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B-Type Natriuretic Peptide Testing: A Rapid Review

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Conflict of Interest Statement

All reports prepared by the Division of Evidence Development and Standards at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Clinical questions are developed by the Division of Evidence Development and Standards at Health Quality Ontario in consultation with experts, end-users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials (RCTs), and guidelines. Systematic reviews are evaluated using a rating scale developed for this purpose. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies included in the systematic review are retrieved and a maximum of two outcomes are graded. If no well-conducted systematic reviews are available, RCTs and/or guidelines are evaluated. Because rapid reviews are completed in very short timeframes, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

Disclaimer

This rapid review is the work of the Division of Evidence Development and Standards at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current to the date of the literature search specified in the Research Methods section, as appropriate. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. Health Quality Ontario works with clinical experts, scientific collaborators, and field evaluation partners to develop and publish research that evaluates the effectiveness and cost-effectiveness of health technologies and services in Ontario.

Based on the research conducted by Health Quality Ontario and its partners, the Ontario Health Technology Advisory Committee (OHTAC)—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy makers.

Rapid reviews, evidence-based analyses and their corresponding OHTAC recommendations, and other associated reports are published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

About Health Quality Ontario Publications

To conduct its rapid reviews, Health Quality Ontario and/or its research partners reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, Health Quality Ontario collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario can add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Permission Requests

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http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews.

Table of Contents

List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
CI	Confidence interval
HF	Heart failure
LVEF	Left ventricular ejection fraction
OR	Odds ratio
RCT	Randomized controlled trial

Background

As legislated in Ontario's *Excellent Care for All Act*, Health Quality Ontario's mandate includes the provision of objective, evidence-informed advice about health care funding mechanisms, incentives, and opportunities to improve quality and efficiency in the health care system. As part of its Quality-Based Funding (QBF) initiative, Health Quality Ontario works with multidisciplinary expert panels (composed of leading clinicians, scientists, and administrators) to develop evidence-based practice recommendations and define episodes of care for selected disease areas or procedures. Health Quality Ontario's recommendations are intended to inform the Ministry of Health and Long-Term Care's Health System Funding Strategy.

For more information on Health Quality Ontario's Quality-Based Funding initiative, visit www.hqontario.ca.

Objective of Analysis

The objective of this analysis was to determine the following:

- the diagnostic accuracy of in-hospital B-type natriuretic peptide (BNP) measurement for heart failure (HF)
- the prognostic accuracy of BNP for triage of HF patients when used in the emergency department
- the prognostic accuracy of in-hospital BNP measurement for HF before hospital discharge

Clinical Need and Target Population

BNP in the Diagnosis and Prognosis of Heart Failure

Acute dyspnea (shortness of breath) is a common presentation to emergency care, and HF is an important cause of dyspnea. (1) However, there is no gold standard for establishing HF; even following clinical assessment, chest x-rays, and electrocardiography, diagnostic uncertainty may remain. (2) B-type natriuretic peptide (BNP) and the N-terminal peptide of its precursor proBNP are secreted by cardiomyocytes in response to excessive stretching and have been proposed as useful markers for helping to distinguish between cardiac and noncardiac causes of dyspnea. (2)

After a diagnosis of HF is established, BNP may also provide prognostic information to inform patients about likely outcomes and clinicians about the necessary aggressiveness of treatment. (2)

Rapid Review

Research Questions

- What is the diagnostic accuracy of in-hospital BNP measurement for HF?
- What is the prognostic accuracy of BNP for triage of HF patients when used in the emergency department?
- What is the prognostic accuracy of in-hospital BNP measurement for HF before hospital discharge?

Research Methods

Literature Search

A literature search was performed on October 5, 2012, using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2000, until October 5, 2012. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language full-text reports
- published between January 1, 2000, and October 5, 2012
- health technology assessments, systematic reviews, and meta-analyses
- studies describing in-hospital diagnostic or prognostic accuracy of BNP measurement for HF

Exclusion Criteria

- randomized controlled trials, observational studies, case reports, editorials, letters to the editor

Outcomes of Interest

- mortality
- rehospitalization

Expert Panel

In August 2012, an Expert Advisory Panel on Episode of Care for Congestive Heart Failure was struck. Members of the panel included physicians, personnel from the Ministry of Health and Long-Term Care, and representation from the community laboratories.

The role of the Expert Advisory Panel on Episode of Care for Congestive Heart Failure was to contextualize the evidence produced by Health Quality Ontario and provide advice on the components of a high-quality episode of care for HF patients presenting to an acute care hospital. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of Expert Advisory Panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodological quality of systematic reviews. (3)

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (4) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials are high quality, whereas observational studies are low quality. (4) Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding. (4) For more detailed information, please refer to the latest series of GRADE articles. (4)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	Very confident that the true effect lies close to the estimate of the effect
Moderate	Moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect
Very Low	Very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Literature Search

The database search yielded 276 citations published between January 1, 2000, and October 5, 2012 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

Two studies (2 systematic reviews) met the inclusion criteria. The reference lists of the included studies were hand searched to identify any additional potentially relevant studies, but no additional citations were included, for a total of 2 included citations.

One systematic review related to the diagnostic accuracy of BNP was identified. (1) The AMSTAR score for this study was 5 out of 11.

No studies were identified that assessed the prognostic accuracy of BNP for triage of HF patients when used in the emergency department or for in-hospital measurement for HF before hospital discharge. However, 1 systematic review related to the prognostic accuracy of BNP was identified in which patients were not restricted to an emergency department or hospital or acute HF. (5) The AMSTAR score for this study was 3 out of 11.

A summary of the results appears in Table 1.

Table 1: Summary of Systematic Reviews on BNP Testing

Author, Year	Population/Setting	Types of Studies Included	Number of Studies, Sample Size	Outcomes	Limitations
Diagnosis					
Lam et al., 2010 (1)	Patients presenting with acute dyspnea in the emergency department	RCTs that compared BNP testing with routine care to diagnose HF in patients presenting with acute dyspnea	5 RCTs N = 2,513 patients	*BNP vs. routine care* • All-cause hospital mortality: OR 0.96 (95% CI 0.65–1.41); *P* = 0.83; n = 2,488 patients • Admission rates: OR 0.85 (95% CI 0.67–1.01); *P* = 0.06; n = 2,488 patients • 30-day readmission: OR 0.88 (95% CI 0.64–1.20); *P* = 0.41; n = 1,948 patients • Length of hospital stay: mean difference –1.22 days (95% CI, –2.31 to –0.14 days); *P* value not reported; n = 2,417 patients • Length of critical care unit stay: mean difference –0.56 days (95% CI –1.06 to –0.05 days); *P* value not reported; n = 2,041 patients	• Statistical heterogeneity was not reported, although some outcomes were stated to be heterogeneous (e.g., length of hospital stay) • Studies from different healthcare systems: Australia, Canada, Switzerland, United States, Netherlands (first point of contact senior vs. junior physicians)
Prognosis					
Doust et al., 2005 (5)	Various HF patients; not restricted to emergency department or hospital or acute HF Inclusion criteria for studies consisted of patients who: • were referred to HF clinics • were a subset of patients in drug trials • were undergoing cardiac catheterization • were seen in an internal medicine clinic • were admitted to hospital for HF • were being considered for heart transplantation	No restrictions to study type; observational (not all consecutive cohorts)	19 studies Pooled estimate used 4 studies (n = 652 patients)	• 4 studies estimated relative risk of all-cause mortality by using a continuous measure of BNP; this gave an estimate of the relative risk of death per 100 pg/mL of 35% (95% CI 22%–49%); heterogeneity $\chi^2 = 6.3$; *P* = 0.09 • Studies that used dichotomous measures showed considerable variation in results: "The pooled estimate from the studies using a continuous measure was consistent with the results seen of the largest study using a dichotomized measure"	• Difficult to assess how well the patients were followed up and how well outcomes were ascertained in each study • 3 studies reported that some patients in the study were lost to follow-up; the remainder either reported complete follow-up or the calculations imply complete follow-up • Different ways of diagnosing HF reported (e.g., LVEF < 30%, 40%, 45% or 50%; "clinical assessment"; not reported; "excluded trauma, unstable angina or myocardial infarction") • Ascertainment of the outcome being blinded was not reported in several studies

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; OR, odds ratio; RCT, randomized controlled trial.

Conclusions

- No studies were identified that specifically assessed the prognostic accuracy of BNP for triage of HF patients when used in the emergency department or in-hospital BNP measurement for HF before hospital discharge.
- There is moderate quality evidence that BNP testing to diagnose HF in patients presenting to the emergency department with acute dyspnea does not significantly reduce mortality or rehospitalization.

Acknowledgements

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Episode of Care for Congestive Heart Failure Expert Panel

Name	Title	Organization
Dr. David Alter	Senior Scientist	Institute for Clinical Evaluative Sciences Research Program Director and Associate Staff, The Cardiac and Secondary Prevention Program at the Toronto Rehabilitation Institute-UHN Associate Professor of Medicine, University of Toronto
Dr. Douglas Lee	Scientist	Institute for Clinical Evaluative Sciences
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Dr. Susanna Mak	Cardiologist	University of Toronto, Department of Medicine, Division of Cardiology, Mount Sinai Hospital
Dr. Lisa Mielniczuk	Medical Director, Pulmonary Hypertension Clinic	University of Ottawa Heart Institute
Dr. Peter Liu	President, International Society of Cardiomyopathy and Heart Failure of the World Heart Federation Director, National C-CHANGE Program Scientific Director/VP Research, University of Ottawa Heart Institute Professor of Medicine	University of Ottawa Heart Institute
Dr. Robert McKelvie	Professor of Medicine, Cardiologist	McMaster University, Hamilton Health Sciences
Dr. Malcolm Arnold	Professor of Medicine	University of Western Ontario, London Health Sciences Centre
Dr. Stuart Smith	Chief of Cardiovascular Services Director, Heart Failure Program	St. Mary's General Hospital
Dr. Atilio Costa Vitali	Assistant Professor of Medicine Division of Clinical Science	Sudbury Regional Hospital

Dr. Jennifer Everson	Physician Lead	Hamilton Niagara Haldimand Brant Local Health Integration Network
Dr. Lee Donohue	Family Physician	Ottawa
Linda Belford	Nurse Practitioner, Practice Leader PMCC	University Health Network
Jane MacIver	Nurse Practitioner Heart Failure/Heart Transplant	University Health Network
Sharon Yamashita	Clinical Coordinator, Critical Care	Sunnybrook Health Sciences Centre
Claudia Bucci	Clinical Coordinator, Cardiovascular Diseases	Sunnybrook Health Sciences Centre
Andrea Rawn	Evidence Based Care Program Coordinator	Grey Bruce Health Network
Darlene Wilson	Registered Nurse	Heart Function Clinic, Trillium Health Centre
Kari Kostiw	Clinical Coordinator	Health Sciences North Ramsey Lake Health Centre
Janet Parr	CHF Patient	
Heather Sherrard	Vice President, Clinical Services	University of Ottawa Heart Institute
Sue Wojdylo	Manager, Case Costing	Lakeridge Health
Jane Chen	Manager of Case Costing	University Health Network
Nancy Hunter	LHIN Liaison & Business Development	Cardiac Care Network of Ontario
Ministry Representatives		
Gary Coleridge	Senior Program Consultant	Ministry of Health and Long-Term Care
Louie Luo	Senior Methodologist	Ministry of Health and Long-Term Care

Appendices

Appendix 1: Literature Search Strategies

Database: Ovid MEDLINE(R) <1946 to September Week 4 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 04, 2012>, Embase <1980 to 2012 Week 39>
Search Strategy:

#	Searches	Results
1	exp Heart Failure/	325741
2	(((cardia? or heart) adj (decompensation or failure or incompetence or insufficiency)) or cardiac stand still or ((coronary or myocardial) adj (failure or insufficiency))).ti,ab.	257108
3	or/1-2	415435
4	Natriuretic Peptide, Brain/ use mesz	8437
5	Brain Natriuretic Peptide/ use emez	13760
6	Nesiritide/ use emez	1222
7	((B-type or brain or type-b) adj (natriuretic peptide* or ventricular natriuretic peptide)).ti,ab.	19688
8	(BNP or bnp-32 or NT-proBNP or natriuretic factor-32).ti,ab.	20419
9	(peptide* adj brain natriuretic).ti,ab.	240
10	(natrecor or nesiritide or noratak).mp.	1788
11	or/4-10	32616
12	Meta Analysis.pt.	36882
13	Meta Analysis/ use emez	66108
14	Systematic Review/ use emez	53391
15	exp Technology Assessment, Biomedical/ use mesz	8864
16	Biomedical Technology Assessment/ use emez	11385
17	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	291582
18	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	3657
19	or/12-18	351351
20	3 and 11 and 19	402
21	limit 20 to english language	363
22	limit 21 to yr="2000 -Current"	358
23	remove duplicates from 22	264

Cochrane Library

Line #	Terms	Results
#1	MeSH descriptor: [Heart Failure] explode all trees	4860
#2	((cardia? or heart) next (decompensation or failure or incompetence or insufficiency)) or cardiac stand still or ((coronary or myocardial) next (failure or insufficiency)):ti,ab,kw (Word variations have been searched)	9323
#3	Enter terms for search #1 or #2	9328
#4	MeSH descriptor: [Natriuretic Peptide, Brain] this term only	695
#5	(B-type or brain or type-b) next (natriuretic peptide* or ventricular natriuretic peptide):ti,ab,kw or BNP or bnp-32 or NT-proBNP or natriuretic factor-32:ti,ab,kw or peptide* next brain natriuretic:ti,ab,kw or natrecor or nesiritide or noratak (Word variations have been searched)	891
#6	#4 or #5	891
#7	#3 and #6	505 from 2000 to 2012

4 CDSR; 22 DARE; 15 HTA

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES	510
2	(((cardia? OR heart) ADJ (decompensation OR failure OR incompetence OR insufficiency)) OR cardiac stand still OR ((coronary OR myocardial) ADJ (failure OR insufficiency))):TI	311
3	#1 OR #2	546
4	MeSH DESCRIPTOR Natriuretic Peptide, Brain	79
5	((B-type OR brain OR type-b) ADJ (natriuretic peptide* OR ventricular natriuretic peptide)):TI OR (BNP OR bnp-32 OR NT-proBNP OR natriuretic factor-32):TI OR (peptide* ADJ brain natriuretic):TI OR (natrecor OR nesiritide OR noratak)	36
6	#4 OR #5	82
7	#3 AND #6	49

36 results in HTA/DARE=2000-current

Appendix 2: GRADE Tables

Table A1: GRADE Evidence Profile for B-Type Natriuretic Peptide Testing

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Prognosis							
1 systematic review of 4 single cohort series	Very serious limitations (–2)[a]	No serious limitations	Serious limitations (–1)[b]	No serious limitations	Undetected	None	⊕ Very Low
Diagnosis							
1 systematic review of 5 RCTs	Serious limitations (–1)[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

Abbreviations: LVEF; left ventricular ejection fraction; RCT, randomized controlled trial

[a]Authors found that the reporting quality of studies varied. Difficult to assess how well patients were followed up and how well outcomes were ascertained in each study. Three studies reported that some patients in the study were lost to follow-up; the remainder either reported complete follow-up or the calculations imply complete follow-up. Different ways of diagnosing HF reported (e.g., LVEF < 30%, 40%, 45% or 50%; "clinical assessment"; not reported; "excluded trauma, unstable angina or myocardial infarction"). Ascertainment of the outcome being blinded was not reported in several studies.

[b]Various HF patients. Not restricted to emergency department or hospital or acute HF. Inclusion criteria for studies consisted of patients who were referred to HF clinics; were a subset of patients in drug trials; were undergoing cardiac catheterization; were seen in an internal medicine clinic; were admitted to hospital for HF; or were being considered for heart transplantation.

[c]Statistical heterogeneity was not reported, although some outcomes were stated to be heterogeneous (e.g., length of hospital stay). Studies were from different healthcare systems: Australia, Canada, Switzerland, United States, Netherlands (first point of contact for the patient was different between studies e.g., senior vs. junior physicians). All studies reported adequate sequence generation and allocation concealment for randomization except for 1 study. Four of the 5 RCTs reported no blinding of physicians. Two of the 5 RCTs reported blinding of participants, and 3 of the 5 RCTs reported blinding outcome assessors.

References

(1) Lam LL, Cameron PA, Schneider HG, Abramson MJ, Muller C, Krum H. Meta-analysis: effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. Ann Intern Med. 2010;153(11):728-35.

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(3) Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.

(4) Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.

(5) Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ. 2005;330(7492):625.

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