

Role of Natriuretic Peptides in Diagnosing Heart Failure

SBU ALERT REPORT NO 2006-05 • 2006-09-26 • WWW.SBU.SE/ALERT



Summary and Conclusions

TECHNOLOGY AND TARGET GROUP Approximately 200 000 people in Sweden have symptomatic heart failure. In addition, about equally as many have asymptomatic, impaired cardiac function. Around 30 000 new cases appear annually. Common symptoms of heart failure are shortness of breath, fatigue, and swollen legs. These symptoms alone, however, are not sufficient to confirm the diagnosis of heart failure. Establishing a diagnosis of heart failure also requires confirmation of impaired cardiac function, usually through echocardiography (ultrasound examination of the heart). This is a labor-intensive and relatively expensive diagnostic procedure. Measuring the concentration of B-type natriuretic peptides (BNP and N-terminal proBNP) in the blood is intended to help better determine if the symptoms are caused by heart failure, or other conditions. These peptides are produced at a higher rate as the load increases on the ventricular muscles of the heart. BNP and N-terminal proBNP can be analyzed by so-called point-of-care methods that yield results within about 15 minutes. A rapid test result benefits the physician and patient alike, assuming that diagnostic quality is satisfactory.

PRIMARY QUESTION Does determining the concentration of B-type natriuretic peptides (BNP and N-terminal proBNP) in the blood facilitate and improve diagnostics in heart failure?

PATIENT BENEFIT Several studies have shown that natriuretic peptide testing has a high negative predictive value, which means that one can rule out with considerable certainty that a patient has heart failure. This knowledge can help accelerate the diagnosis of other possible disorders. However, the positive predictive value of the test is not equally as high. Hence, it is necessary to complement the test with an assessment of cardiac function to determine, usually through echocardiography, whether or not the

patient has heart failure. Further research is required to determine the optimum decision cut-points for use in clinical practice.

ECONOMIC ASPECTS The cost of taking a sample and analyzing BNP or N-terminal proBNP is approximately 200 to 350 Swedish kronor (SEK). By comparison, the cost for echocardiography is 1500 to 2500 SEK. Since analysis of natriuretic peptides can identify patients with a low probability for heart failure, further examination by echocardiography in this patient group could be avoided.

SBU's appraisal of the evidence

Moderately strong scientific evidence (Evidence grade 2)* shows that BNP or N-terminal proBNP can be used, with good reliability, to rule out heart failure. However, evidence remains insufficient* concerning the cost effectiveness of the method relative to other methods of diagnosing heart failure.

* Criteria for Evidence Grading SBU's Conclusions

Evidence Grade 1 – Strong Scientific Evidence. The conclusion is corroborated by at least two independent studies with high quality and internal validity, or a good systematic overview.

Evidence Grade 2 – Moderately Strong Scientific Evidence. The conclusion is corroborated by one study with high quality and internal validity, and at least two studies with medium quality and internal validity.

Evidence Grade 3 – Limited Scientific Evidence. The conclusion is corroborated by at least two studies with medium quality and internal validity.

Insufficient Scientific Evidence. No conclusions can be drawn when there are not any studies that meet the criteria for quality and internal validity.

Contradictory Scientific Evidence. No conclusions can be drawn when there are studies with the same quality and internal validity whose findings contradict each other.

References

- Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26(11):1115-40.
- Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC et al. The epidemiology of heart failure. *Eur Heart J* 1997;18(2):208-25. Review.
- McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. *Heart* 2000;83(5):596-602. Review.
- Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA et al. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000;83(5):505-10.
- Schaufelberger M, Swedberg K, Koster M, Rosen M, Rosengren A. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden; Data from the Swedish Hospital Discharge Registry 1988 to 2000. *Eur Heart J* 2004;25(4):300-7.
- Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;292(3):344-50.
- MacIntyre K, Capewell S, Stewart S, Chalmers JW, Boyd J, Finlayson A et al. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. *Circulation* 2000;102(10):1126-31.
- Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;347(18):1397-402.
- McMurray J, McDonagh T, Morrison CE, Dargie HJ. Trends in hospitalization for heart failure in Scotland 1980-1990. *Eur Heart J* 1993;14(9):1158-62.
- Ryden-Bergsten T, Andersson F. The health care costs of heart failure in Sweden. *J Intern Med* 1999;246(3):275-84.
- Remes J, Miettinen H, Reunanen A, Pyöralä K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12(3):315-21.
- Hobbs FD, Jones MI, Allan TF, Wilson S, Tobias R. European survey of primary care physician perceptions on heart failure diagnosis and management (Euro-HF). *Eur Heart J* 2000;21(22):1877-87.
- Stein BC, Levin RI. Natriuretic peptides: physiology, therapeutic potential, and risk stratification in ischemic heart disease. *Am Heart J* 1998;135(5 Pt 1):914-23. Review.
- Ruskoaho H. Cardiac hormones as diagnostic tools in heart failure. *Endocr Rev* 2003;24(3):341-56.
- Kuhn M. Molecular physiology of natriuretic peptide signalling. *Basic Res Cardiol* 2004;99(2):76-82.
- Pandey KN. Biology of natriuretic peptides and their receptors. *Peptides* 2005;26(6):901-32.
- Clerico A, Del Ry S, Giannessi D. Measurement of cardiac natriuretic hormones (atrial natriuretic peptide, brain natriuretic peptide, and related peptides) in clinical practice: the need for a new generation of immunoassay methods. *Clin Chem* 2000;46(10):1529-34.
- Rawlins ML, Owen WE, Roberts WL. Performance characteristics of four automated natriuretic peptide assays. *Am J Clin Pathol* 2005;123(3):439-45.
- Apple FS, Panteghini M, Ravkilde J, Mair J, Wu AH, Tate J et al; Committee on Standardization of Markers of Cardiac Damage of the IFCC. Quality specifications for B-type natriuretic peptide assays. *Clin Chem* 2005;51(3):486-93.
- Fischer Y, Filzmaier K, Stiegler H, Graf J, Fuhs S, Franke A et al. Evaluation of a new, rapid bedside test for quantitative determination of B-type natriuretic peptide. *Clin Chem* 2001;47(3):591-4.
- Yeo KT, Wu AH, Apple FS, Kroll MH, Christenson RH, Lewandrowski KB et al. Multicenter evaluation of the Roche NT-proBNP assay and comparison to the Biosite Triage BNP assay. *Clin Chim Acta* 2003;338(1-2):107-15.
- Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Head-to-head comparison of the diagnostic utility of BNP and NT-proBNP in symptomatic and asymptomatic structural heart disease. *Clin Chim Acta* 2004;341(1-2):41-8.
- Murdoch DR, Byrne J, Farmer R, Morton JJ. Disparity between studies of the stability of BNP in blood: comparison of endogenous and exogenous peptide. *Heart* 1999;81(2):212-3.
- Belenky A, Smith A, Zhang B, Lin S, Despres N, Wu AH et al. The effect of class-specific protease inhibitors on the stabilization of B-type natriuretic peptide in human plasma. *Clin Chim Acta* 2004;340(1-2):163-72.
- Downie PF, Talwar S, Squire IB, Davies JE, Barnett DB, Ng LL. Assessment of the stability of N-terminal pro-brain natriuretic peptide in vitro: implications for assessment of left ventricular dysfunction. *Clin Sci* 1999;97(3):255-8.
- Barnes SC, Collinson PO, Galasko G, Lahiri A, Senior R. Evaluation of N-terminal pro-B type natriuretic peptide analysis on the Elecsys 1010 and 2010 analysers. *Ann Clin Biochem* 2004;41(Pt 6):459-63.
- Alehagen U, Lindstedt G, Eriksson H, Dahlström U. Utility of the amino-terminal fragment of pro-brain natriuretic peptide in plasma for the evaluation of cardiac dysfunction in elderly patients in primary health care. *Clin Chem* 2003;49(8):1337-46.
- Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Comparison of the Biomedica NT-proBNP enzyme immunoassay and the Roche NT-proBNP chemiluminescence immunoassay: implications for the prediction of symptomatic and asymptomatic structural heart disease. *Clin Chem* 2003;49(6 Pt 1):976-9.
- Hammerer-Lercher A, Ludwig W, Falkensammer G, Müller S, Neubauer E, Puschendorf B et al. Natriuretic peptides as markers of mild forms of left ventricular dysfunction: effects of assays on diagnostic performance of markers. *Clin Chem* 2004;50(7):1174-83.
- Prontera C, Ermdin M, Zucchelli GC, Ripoli A, Passino C, Clerico A. Analytical performance and diagnostic accuracy of a fully-automated electrochemiluminescent assay of the N-terminal fragment of brain natriuretic peptide in patients with cardiomyopathy: comparison with immunoradiometric assay methods for brain natriuretic peptide and atrial natriuretic peptide. *Clin Chem Lab Med* 2004;42(1):37-44.
- Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail* 2005;7(4):537-41.
- Kazanegra R, Cheng V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. *J Card Fail* 2001;7(1):21-9.
- Gegenhuber A, Mueller T, Firlinger F, Lenz K, Poelz W, Haltmayer M. Time course of B-type natriuretic peptide (BNP) and N-terminal proBNP changes in patients with decompensated heart failure. *Clin Chem* 2004;50(2):454-6.
- Johnson W, Omland T, Hall C, Lucas C, Myking OL, Collins C et al. Neurohormonal activation rapidly decreases after intravenous therapy with diuretics and vasodilators for class IV heart failure. *J Am Coll Cardiol* 2002;39(10):1623-9.

SBU – The Swedish Council on Technology Assessment in Health Care

SBU is an independent public authority which has the mandate of the Swedish Government to comprehensively assess healthcare technology from medical, economic, ethical, and social standpoints. SBU Alert is a system for identification and early assessment of new methods in health care.

P.O. Box 5650, SE-114 86 Stockholm, Sweden • alert@sbu.se

This summary is based on a report prepared at SBU in collaboration with Prof. **Ulf Dahlström**, Linköping University Hospital, Linköping and Prof. Emeritus **Göran Lindstedt**, Sahlgrenska Academy, Göteborg University, Göteborg and Chair of the Expert group on endocrinology at EQUALIS, Uppsala. It has been reviewed by Prof. **Karl Swedberg**, Sahlgrenska University Hospital, Göteborg.

The complete report is available only in Swedish.

35. McNairy M, Gardetto N, Clopton P, Garcia A, Krishnaswamy P, Kazanegra R et al. Stability of B-type natriuretic peptide levels during exercise in patients with congestive heart failure: implications for outpatient monitoring with B-type natriuretic peptide. *Am Heart J* 2002;143(3):406-11.
36. Wijbenga JA, Balk AH, Boomsma F, Man in 't Veld AJ, Hall C. Cardiac peptides differ in their response to exercise. Implications for patients with heart failure in clinical practice. *Eur Heart J* 1999;20(19):1424-8.
37. Sabatine MS, Morrow DA, de Lemos JA, Omland T, Desai MY, Tanasijevic M et al. Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. *J Am Coll Cardiol* 2004;44(10):1988-95.
38. Weber M, Dill T, Arnold R, Rau M, Ekinci O, Muller KD et al. N-terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris. *Am Heart J* 2004;148(4):612-20.
39. Prontera C, Storti S, Emdin M, Passino C, Zyw L, Zucchelli GC et al. Comparison of a fully automated immunoassay with a point-of-care testing method for B-type natriuretic peptide. *Clin Chem* 2005;51(7):1274-6.
40. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;40(5):976-82.
41. Doust JA, Glasziou PP, Pietrzak E, Dobson AJ. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. *Arch Intern Med* 2004;164(18):1978-84.
42. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347(3):161-7.
43. McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002;106(4):416-22.
44. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *J Am Coll Cardiol* 2003;42(4):728-35.
45. Ray P, Arthaud M, Birolleau S, Isnard R, Lefort Y, Boddaert J et al. Comparison of brain natriuretic peptide and probrain natriuretic peptide in the diagnosis of cardiogenic pulmonary edema in patients aged 65 and older. *J Am Geriatr Soc* 2005;53(4):643-8.
46. Logeart D, Saudubray C, Beyne P, Thabut G, Ennezat PV, Chavelas C. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. *J Am Coll Cardiol* 2002;40(10):1794-800.
47. McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE et al. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1998;351(9095):9-13.
48. McDonagh TA, Holmer S, Raymond I, Luchner A, Hildebrandt P, Dargie HJ. NT-proBNP and the diagnosis of heart failure: a pooled analysis of three European epidemiological studies. *Eur J Heart Fail* 2004;6(3):269-73.
49. Silver MA, Maisel A, Yancy CW, McCullough PA, Burnett JC Jr, Francis GS et al; BNP Consensus Panel. BNP Consensus Panel 2004: A clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. *Congest Heart Fail* 2004;10(5 Suppl 3):1-30. Review.
50. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;350(9088):1349-53.
51. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. *BMJ* 2002;324(7352):1498.
52. Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol* 2003;42(10):1793-800.
53. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 2004;350(7):647-54.
54. Mueller C, Laule-Kilian K, Frana B, Rodriguez D, Rudez J, Scholer A et al. The use of B-type natriuretic peptide in the management of elderly patients with acute dyspnoea. *J Intern Med* 2005;258(1):77-85.
55. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005;95(8):948-54.
56. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. *Heart* 2005;91(5):606-12.
57. Dahlström U. Can natriuretic peptides be used for the diagnosis of diastolic heart failure? *Eur J Heart Fail* 2004;6(3):281-7. Review.
58. Sim V, Hampton D, Phillips C, Lo SN, Vasishta S, Davies J et al. The use of brain natriuretic peptide as a screening test for left ventricular systolic dysfunction – cost-effectiveness in relation to open access echocardiography. *Fam Pract* 2003;20(5):570-4.
59. Jernberg T, Boman K, James S, Lindahl B, Stridsberg M, Swedberg K et al. BNP eller NT-proBNP bör analyseras vid misstänkt hjärtsvikt. Riktlinjer för analys och tolkning. *Läkartidningen* 2006;103(17):1289-92, 1295.
60. Nielsen LS, Svanegaard J, Klitgaard NA, Egeblad H. N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea. *Eur J Heart Fail* 2004;6(1):63-70.
61. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* 1997;96(2):509-16.
62. Richards AM, Doughty R, Nicholls MG, MacMahon S, Sharpe N, Murphy J et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. Australia-New Zealand Heart Failure Group. *J Am Coll Cardiol* 2001;37(7):1781-7.
63. Swedberg K. Impact on mortality of plasma NT-proBNP in chronic heart failure in patients treated with beta-blockers: Results from COMET. *Circulation* 2004 (Suppl).
64. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000;355(9210):1126-30.
65. Cowie MR, Jourdain P, Maisel A, Dahlström U, Follath F, Isnard R et al. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003;24(19):1710-8. Review.