Technoleg Iechyd Cymru
Health Technology Wales

HEALTH TECHNOLOGY WALES (HTW) GUIDANCE 026 (October 2021)

Natriuretic peptides to *rule-in* and *rule-out* a diagnosis of acute heart failure in adults in the emergency department setting

HTW Guidance:

The evidence supports the routine adoption of N-terminal pro B-type natriuretic peptide (NT-proBNP) measurement to *rule-in* and *rule-out* acute heart failure in adults presenting to the emergency department in whom there is clinical suspicion of this diagnosis.

The addition of NT-proBNP measurement to routine clinical assessment may reduce length of hospital stay and the rate of re-hospitalisations.

Health economic modelling indicates that NT-proBNP to *rule-in* and *rule-out* acute heart failure is the most cost-effective strategy.

Why did Health Technology Wales (HTW) appraise this topic?

Acute heart failure (AHF) is the most common reason for emergency admission to hospital in England and Wales in adults older than 65 years, and the prevalence is increasing because of a progressively aging population. AHF can be challenging to diagnose since the symptoms often overlap with other acute conditions and patients with AHF often have other co-morbidities.

There is no single diagnostic test for heart failure. Diagnosis relies on a combination of clinical, imaging and biochemical assessment. Testing for the presence of elevated levels of natriuretic peptides, such as NT-proBNP and BNP, facilitates the diagnosis of AHF although other conditions can also lead to increased levels of these proteins.

National Institute for Health and Care Excellence (NICE) AHF guidelines (2014) recommend the measurement of BNP or NT-proBNP to *rule-out* AHF, but they do not make any recommendations for ruling-in AHF. A strategy of using BNP or NT-proBNP to *rule-in* as well as *rule-out* AHF could allow for the better targeting of investigations as well as earlier diagnosis and treatment, which may lead to better clinical outcomes, and use of healthcare resources.

HTW identified this topic through HealthTechConnect.

The status of HTW guidance is that NHS Wales should adopt this guidance or justify why it has not been followed. HTW will evaluate the impact of its guidance.

Evidence Summary

Refer to Evidence Appraisal Report 026 (EAR026) for a full report of the evidence supporting this Guidance. HTW undertook an evidence review, which aimed to address the following question: what is the clinical and cost effectiveness of NT-proBNP or BNP as a diagnostic test to *rule-in* and *rule-out* AHF in adults in the emergency department setting, compared with NT-proBNP, BNP, or standard care to *rule-out* AHF?

HTW researchers identified two meta-analyses investigating the diagnostic accuracy of NT-proBNP and BNP. Hill et al (2014) looked at age-specific *rule-in* and age-independent *rule-out* cut-offs for NT-proBNP. They also assessed the impact of age on BNP levels. Roberts et al. (2015) was a meta-analysis conducted as part of the development of the NICE AHF guideline (NICE 2014). This analysis did not consider age as a factor affecting NT-proBNP or BNP levels. Three additional diagnostic accuracy studies were also identified. Based on evidence from the two meta-analyses and additional observational studies, NT-proBNP and BNP testing was shown to have a consistently higher sensitivity than specificity, with sensitivity decreasing and specificity increasing as the diagnostic threshold increases.

The majority of the evidence identified by HTW researchers assessed the diagnostic test accuracy of NT-proBNP or BNP using *rule-in* or *rule-out* strategies. Using a *rule-in* and *rule-out* strategy means that there is a 'grey area' between the thresholds. Patients with levels in the 'grey area' need careful clinical assessment as well as additional testing with, for example, echocardiography. Two observational studies investigated the diagnostic accuracy of natriuretic peptides that revealed results in this 'grey area' and one of these studies reported that the diagnostic performance of NT-proBNP within the 'grey area' was comparable to that of the entire population.

Whilst the majority of the evidence identified evaluated the diagnostic accuracy of NT-proBNP or BNP, studies were identified that reported that NT-proBNP and BNP testing improves clinical outcomes compared to clinical judgement alone. A meta-analysis found that natriuretic peptide testing can reduce the length of hospital stay by at least one day. However, it is unclear whether *rule-in* and *rule-out* thresholds were used. Further evidence from randomised controlled trials showed that NT-proBNP testing reduced readmission rates and the duration of the initial emergency department visit while BNP testing reduced time spent in hospital over the following year.

No economic evidence was identified that compared BNP or NT-proBNP *rule-in* and *rule-out* with *rule-out* alone. HTW adapted a manufacturer-submitted cost-utility analysis and the model undertaken for NICE CG187 to estimate the cost effectiveness of diagnostic strategies using BNP or NT-proBNP. All of the BNP and NT-proBNP testing strategies were found to be more costly and more effective than clinical decision alone. The resulting ICERs were below a threshold of £20,000 per QALY indicating that the BNP and NT-proBNP strategies were cost-effective in comparison to clinical decision alone. When comparing all strategies against each other, the NT-proBNP *rule-in*/*rule-out* strategy was found to be the optimal strategy overall. BNP *rule-out* was more costly and less effective than NT-proBNP *rule-in*/*rule-out* and was therefore dominated. NT-proBNP *rule-out* was more effective but more costly than NT-proBNP *rule-in*/*rule-out* with a resulting ICER of £31,192 per QALY indicating that it was not cost-effective in comparison to NT-proBNP *rule-in*/*rule-out*.

The results were found to be robust in deterministic sensitivity analysis with the NT-proBNP *rule-in* and *rule-out* strategy found to be optimal in most modelled scenarios. In probabilistic sensitivity analysis, at a threshold of £20,000 per QALY, BNP *rule-out* only was found to have a 58% probability of being cost effective while NT-proBNP *rule-in* and *rule-out* had a 42% probability of being cost-effective.

The appropriate mechanism for patient engagement was determined and the patient perspective was considered where possible. As part of a 2021 Ontario Health Technology Assessment of BNP and NT-proBNP in adults with suspected heart failure, 21 people who had received the tests or their family members were interviewed and gave BNP and NT-proBNP testing strong support. The main reason for support was the potential time saved by receiving a speedier diagnosis.

Appraisal Panel considerations

- The Appraisal Panel heard from a clinical expert that heart failure has a poor prognosis, but that effective treatments are available making an early diagnosis essential. The expert advised that echocardiography is the gold standard for confirming a diagnosis of heart failure and may provide additional information about a possible cause. However, there may be a delay in undertaking echocardiography and the current demand for this test is considerable. Any additional biochemical testing that provides reliable and rapidly available results may therefore be of particular clinical value.
- Clinical experts explained that natriuretic peptide tests are widely acknowledged as useful adjunct tests to clinical history, examination, ECG and imaging investigations in the diagnosis of AHF, and that results may be helpful to both *rule-out* and *rule-in* AHF. Ruling-in a diagnosis of AHF means that patients can be treated earlier with the possibility of improved clinical outcome, shorter hospital stays and reduced costs. The experts also pointed out that, at present, the use of natriuretic peptide *rule-in* testing may be particularly useful to help differentiate AHF from COVID-19, since some of the signs and symptoms of COVID-19 are similar to those of AHF.
- The Appraisal Panel discussed the evidence of the clinical effectiveness of natriuretic peptide measurements for the diagnosis of AHF (see Evidence Summary, above). A clinical expert advised that the laboratory based natriuretic peptide testing methods included in the studies are representative of those used in day-to-day clinical practice in NHS Wales. He stated that he is not aware of any sites in NHS Wales using point-of-care (POC) testing, but he is aware that there are some sites using laboratory tests. The expert commented that whilst use of POC may be theoretically useful in some smaller general district hospitals, this approach was not adopted in the studies and therefore uncertainty would remain about the diagnostic performance and clinical utility of the results. In addition, one expert commented that there is wide variation in POC resources across all health boards in Wales so that implementation of these tests would be difficult.
- The Appraisal Panel discussed the fact that the studies were conducted in a range of countries but none of the studies were undertaken in the UK. Although the Appraisal Panel acknowledged there may be differences in the running of emergency departments in different countries, clinical practice does not vary fundamentally across the UK, US and Europe.
- The Appraisal panel discussed concerns around the management of patients in the 'grey zone' between *rule-in* and *rule-out* thresholds. While one expert commented that a large number of patients could potentially fall into this 'grey zone', it was also noted by the Appraisal Panel that a relatively small proportion of patients were in the 'grey zone' in the studies in which this was investigated and that the majority of these did not have a final diagnosis of AHF. The panel noted that it is not possible to eliminate this diagnostic 'grey zone' entirely but that the aim of using BNP or NTproBNP testing is to reduce diagnostic uncertainty in a manner that is beneficial to patients and ensures best use of healthcare resources
- The Appraisal Panel noted that while most of the published evidence investigated diagnostic accuracy, there are additional clinical outcome data from well-performed randomised controlled trials and a meta-analysis. From these studies, the Appraisal Panel concluded that

NT-proBNP testing, in addition to routine clinical assessment, may reduce the length of hospital stay, time spent in the emergency department, time spent in hospital over the year following emergency department admission, and 60-day re-hospitalisation rate. Although data from these studies were not used directly in the cost effectiveness model, the model corroborated the conclusions of these studies.

- The Panel considered the results of the HTW cost-utility analysis, which showed that the NT-proBNP *rule-in* and *rule-out* strategy was the optimal strategy in the base case. This result was found to be robust across most modelled scenarios. In probabilistic sensitivity analysis, there was a 58% probability that BNP *rule-out* only was cost effective and a 42% probability that NT-proBNP *rule-in* and *rule-out* was cost effective, at a threshold of £20,000 per QALY. The Panel considered that patient selection is likely to be critical to the clinical and cost-effectiveness of NT-proBNP *rule-in* and *rule-out*, and stressed that testing should be offered as an adjunct to usual care pathways in the emergency department to patients in whom there is diagnostic doubt.
- The Appraisal Panel discussed the variation in the use of natriuretic peptide testing across NHS Wales and the potential barriers to wider uptake. A clinical expert informed the Appraisal Panel that natriuretic peptide tests are one of the most expensive tests in the biochemistry laboratory, with funding challenges for health boards. Furthermore, there will usually be a single provider of the main automated platform, and unless the natriuretic peptide test is from the same provider, the test will have to be run on a stand-alone analyser, which could delay turn-around time. The expert also stated that clinicians would need to ensure that the requesting and interpretation of test results is managed optimally to ensure the most efficient use of resources. Inappropriate testing has the potential to be wasteful and could erode clinical confidence.
- The Appraisal Panel recommended that the wider adoption of the measurement of NT-proBNP in NHS Wales requires well-defined and professionally agreed clinical pathways for the *rule-in* and the *rule-out* of AHF to ensure optimal clinical benefit and the best use of resources.
- The Appraisal Panel considered that the availability of real world audit data would be very beneficial to verify the utility of NT-proBNP measurement to *rule-in* and *rule-out* AHF in adults in the emergency department setting in NHS Wales.

Responsibilities for consideration of this Guidance

Health Technology Wales (HTW) was established by Ministerial recommendation[1,2] to support a strategic, national approach to the identification, appraisal and adoption of non-medicine health technologies into health and care settings. The HTW Appraisal Panel comprises senior representation from all Welsh boards with delegated authority to produce guidance 'from NHS Wales, for NHS Wales'. The status of HTW guidance is 'adopt or justify'. There is an expectation from Welsh Government that HTW guidance is implemented with adoption regularly audited by HTW.[3]

The guidance in this document is intended to assist Welsh care system decision makers to make evidence-informed decisions when determining the place of health technologies and thereby improve the quality of care services.

The content of this HTW guidance was based upon the evidence and factors available at the time of publication. An international evidence base was reviewed and external topic experts and HTW committee members consulted to contextualise available evidence to Wales. Readers are asked to consider the generalisability of the evidence reviewed to NHS Wales and that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. It is acknowledged that evidence constitutes only one of the sources needed for decision making and planning.

This guidance does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

No part of this guidance may be used without the whole of the guidance being quoted in full. This guidance represents the view of HTW at the date noted. HTW guidance is not routinely updated. It may, however, be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the guidance given.

Standard operating procedures outlining HTW's evidence review methods and framework for producing its guidance are available from the HTW website.

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Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control and the views expressed are those of Health Technology Wales.

Chair, Health Technology Wales Appraisal Panel

1. National Assembly for Wales, Health and Social Care Committee. Access to medical technologies in Wales. December 2014.
2. Response to Recommendations from the Health & Social Care Committee: Inquiry into Access to Medical Technologies in Wales. February 2015.
3. Gething, V. Letter to all Health Board Chairs re Funding for Sacral Nerve Stimulation in Wales. VG_01655_17. September 2017.