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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Natriuretic Peptide Testing for Pulmonary Arterial Hypertension: Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Research Questions

1. What is the clinical utility of natriuretic peptide testing for prognosis or guiding therapy for pulmonary arterial hypertension?
2. What is the cost-effectiveness of natriuretic peptide testing for prognosis or guiding therapy for pulmonary arterial hypertension?
3. What are the guidelines for natriuretic peptide testing for pulmonary arterial hypertension?

Key Findings

One systematic review, five non-randomized studies, and three evidence-based guidelines were identified regarding natriuretic peptide testing for pulmonary arterial hypertension.

Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were natriuretic peptide testing and pulmonary arterial hypertension (PAH). Search filters were applied to limit retrieval of a broader search to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials or controlled clinical trials, economic studies, and guidelines. The search was also limited to English language documents published between January 1, 2014 and July 12, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of all ages with pulmonary arterial hypertension
Intervention	Natriuretic peptide testing (BNP/NT-proBNP blood tests) with or without additional diagnostic tests
Comparator	Q1 & Q2: No natriuretic peptide testing; Other prognostic testing (e.g., cardiac troponin T test, echocardiography) Q3: No comparator

Outcomes	Q1: Clinical utility (e.g., changes to therapy) Q2: Cost-effectiveness Q3: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

One systematic review, five non-randomized studies, and three evidence-based guidelines were identified regarding natriuretic peptide testing for pulmonary arterial hypertension. No relevant health technology assessments, randomized controlled trials, or economic evaluations were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

One systematic review[1] and five non-randomized studies[2-6] were identified regarding the clinical utility of natriuretic peptide testing for pulmonary arterial hypertension. Detailed study characteristics are provided in Table 2.

Overall, the majority of study authors found that natriuretic peptide levels have prognostic value for a variety of endpoints, including death, lung transplantation, heart failure, and development of late pulmonary hypertension.[1-4]

There were mixed findings regarding the clinical utility of natriuretic peptide testing for diagnosis. The authors of one systematic review found it unsuitable in pediatric patients diagnosed with pulmonary hypertension by right heart catherization.[1] However, the authors of one non-randomized study found a significant correlation between echocardiographic results and B-type natriuretic peptide levels in patients with systemic lupus erythematous.[5]

The authors of one non-randomized study assessed the clinical utility of natriuretic peptide testing for screening and found significantly elevated levels in preterm infants diagnosed with pulmonary hypertension by echocardiography.[6]

Three evidence-based guidelines were identified regarding natriuretic peptide testing for pulmonary arterial hypertension.[7-9] The European Society of Cardiology and European Respiratory Society states in their joint guidelines that natriuretic peptide testing should be used for risk assessment in patients with pulmonary arterial hypertension.[7] The American Heart Association and American Thoracic Society recommend that either B-type natriuretic peptide or N-terminal-pro-fragment B-type natriuretic peptide should be measured at diagnosis, and that these levels can be useful in screening for pulmonary hypertension in patients with sickle cell disease.[8] The American Thoracic Society states that natriuretic

peptide testing should not be used for diagnosis but can be used as an alternative to echocardiography for risk assessment.[9]

Table 2: Characteristics of Included Literature

First Author, Year	Study Characteristics	Interventions and Comparators	Outcomes	Conclusions
Systematic Reviews and Meta-analyses				
Ten Kate, 2015[1]	• 14 studies included • Pediatric patients with PH diagnosed by RHC	Several, including: • NT-proBNP testing • RHC	• Prognostic value • Clinical utility as diagnostic marker	• NT-proBNP levels correlate with mortality and therefore have prognostic value • NT-proBNP testing is unsuitable for diagnosis but can be used to monitor patients
Non-Randomized Studies				
Behere, 2019[2]	• Retrospective longitudinal study • Preterm infants with BPD • N = 37 • Follow-up ranged from 14 to 91 weeks	• Serum BNP testing • Echocardiography	Prognostic value (endpoint of late PH)	• Infants who developed late PH had significantly elevated BNP at initial screening • BNP levels correlate with echocardiographic evaluation
Geenen, 2019[3]	• Prospective study • Patients with PH diagnosed by RHC • N = 106 • Median follow-up 24 months	• Several biomarkers, including NT-proBNP • REVEAL risk score	Prognostic value (endpoints of death, lung transplantation, and or heart failure)	• Elevated NT-proBNP is significantly associated with endpoints • NT-proBNP does not yield prognostic value independent of REVEAL risk score
Stepnowska, 2018[4]	• Prospective study • Patients with PAH • N = 47	Several, including BNP testing	Prognostic value (endpoint of death)	• Elevated BNP is independent predictor of mortality
Ghofraniha, 2017[5]	• Cross-sectional study • Patients with SLE diagnosed with PAH by echocardiography • N = 50	Several, including: • Serum BNP testing • Echocardiography	Clinical utility as diagnostic marker	Significant correlation between echocardiographic results and BNP levels
Montgomery, 2016[6]	• Cross-sectional study • Preterm infants • N = 20	• NT-proBNP testing • Echocardiography • Amino acid levels	Clinical utility as screening marker	• NT-proBNP levels are significantly elevated in patients diagnosed with PH by echocardiogram • Elevated NT-proBNP has significant correlation with low citrulline

6WMT = six-minute walk test; BNP = B-type natriuretic peptide; BPD = bronchopulmonary dysplasia; NT-proBNP = N-terminal-pro-fragment B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; TnT = cardiac troponin T; RHC = right heart catheterization; SLE = systemic lupus erythematous.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Ten Kate CA, Tibboel D, Kraemer US. B-type natriuretic peptide as a parameter for pulmonary hypertension in children. A systematic review. *Eur J Pediatr*. 2015 Oct;174(10):1267-1275.
PubMed: PM26298682

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

2. Behere S, Alapati D, McCulloch MA. Screening Echocardiography and Brain Natriuretic Peptide Levels Predict Late Pulmonary Hypertension in Infants with Bronchopulmonary Dysplasia. *Pediatr Cardiol*. 2019 Jun;40(5):973-979.
PubMed: PM30937503

3. Geenen LW, Baggen VJM, Koudstaal T, et al. The prognostic value of various biomarkers in adults with pulmonary hypertension; a multi-biomarker approach. *Am Heart J*. 2019 Feb;208:91-99.
PubMed: PM30580131

4. Stepnowska E, Lewicka E, Dabrowska-Kugacka A, et al. Predictors of poor outcome in patients with pulmonary arterial hypertension: A single center study. *PLoS One*. 2018;13(4):e0193245.
PubMed: PM29684090

5. Ghofraniha L, Mirfeizi Z, Khabbaz FS, Vakilian F, Eslami S. Correlation of echocardiographic findings of pulmonary hypertension with six-minute walk test and plasma pro b-type natriuretic peptide level in systemic lupus erythematous. *Electron Physician*. 2017 Aug;9(8):5122-5128.
PubMed: PM28979751

6. Montgomery AM, Bazzy-Asaad A, Asnes JD, Bizzarro MJ, Ehrenkranz RA, Weismann CG. Biochemical Screening for Pulmonary Hypertension in Preterm Infants with Bronchopulmonary Dysplasia. *Neonatology*. 2016;109(3):190-194.
PubMed: PM26780635

Economic Evaluations

No literature identified.

Guidelines and Recommendations

7. Galiè N, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119 https://www.ncbi.nlm.nih.gov/pubmed/26320113
See: Sections 5.1.9, 6.2.3, 6.2.4, and 7.1.1

8. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension Guidelines From the American Heart Association and American Thoracic Society. Circulation; 2015 Nov 24;132(21):2037-99. https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000329?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
See: Sections 3 and 14

9. Klings ES, et al. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med. 2014 Mar 15;189(6):727-40; http://www.thoracic.org/statements/resources/pvd/sickle-cell-disease.pdf
See: Diagnosis of PH in SCD, page 729; Estimating Mortality Risk in SCD, page 732

Appendix — Further Information

Systematic Reviews and Meta-analyses – Unknown Comparator

10. Giannakoulas G, Mouratoglou SA, Gatzoulis MA, Karvounis H. Blood biomarkers and their potential role in pulmonary arterial hypertension associated with congenital heart disease. a systematic review. *Int J Cardiol*. 2014 Jul 1;174(3):618-623.
PubMed: PM24814894

Randomized Controlled Trials – Unknown Comparator

11. Chin KM, Rubin LJ, Channick R, et al. Association of N-Terminal Pro Brain Natriuretic Peptide and Long-Term Outcome in Patients With Pulmonary Arterial Hypertension. *Circulation*. 2019 May 21;139(21):2440-2450.
PubMed: PM30982349

Non-Randomized Studies

Unknown Comparator

12. Al-Naamani N, Palevsky HI, Lederer DJ, et al. Prognostic Significance of Biomarkers in Pulmonary Arterial Hypertension. *Annals of the American Thoracic Society*. 2016 Jan;13(1):25-30.
PubMed: PM26501464

Alternative Population

13. Konig K, Guy KJ, Nold-Petry CA, et al. BNP, troponin I, and YKL-40 as screening markers in extremely preterm infants at risk for pulmonary hypertension associated with bronchopulmonary dysplasia. *Am J Physiol Lung Cell Mol Physiol*. 2016 Dec 1;311(6):L1076-l1081.
PubMed: PM27760764

Guidelines and Recommendations – Methodology Not Specified

14. Williams B, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018 Oct;36(10):1953-2041.
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Arterial-Hypertension-Management-of
See: Table 30, page 3074

15. Pattathu J, Gorenflo M, Hilgendorff A, et al. Genetic testing and blood biomarkers in paediatric pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart*. 2016 May;102 Suppl 2:ii36-41.
PubMed: PM27053696

Review Articles

16. Bendapudi P, Rao GG, Greenough A. Diagnosis and management of persistent pulmonary hypertension of the newborn. *Paediatr Respir Rev*. 2015 Jun;16(3):157-161. PubMed: PM25765845

17. Lohani O, Colvin KL, Yeager ME. Biomarkers for pediatric pulmonary arterial hypertension: challenges and recommendations. *Paediatr Respir Rev*. 2015 Sep;16(4):225-231. PubMed: PM26036720

Additional References

18. Report to the Medical Services Advisory Committee on real world outcomes of Application 1087: Brain natriuretic peptide assays in the diagnosis and monitoring of heart failure. Canberra (AU): Medical Services Advisory Committee. 2017; http://www.msac.gov.au/internet/msac/publishing.nsf/Content/B68AAF8993749793CA25801000123B83/$File/1087%20-%20PvA%20PSD%20-%20April%202017.pdf *See: Section 6*

19. Quinlivan A, Thakkar V, Stevens W, et al. Cost savings with a new screening algorithm for pulmonary arterial hypertension in systemic sclerosis. *Intern Med J*. 2015 Nov;45(11):1134-1140. PubMed: PM26337683