARE, CCTR	Licensed Product CEBAM (OVID-screen)	(organisation$ or reimbursement or health insurance or financ$) AND (natriuretic peptide, brain or b-type natriuretic peptide or b type natriuretic peptide or natriuretic peptide type b or natriuretic peptide, type b or ((BNP and "b type") or (BNP and "type b) OR (BNP AND B-type") or (BNP and "B Type") or (pro-bnp or probnp or nt-pro-bnp or nt-probnp or ntprobnp))) AND (acute dyspnea or dyspnoea or (shortness adj breath) or (CHF or congestive heart failure or hf or heart failure or left ventric$ dysfunction$))	NA	6
	British Nursing Index (BNI)				
	Cumulative Index to Nursing and Allied Health Literature CINHAL				
	OVID MEDLINE ® OVID MEDLINE In-Process and Other None Indexed Citations				
*"NA": no (other than default) limitations apply					

11.11. APPENDIX 11: GLOSSARY OF TERMS

ACC	American College of Cardiology
AHA	American Heart Association
AHF	Acute Heart Failure
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CHF	Chronic Heart Failure
ECG	Electrocardiogram
ED	Emergency Department
EF	Ejection Fraction
ESC	European Society of Cardiology
GP	General Practioner
HF	Heart Failure
HTA	Health Technology Assessment
ICSI	Institute for Clinical Systems Improvement
LR	Likelihood Ratio
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
NHS	National Health Service
NPs	Natriuretic Peptides (essentially indicating BNP AND NT-proBNP)
NPS	Natriuretic Peptides System
NT-proBNP	amino terminal pro Brain Natriuretic Peptide
NYHA	New York Heart Association
PLVEF	Preserved Left Ventricular Ejection Fraction
PPV	Positive Predictive Value
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
SR	Systematic Review

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Wettelijk depot : D/2005/10.273/34

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21. HTA Stomamateriaal in België. D/2005/10.273/27.
22. HTA Positronen Emissie Tomografie in België. D/2005/10.273/29.
23. HTA De electieve endovasculaire behandeling van het abdominale aorta aneurysma (AAA). D/2005/10.273/32.
24. Het gebruik van natriuretische peptides in de diagnostische aanpak van patiënten met vermoeden van hartfalen. D/2005/10.273/34.

Inlichtingen

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