



## Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	N-terminal pro-brain natriuretic peptide (NT-proBNP) as a biomarker for heart failure
Topic exploration report number:	TER170

### Introduction and aims

Heart failure is a progressive medical condition in which the heart is unable to pump blood around the body properly. Acute heart failure can present suddenly as a new diagnosis in people with no previous symptoms or as worsening of chronic heart failure (CHF). This can be due to damage to the heart muscle, a heart valve not functioning properly, an abnormal heart rhythm and other rarer causes (NICE 2014).

Heart failure can be challenging to diagnose, as symptoms and signs often overlap with other conditions. There is no single diagnostic test for heart failure. Diagnosis relies on clinical judgement based on a combination of history, physical examination and appropriate investigations such as electrocardiography (ECG), chest X-ray and blood tests (NICE 2018).

Biomarker tests can assist with the diagnosis of heart failure. Biomarkers are substances measurable in the bloodstream, which can be used to diagnose and monitor disease. B-type natriuretic peptide (BNP) is a hormone released from the heart when the walls of the heart are stretched or there is pressure overload. N-terminal pro B-type natriuretic peptide (NT-proBNP) is a non-active prohormone that is released from the same molecule that produces BNP. BNP and NT-proBNP are classed as natriuretic peptides. Testing of blood for the presence of natriuretic peptides facilitates diagnosis because NT-proBNP and BNP levels are generally elevated in individuals with acute heart failure. However, other factors are also associated with differing levels of these natriuretic peptides, which can complicate the interpretation of test results.

The topic proposer states that NT-proBNP is recognised as the gold standard biomarker for heart failure, and that due to its very high sensitivity at the 'rule-out' threshold, provides a simple and rapid exclusion of the diagnosis of heart failure. Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of NT-proBNP as a biomarker for acute and chronic heart failure.

### Summary of findings

Guidelines from the National Institute for Health and Care (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) state that levels of NT-proBNP should be measured in people with suspected heart failure. There are a number of systematic reviews, which suggest that NT-proBNP is an effective way to support with the diagnosis of heart failure, although they are not always based on randomised-controlled trials (RCTs). We identified one RCT studying the economic and quality-of-life outcomes of NT-proBNP for heart failure.

## Evidence

### UK guidelines and guidance

NICE and SIGN guidelines in people with suspected heart failure state that levels of NT-proBNP should be measured prior to commencing therapy.

### Other guidelines and guidance

The National Clinical Programme for Pathology guidance in Ireland recommends that measuring NT-proBNP is a useful way of supporting the diagnosis of ambulatory and acute decompensated heart failure.

### Systematic reviews and meta-analyses

Since publication of NICE guidelines in 2014, we identified seven systematic reviews, five of which suggest there might be benefit to using NT-proBNP as a biomarker for acute and chronic heart failure. Although all of the systematic reviews also included meta-analyses, not all of them included RCTs. One systematic review and meta-analysis of RCTs suggests that there is no benefit to using natriuretic peptide-guided therapy over guideline-directed therapy for heart failure, and another systematic review of RCTs provided unclear evidence as to whether NT-proBNP-guided treatment was more effective than a health plan alone. One individual patient data meta-analysis suggests that there is benefit to using NT-proBNP to support the diagnosis of acute and chronic heart failure.

### Primary evidence

We searched for RCTs studying NT-proBNP as a biomarker for heart failure in addition to those included in the systematic reviews and meta-analyses. We identified one RCT studying the economic and quality-of-life outcomes of NT-proBNP in comparison to usual care in high-risk patients with heart failure and reduced ejection fraction. The RCT concluded that NT-proBNP-guided heart failure therapy was no more effective than usual care in improving quality of life outcomes.

### Economic evaluations

The cost-effectiveness analysis that supports NICE clinical guideline 187 used only the 'rule-out' threshold for NT-proBNP and found that it was cost effective over standard care. We identified an RCT, which showed that NT-proBNP-guided heart failure therapy had higher total costs than usual care in high-risk patients with heart failure and reduced ejection fraction.

## Areas of uncertainty

We identified numerous systematic reviews and meta-analyses studying NT-proBNP as a biomarker for heart failure. We found limited evidence of the cost effectiveness of NT-proBNP, and any further assessment would need to involve more detailed searches for sources that can be used to assess the cost effectiveness of NT-proBNP in the population of interest.

## Conclusions

The majority of the evidence we identified suggests that measuring NT-proBNP levels might be a useful biomarker for heart failure. The evidence we identified on the cost effectiveness of NT-proBNP is limited, and more detailed searches are needed if further assessment is undertaken.

## Brief literature search results

Resource	Results
HTA organisations	
<a href="#">Healthcare Improvement Scotland</a>	We did not identify any relevant evidence from this source.
<a href="#">Health Technology Assessment Group</a>	National Clinical Programme for Pathology, Clinical Advisory Group for Pathology, National Clinical Advisor and Group lead. 2019. National laboratory handbook. Laboratory testing for natriuretic peptides (NP)-BNP/NT-proBNP: <a href="https://www.hse.ie/eng/about/who/cspd/ncps/pathology/resources/natriuretic-peptide-testing-guideline1.pdf">https://www.hse.ie/eng/about/who/cspd/ncps/pathology/resources/natriuretic-peptide-testing-guideline1.pdf</a>
<a href="#">Health Information and Quality Authority</a>	We did not identify any relevant evidence from this source.
UK guidelines and guidance	
<a href="#">SIGN</a>	SIGN 147. National clinical guideline. Management of chronic heart failure. March 2016: <a href="https://www.sign.ac.uk/sign-147-management-of-chronic-heart-failure.html">https://www.sign.ac.uk/sign-147-management-of-chronic-heart-failure.html</a>
<a href="#">NICE</a>	<p><b>Acute heart failure</b>            NICE pathway. Acute heart failure. Published October 2014. Last updated April 2019: <a href="https://pathways.nice.org.uk/pathways/acute-heart-failure">https://pathways.nice.org.uk/pathways/acute-heart-failure</a>            NICE quality standard (QS103). Acute heart failure. December 2015: <a href="https://www.nice.org.uk/guidance/qs103">https://www.nice.org.uk/guidance/qs103</a>            NICE clinical guideline (CG187). Acute heart failure: diagnosis and management. October 2014: <a href="https://www.nice.org.uk/guidance/cg187">https://www.nice.org.uk/guidance/cg187</a></p> <p><b>Chronic heart failure</b>            NICE pathway. Chronic heart failure. Published May 2011. Last updated September 2019: <a href="https://pathways.nice.org.uk/pathways/chronic-heart-failure">https://pathways.nice.org.uk/pathways/chronic-heart-failure</a>            NICE guideline (NG106). Chronic heart failure in adults: diagnosis and management. September 2018: <a href="https://www.nice.org.uk/guidance/ng106">https://www.nice.org.uk/guidance/ng106</a>            NICE quality standard (QS9). Chronic heart failure in adults. Last updated September 2018: <a href="https://www.nice.org.uk/guidance/qs9">https://www.nice.org.uk/guidance/qs9</a></p>
Secondary literature and economic evaluations	
<a href="#">ECRI</a>	We did not identify any relevant evidence from this source.
<a href="#">EUnetHTA</a>	We did not identify any relevant evidence from this source.
<a href="#">Cochrane library</a>	<p><b>Chronic heart failure</b>            McLellan J, Heneghan CJ, Perera R, Clements AM, Glasziou PP, Kearley KE, Piduck N, Roberts NW, Tyndel S, Wright FL, Bankhead C. December 2016. B-type natriuretic peptide-guided treatment for heart failure. Cochrane Systematic Review - Intervention: <a href="https://doi.org/10.1002/14651858.CD008966.pub2">https://doi.org/10.1002/14651858.CD008966.pub2</a></p>

Medline

**Acute heart failure**

Martindale JL; Wakai A; Collins SP; Levy PD; Diercks D; Hiestand BC; Fermann GJ; deSouza I; Sinert R. 2016. Diagnosing Acute Heart Failure in the Emergency Department: A Systematic Review and Meta-analysis. *Academic Emergency Medicine*. 23(3):223-42

Natriuretic Peptides Studies Collaboration; Willeit P; Kaptoge S; Welsh P; Butterworth AS; Chowdhury R; Spackman SA; Pennells L; Gao P; Burgess S; Freitag DF; Sweeting M; Wood AM; Cook NR; Judd S; Trompet S; Nambi V; Olsen MH; Everett BM; Kee F; Arnlov J; Salomaa V; Levy D; Kauhanen J; Laukkanen JA; Kavousi M; Ninomiya T; Casas JP; Daniels LB; Lind L; Kistorp CN; Rosenberg J; Mueller T; Rubattu S; Panagiotakos DB; Franco OH; de Lemos JA; Luchner A; Kizer JR; Kiechl S; Salonen JT; Goya Wannamethee S; de Boer RA; Nordestgaard BG; Andersson J; Jorgensen T; Melander O; Ballantyne ChM; DeFilippi Ch; Ridker PM; Cushman M; Rosamond WD; Thompson SG; Gudnason V; Sattar N; Danesh J; Di Angelantonio E. 2016. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. *The Lancet Diabetes & Endocrinology*. 4(10):840-9

Schaub JA; Coca SG; Moledina DG; Gentry M; Testani JM; Parikh CR. 2015. Amino-Terminal Pro-B-Type Natriuretic Peptide for Diagnosis and Prognosis in Patients With Renal Dysfunction: A Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology: Heart Failure*. 3(12): 977-89

**Chronic heart failure**

Aimo A; Januzzi JL Jr; Vergaro G; Ripoli A; Latini R; Masson S; Magnoli M; Anand IS; Cohn JN; Tavazzi L; Tognoni G; Gravning J; Ueland T; Nymo SH; Rocca HB; Bayes-Genis A; Lupon J; de Boer RA; Yoshihisa A; Takeishi Y; Egstrup M; Gustafsson I; Gaggin HK; Eggers KM; Huber K; Tentzeris I; Wilson Tang WH; Grodin JL; Passino C; Emdin M. 2019. High-sensitivity troponin T, NT-proBNP and glomerular filtration rate: A multimarker strategy for risk stratification in chronic heart failure. *International Journal of Cardiology*. 277:166-172

Gamino-Arroyo AE; Prado-Galbarro FJ; Garcia-Perez S; Sanchez-Piedra C. 2018. Effectiveness of natriuretic peptide-guided treatment of chronic heart failure. A meta-analysis. *Archivos de Cardiologia de Mexico*. 88(3):171-177

**Unspecified or both acute and chronic heart failure**

Han ZJ; Wu XD; Cheng JJ; Zhao SD; Gao MZ; Huang HY; Gu B; Ma P; Chen Y; Wang JH; Yang CJ; Yan ZH. 2015. Diagnostic Accuracy of Natriuretic Peptides for Heart Failure in Patients with Pleural Effusion: A Systematic Review and Updated Meta-Analysis. *PLoS ONE [Electronic Resource]*. 10(8):e0134376

Khan MS; Siddiqi TJ; Usman MS; Sreenivasan J; Fugar S; Riaz H; Murad MH; Mookadam F; Figueredo VM. 2018. Does natriuretic peptide monitoring improve outcomes in heart failure patients? A systematic review and meta-analysis. *International Journal of Cardiology*. 263:80-87.

Primary studies

<p>Medline</p>	<p>Mark DB; Cowper PA; Anstrom KJ; Sheng S; Daniels MR; Knight JD; Baloch KN; Davidson-Ray L; Fiuzat M; Januzzi JL Jr; Whellan DJ; Pina IL; Ezekowitz JA; Adams KF; Cooper LS; O'Connor CM; Felker GM. 2018. Economic and Quality-of-Life Outcomes of Natriuretic Peptide-Guided Therapy for Heart Failure. <i>Journal of the American College of Cardiology</i>. 72(21):2551-2562</p> <p>Khezri BS; Helmersson-Karlqvist J; Larsson A. 2014. Estimation of the possible economic effects of a sequential testing strategy with NT-proBNP before echocardiography in primary care. <i>Clinical Laboratory</i>. 60(6):881-6</p> <p>Januzzi JL Jr; Chen-Tournoux AA; Christenson RH; Doros G; Hollander JE; Levy PD; Nagurney JT; Nowak RM; Pang PS; Patel D; Peacock WF; Rivers EJ; Walters EL; Gaggin HK; ICON-RELOADED Investigators. 2018. N-Terminal Pro-B-Type Natriuretic Peptide in the Emergency Department: The ICON-RELOADED Study. <i>Journal of the American College of Cardiology</i>. 71(11):1191-1200</p> <p>Khanam SS; Choi E; Son JW; Lee JW; Youn YJ; Yoon J; Lee SH; Kim JY; Ahn SG; Ahn MS; Kang SM; Baek SH; Jeon ES; Kim JJ; Cho MC; Chae SC; Oh BH; Choi DJ; Yoo BS. 2018. Validation of the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) heart failure risk score and the effect of adding natriuretic peptide for predicting mortality after discharge in hospitalized patients with heart failure. <i>PLoS ONE</i>. 13(11):e0206380</p>
<p>Ongoing primary or secondary research</p>	
<p><a href="#">PROSPERO database</a></p>	<p>BNP and NT-proBNP as prognostic markers in patients with heart failure: a protocol for an overview of systematic reviews [CRD42018102426]</p>
<p>Other</p>	
<p>Evidence provided by the topic proposer</p>	<p>Juniper M, Great Western Hospitals NHS Foundation Trust, Smith N C E, Koomson D, Protopapa K, Mason M. Failure to Function. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD). 2018. <a href="https://www.hqip.org.uk/wp-content/uploads/2018/11/Ref.-67-NCEPOD-Acute-Heart-Failure-report-2018-FINAL.pdf">https://www.hqip.org.uk/wp-content/uploads/2018/11/Ref.-67-NCEPOD-Acute-Heart-Failure-report-2018-FINAL.pdf</a></p> <p>Joost H.W. Rutten, Ewout W. Steyerberg, Frans Boomsma, Jan L.C.M. van Saase, Jaap W. Deckers, Henk C. 2008. Hoogsteden, Jan Lindemans, Anton H. van den Meiracker, N-terminal pro-brain natriuretic peptide testing in the emergency department: Beneficial effects on hospitalization, costs, and outcome. <i>American Heart Journal</i>. Volume 156, Issue 1, Pages 71-77. <a href="https://doi.org/10.1016/j.ahj.2008.02.021">https://doi.org/10.1016/j.ahj.2008.02.021</a>.</p> <p>Taylor CJ, Monahan M, Roalfe AK, et al. Southampton (UK): NIHR Journals Library; 2017 April REFER (REfer for Echocardiogram) study: a prospective validation and health economic analysis of a clinical decision rule, NT-proBNP or their combination in the diagnosis of heart failure in primary care. Available at: <a href="https://www.ncbi.nlm.nih.gov/books/NBK425981/#s4-1">https://www.ncbi.nlm.nih.gov/books/NBK425981/#s4-1</a></p> <p>K Athanasakis, et al. 2015. Budget Impact Analysis of N-Terminal Pro-B-Type Natriuretic Peptide Testing for the Diagnosis and Prognosis of Heart Failure in Greece, Volume 18, Issue 7, Pages A348-349. Available at: <a href="https://www.valueinhealthjournal.com/article/S1098-3015(15)02704-7/fulltext">https://www.valueinhealthjournal.com/article/S1098-3015(15)02704-7/fulltext</a></p>

	<p>Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, McMurray JJ V et al. 2015. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting <i>BMJ</i>; 350 :h910</p> <p>Gaggin H.K, et al. 2018. N-Terminal Pro-B-Type Natriuretic Peptide in the Emergency Department: The ICON-RELOADED Study. <i>Journal of American College of Cardiology</i>. Volume 71, Issue 11, Pages 1191-1200. Available at: <a href="https://www.sciencedirect.com/science/article/pii/S0735109718301669?via%3Dihub">https://www.sciencedirect.com/science/article/pii/S0735109718301669?via%3Dihub</a></p> <p>McCullagh P.A, et al. 2002. B-Type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure. <i>Circulation</i>. 2002;106:416-422. Available at: <a href="https://www.ahajournals.org/doi/full/10.1161/01.cir.0000025242.79963.4c?url_ver=Z39.88-2003&amp;rfr_id=ori%3Arid%3Acrossref.org&amp;rfr_dat=cr_pub%3Dpubmed">https://www.ahajournals.org/doi/full/10.1161/01.cir.0000025242.79963.4c?url_ver=Z39.88-2003&amp;rfr_id=ori%3Arid%3Acrossref.org&amp;rfr_dat=cr_pub%3Dpubmed</a></p>
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<b>Date of search:</b>	December 2019
<b>Concepts used:</b>	Heart failure, NT-proBNP, N-terminal pro-brain natriuretic peptide, systematic review, economic studies