CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Natriuretic Peptide Testing for Monitoring of Heart Failure Therapy: A Review of Clinical Effectiveness, Clinical Utility, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	August 19, 2019
Report Length:	29 Pages

CADTH

Authors: Srabani Banerjee, Suzanne McCormack

Cite As: Natriuretic peptide testing for monitoring of heart failure therapy: a review of clinical effectiveness, clinical utility, cost-effectiveness, and guidelines. Ottawa: CADTH; 2019 Aug. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to Requests@CADTH.ca

Abbreviations

BNP	B-type natriuretic peptide
CI	confidence interval
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with a reduced ejection fraction
iNMB	Incremental net monetary benefit
NP	natriuretic peptide
NT-proBNP	N (or amino)-terminal pro-B-type natriuretic peptide
QALY	Quality adjusted life year

Context and Policy Issues

Heart failure (HF) is a complex condition, in which the heart is unable to pump enough blood to meet all the needs of the body.[1,2] HF is mainly of two types: heart failure with a reduced ejection fraction (HFrEF) and heart failure with a preserved ejection fraction (HFpEF).[2] HFrEF is caused by left ventricular systolic dysfunction because the left ventricle becomes weak and is unable to contract properly.[2] In HFpEF, the left ventricle becomes stiff, making it difficult for the heart chamber to fill with blood.[2] Typical symptoms include breathlessness, ankle swelling and fatigue.[1]

Heart failure is a costly health condition and is a major public health concern.[3] In Canada, approximately 669,600 (3.6%) persons aged 40 years or older, live with diagnosed HF.[4] The estimated cost resulting from hospital admissions for which HF was the primary diagnosis was $482 million in 2013; the number of HF patients admitted being 45,600. By 2030, the number of patients admitted with HF is expected to rise to 54,000 and the associated cost to increase to $2.8 billion.[3]

Pharmacological treatment for HF includes drugs such as angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, and mineralocorticoid receptor antagonist.[5] It has been reported that it may be difficult to recognize the early signs of worsening HF and that sometimes sub-optimal doses of drugs are used for fear of adverse events such as renal dysfunction and hypotension.[6] Biomarkers such as neuropeptides (NPs) may provide an objective assessment of HF severity and enable use of appropriate drug doses for HF therapy.[6]

The NPs, B-type natriuretic peptide (BNP) and N (or amino) terminal pro-B-type natriuretic peptide (NT-proBNP) are released by the myocardium in response to volume and pressure overload.[7] In HF patients natriuretic peptide (NP) levels are elevated.[7] Measurement of NP levels in plasma has been used for diagnosis and prognosis of HF patients, but its role. in guiding therapy for patients with HF appears uncertain.[7-9]

The purpose of this report is to review the clinical effectiveness, clinical utility, and cost-effectiveness of. natriuretic peptide testing for monitoring of heart failure therapy. Additionally, this report aims to review the evidence-based guidelines regarding natriuretic peptide testing for monitoring of heart failure therapy.

Research Questions

1. What is the clinical effectiveness and clinical utility of natriuretic peptide testing for the monitoring of heart failure therapy?

2. What is the cost-effectiveness of natriuretic peptide testing for the monitoring of heart failure therapy?
3. What are the guidelines for natriuretic peptide testing for the monitoring of heart failure therapy?

Key Findings

Four relevant systematic reviews were identified. Three systematic reviews showed that the between group differences for natriuretic peptide (NP)-guided therapy compared with clinically-guided therapy for heart failure (HF) patients were statistically significant with respect to HF-related hospitalization, favoring NP-guided therapy. However some uncertainty remains as in two of the three systematic reviews, the confidence intervals indicated marginal significance. Overall for the other outcomes (all-cause mortality, HF-related mortality, all cause hospitalization, and quality of life), there were no statistically significant between group differences for NP-guide therapy compared with clinically-guided therapy for HF patients. Overall the clinical effectiveness and clinical utility of the use of NP-guided therapy for HF patients remains uncertain.

One economic evaluation showed that NP-guided therapy appeared to be cost-effective for patients, who were less than 75 years of age and with heart failure with reduced ejection fraction considering a willingness-to-pay threshold of £20,000 and if NP-guided therapy is considered effective.

Two guidelines suggested that NP-guided therapy may be considered for HF patients less than 75 years of age (one guideline mentioned that the recommendation was weak, and another guideline did not specify the strength of the recommendation).

Methods

Literature Search 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 heart failure. Search filters were applied to limit retrieval 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 18, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of all ages with chronic heart failure
Intervention	Natriuretic peptide testing (BNP/NT-proBNP blood tests) for monitoring therapy with/without additional diagnostic test(s)
Comparator	Q1-2: No natriuretic peptide testing; Other prognostic testing (cardiac troponin T test, echocardiography) Q3: No comparators
Outcomes	Q1: Clinical effectiveness and clinical utility (e.g. mortality, readmission, emergency room visit, change in management/treatment plan) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, economic evaluations, and evidence-based guidelines

BNP = B-type natriuretic peptide; NT-proBNP = N terminal proBNP

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Studies on acute heart failure were excluded. Studies which reported on use of natriuretic peptides for diagnosis or prognosis of HF patients and not for monitoring of therapy in HF patients were excluded. Primary studies already included in a selected systematic review were excluded. Systematic reviews with all primary studies included in a more recent systematic review were excluded unless additional relevant information was presented. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 checklist,[10] economic studies were assessed using the Drummond checklist,[11] and guidelines were assessed with the AGREE II instrument.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 430 citations were identified in the literature search. Following screening of titles and abstracts, 402 citations were excluded and 28 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full text review. Of these 31 potentially relevant articles, 24 publications were excluded for various reasons, and seven publications met the inclusion criteria and were included in this report. These comprised one HTA report,[2] four systematic reviews,[1,6,9,13] and two evidence-based guidelines.[5,14,15] No economic evaluations other than the one included in the HTA report[2] were identified. Appendix 1 presents the PRISMA[16] flowchart of the study selection.

Summary of Study Characteristics

The HTA report[2] included a systematic review of clinical effectiveness and an economic evaluation. Only the economic evaluation from this HTA report is described in this current report. The reason being that a more recent systematic review[6] with additional studies was published by the same group, and is included here, in this current report. The economic findings are presented in the economic section of this current report. Characteristics of the selected systematic reviews, economic evaluation, and guidelines are summarized, and additional details are provided in Appendix 2 (Table 2, Table 3, and Table 4, respectively)

Study Design

The four selected systematic reviews,[1,6,9,13] were published between 2016 and 2018, and included information from RCTs. Two systematic reviews[6,13] included RCTs published between 2000 and 2017, one systematic review[1] included RCTs published between 2000 and 2015; and one systematic review[9] included RCTs published between 2000 and 2013. All the four systematic reviews included meta-analyses. There was overlap in the studies included in the systematic reviews (Appendix 5, Table 11).

The economic evaluation[2] was included in the HTA report published in 2017. It used the perspective of the UK National Health Service and a lifetime time horizon. A Markov model was used. Efficacy data were obtained from a meta-analysis and resource use data was obtained from a cohort study.

Two relevant evidence-based guidelines[5,15] published in 2016 and 2017 were identified. In both the guidelines recommendations were formulated by consensus. In one guideline[5] the recommendations were graded and in one guideline[15] explicit grading was not presented, instead specific wording (such as “should be considered” or “may be considered”) was used to indicate the strength of the recommendation.

Country of Origin

Countries indicated for the first authors of the systematic reviews were UK,[1,6] US,[13] and Mexico.[9] Country indicated for the first author of the HTA report which included an economic evaluation was the UK.[2] Of the two guidelines, one was from Canada[14] and the other from the UK.[15]

Patient Population

The four systematic reviews,[1,6,9,13] involved adult patients with HF. Of these systematic reviews, one systematic review[9] included only chronic HF patients. The second systematic review[13] included both acute and chronic HF patients and presented data separately for the two groups. The remaining two systematic reviews did not specify if the patients had chronic or acute HF.[1,6] Number of patients in the studies ranged between 41 and 894. The mean age of patients ranged between 60 and 80 years; proportion of male patients ranged between 32% and 86%. Left ventricle ejection fraction (LVEF) levels and New York Heart Association (NYHA class) for the HF patients varied amongst the studies included in the systematic reviews (Appendix 2, Table 2). One systematic review reported that majority of the patients had HFrEF.

The economic evaluation[2] involved patients with HF. It was assumed that the mean ages of HF patients at inception of treatment were 65 and 81 years respectively, for the younger subgroup (< 75 years) and for the older subgroup (≥ 75 years).

For one guideline[5] the target population was patients with HF and it was intended for clinicians and policy makers. In the second guideline,[15] the target population was patients with chronic HF and it was intended for healthcare professionals, policy makers, patients and their care givers.

Interventions and Comparators

In the systematic reviews,[1,6,9,13] NP-guided therapy was compared with standard clinically guided therapy. NP includes BNP and NT-proBNP. The economic evaluation[2] compared NP-guided therapy with clinically guided therapy (i.e. symptom-guided therapy or usual care). One guideline[5] mentions BNP or NT-proBNP guided treatment; and the second guideline[15] mentions NT-pro BNP guided treatment.

Outcomes

All four systematic reviews[1,6,9,13] reported on all-cause mortality, HF-related mortality (or cardiovascular mortality), all-cause hospitalization, and HF-related hospitalization. Other outcomes reported included quality of life (QoL),[1,6] adverse events,[6] symptomatic hypotension,[13] and renal dysfunction.[13] Duration of follow-up was variable: 3 months to 36 months,[13] 4 months to 2.5 years,[6] 1 month to 54 months;[1] and in one systematic review[9] the mean duration of follow-up was 12 months.

The economic evaluation[2] reported incremental net monetary benefit (iNMB).(iNMB = λ x [incremental effectiveness] – [incremental cost]), where λ denotes the willingness-to-pay threshold)

One guideline[5] presented recommendation on BNP- or NT-proBNP guided treatment for patients with HF. The second guideline[15] provided recommendation on NT-proBNP guided treatment for patients with HF.

Summary of Critical Appraisal

The critical appraisal of the included systematic reviews, economic evaluation, and guidelines are presented below and details are available in Appendix 3, (Table 5, Table 6, and Table 7 respectively)

In all four systematic reviews,[1,6,9,13] the objective was stated; a comprehensive literature search was conducted; study selection was described; a list of included studies was presented; article selection was done in duplicate; study characteristics were described; publication bias was explored when feasible and potential for bias seemed unlikely; and conflicts of interest were declared and no issues were apparent. In three systematic reviews[1,9,13] data extraction was done in duplicate, and in one systematic review[6] it was not explicitly stated that data extraction was done in duplicate, however, quality assessment was done in duplicate. In three systematic reviews[1,6,13] quality assessment was conducted and the studies were judged to be of low or very low quality, and in one systematic review[9] quality assessment was not conducted. All four systematic reviews included meta-analyses. In most of the meta-analyses, statistical heterogeneity (I^2 value) was less than 50%, However, in some instances, the effect estimates for individual studies varied (positive or negative effect), hence the summary estimate gives an overall effect but the results may vary depending on specific patient population and the therapies involved.

In the economic evaluation[2] the objective, strategies compared, time horizon, perspective, and sources of clinical and cost data were stated. Incremental analysis and sensitivity analysis were conducted. The conclusions were consistent with the results reported.

Indirect costs do not appear to have been considered, and discounting was not mentioned. Conflicts of interest were declared, and one of the 12 authors had an association with industry; potential for bias was unclear.

In the guidelines[5,15] the scope and purpose were stated, the intended users were stated, and the guideline development group comprised of members with relevant expertise. For one guideline,[15] the guideline development group also included a lay representative. Details of the methodology were not presented in the guideline documents, however, it was mentioned that the methodology used was according to the guideline development manual and appeared to be rigorous. Also, according to the guideline development manual, authors were required to declare their conflicts of interest and a policy was in place to address potential conflicts. The guidelines were externally reviewed.

Summary of Findings

Findings are summarized below and details are available in Appendix 4 (Table 8, Table 9, and Table 10)

Clinical Effectiveness and Clinical Utility of NP-guided therapy for patients with HF

One systematic review[13] found that for HF patients, with respect to overall-mortality, HF-related mortality, overall hospitalization, and HF-related hospitalization, there were no statistically significant differences between NP-guided treatment and clinically guided treatment. The second systematic review[6] found that there were no statistically significant differences with respect to all-cause mortality, cardiovascular mortality, all-cause hospitalization, and adverse events; and that with respect to HF-related hospitalization the between group difference was statistically significant, appearing to favor NP-guided treatment, however some uncertainty remains as indicated by the confidence interval (CI): 0.68 to 0.98. Subgroup analyses showed that for the subgroup of HF patients aged less than 75 years, the between group differences were statistically significant for NP-guided therapy compared to clinically guided treatment, with respect to all-cause mortality, and all cause hospitalization, appearing to favor NP-guided therapy, however there remains uncertainty as indicated by the confidence intervals (CIs): 0.53 to 0.92, and 0.68 to 0.99, respectively. For the subgroup of HF patients aged 75 years or older there were no statistically significant between group differences with respect to all-cause mortality, all cause hospitalization, or HF-related hospitalization. The third systematic review[1] found that there were no statistically significant differences with respect to all-cause mortality, HF-related mortality, and all-cause hospitalization; and that with respect to HF-related hospitalization the between group difference was statistically significant (CI: 0.61 to 0.80), appearing to favor NP-guided treatment. All three systematic reviews[1,6,13] reported that the findings were based on low or very low quality studies. The fourth systematic review[9] found that there were no statistically significant differences with respect to HF-related mortality and overall hospitalization for NP-guided treatment compared to clinically guided treatment for chronic HF patients; and that with respect to overall mortality and HF-related hospitalization the between group differences were statistically significant, appearing to favor NP-guided treatment, however uncertainty remains as indicated by the CIs:0.57 to 0.95, and 0.29 to 0.98 respectively. Additional details are presented in Appendix 4, Table 8.

In summary, three[1,6,9] of the four systematic reviews[1,6,9,13] showed that the between group differences for NP-guide therapy compared with clinically-guided therapy for HF patients were statistically significant with respect to HF-related hospitalization, however some uncertainty remains as in two systematic reviews[6,9] the CIs indicated marginal significance.

Overall, for the other outcomes (all-cause mortality, HF-related mortality, all cause hospitalization, and QoL), there were no statistically significant between group differences for NP-guide therapy compared with clinically-guided therapy for HF patients. Furthermore, the findings were based on studies of low or very low quality. Overall the clinical effectiveness and clinical utility of the use of NP-guided therapy for HF patients remains uncertain.

Cost-Effectiveness of NP-guided therapy for patients with HF

The HTA by Pufulete et al.[2] reported that NP-guided therapy was more costly and more effective than clinically guided therapy, over the lifetime of patients aged < 75 years with any type of HF (includes both HFrEF] and HFpEF). For patients with any HF, the incremental net monetary benefit (iNMB) was found to be £6,426, 95% confidence interval (CI): £2,401 to £10,075. The positive value of iNMB indicates that the NP-guided therapy was cost-effective in this patient group at the willingness-to-pay threshold of £20,000 per QALY, used by the National Institute for Health and Care Excellence (NICE). The method for iNMB calculation is presented in Appendix 4,Table 9. For patients with HFrEF and < 75 years of age, the iNMB was found to be £5,424, 95% CI: £987 to £9,469. The positive value of iNMB indicates that the NP-guided therapy was cost-effective in this patient group at the £20,000 per QALY threshold. For older patients (age ≥ 75 years) with any HF there is little evidence of meaningful health benefits or cost savings of NP-guided therapy. Additional details are presented in Appendix 4,Table 9.

In summary, NP-guide therapy appeared to be cost-effective for HF patients, who were < 75 years of age and with HFrEF (i.e. the predominant population in the RCTs) considering a willingness-to-pay threshold of £20,000 and NP-guided therapy to be efficacious. However, it should be noted that there is uncertainty in the efficacy of NP-guided treatment as the findings were of marginal statistical significance, and based on low or very low quality studies.

Guidelines for NP-guided therapy for patients with HF

One guideline[5] suggested that BNP or NT-proBNP guided treatment should be considered to decrease HF-related hospitalization for patients with HFrEF; and that the benefit is uncertain in patients older than 75 years (weak recommendation). The second guideline[15] mentioned that NT-proBNP guided treatment may be considered for HF patients under 75 years of age (strength of recommendation was not reported however it was mentioned that for conditional recommendation the wording “considered” is used). Additional details are presented in Appendix 4, Table 10.

Limitations

Though the systematic reviews were generally well conducted, the included studies were of low or very low quality. Two systematic reviews[9,13] reported on chronic HF patients, and the remaining two systematic reviews[1,6] did not specify if the HF patients were chronic or acute HF patients. Hence there is a possibility that in addition to chronic HF patients, acute HF patients may have been include as well in these two systematic reviews.

There was variability among the included RCTs. The NP-guided therapy was implemented in different ways in the RCTs. Information on changes in the medication dose or type of medications were lacking. It is unclear which procedure would work best and in which patients.

The majority of the RCTs were conducted in specialized settings (such as HF clinics), hence the applicability of the findings to other care settings is unclear. None of the RCTs were on pediatric patients with chronic heart failure. The majority of the patients recruited in the RCTs were <75 years of age and with HFrEF, hence applicability to a broader patient population is unclear. Durations of follow-up were less than five years, hence the long-term effects are not known.

Most of the studies were conducted in various countries in Europe, hence generalizability to the Canadian setting is unclear. Also, the perspective used in economic evaluation was that of UK, hence generalizability to the Canadian setting is unclear.

Findings need to be interpreted with caution, considering the limitations.

Conclusions and Implications for Decision or Policy Making

Four systematic reviews,[1,6,9,13] one economic evaluation,[2] and two evidence-based guidelines[5,15] were identified regarding NP-monitoring of heart failure patients.

Three[1,6,9] of the four systematic reviews[1,6,9,13] showed that the between group differences for NP-guide therapy compared with clinically-guided therapy for HF patients were statistically significant with respect to HF-related hospitalization , however some uncertainty remains as in two systematic reviews[6,9] the CIs indicated marginal significance.. Overall, for the other outcomes, there were no statistically significant between group differences for NP-guide therapy compared with clinically-guided therapy for HF patients. Furthermore, the findings were based on studies of low or very low quality. Overall the effectiveness of the use of NP-guided therapy for HF patients remains uncertain. A systematic review[17] published in 2013 (prior to our literature search period), examined if NP-guided therapy for HF patients had benefits over usual care, and concluded that the available evidence was inconclusive.

NP-guide therapy appeared to be cost-effective for HF patients, who were less than 75 years of age and with HFrEF (i.e. the predominant population in the RCTs) considering a willingness-to-pay threshold of £20,000 and NP-guided therapy to be efficacious. However, it should be noted that there is uncertainty in the efficacy of NP-guided treatment as the findings were of marginal statistical significance, and based on low or very low quality studies.

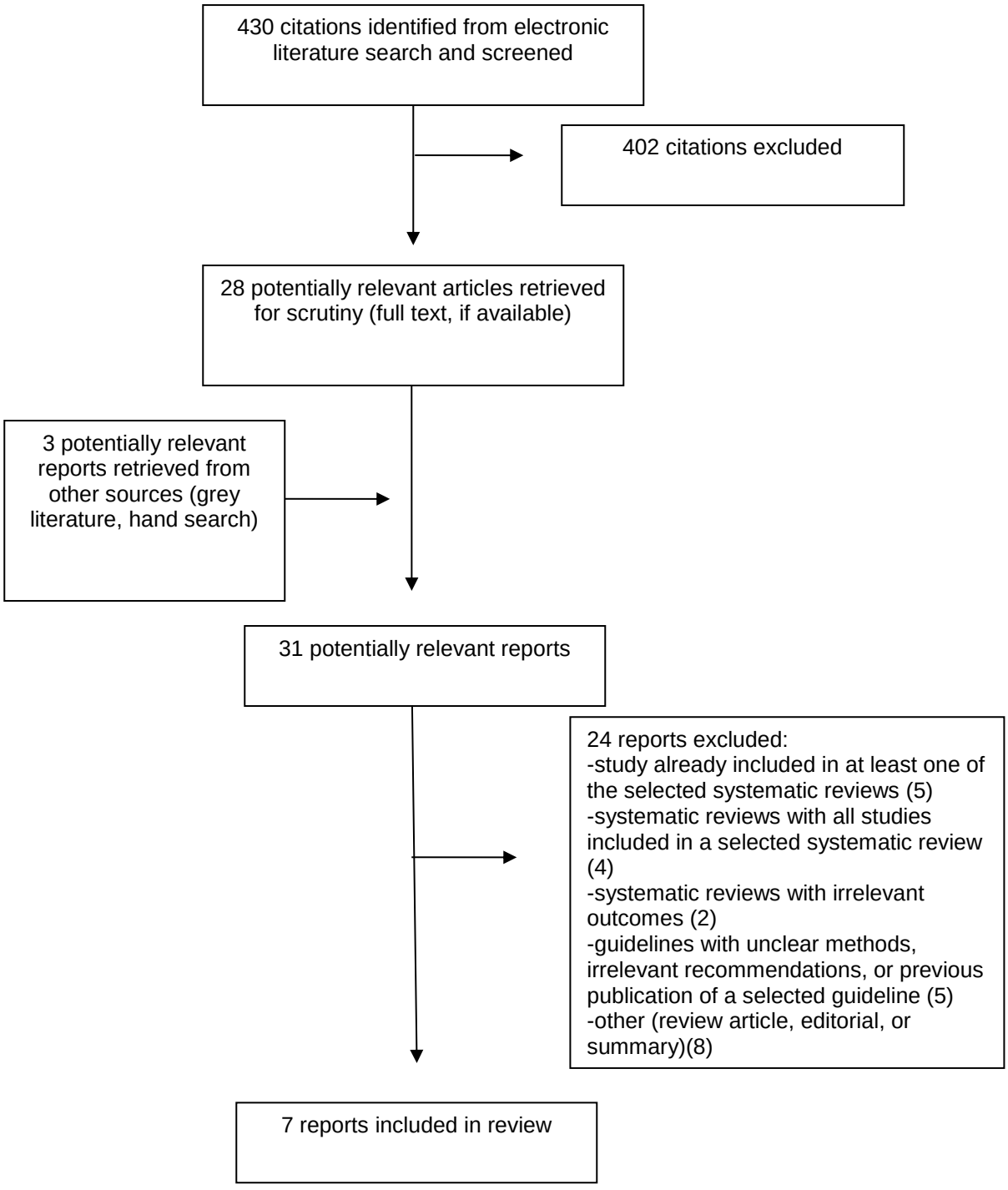
The two guidelines[5,15] suggested that NP-guided therapy may be considered for HF patients less than 75 years of age (one guideline mentioned that the recommendation was weak, and another guideline did not specify the strength of the recommendation).

Future studies are needed to determine which patients are likely to benefit from NP-monitoring and what would be an optimal monitoring strategy.

References

1. McLellan J, Heneghan CJ, Perera R, et al. B-type natriuretic peptide-guided treatment for heart failure. *Cochrane Database Syst Rev.* 2016;12:CD008966.
2. Pufulete M, Maishman R, Dabner L, et al. Effectiveness and cost-effectiveness of serum B-type natriuretic peptide testing and monitoring in patients with heart failure in primary and secondary care: an evidence synthesis, cohort study and cost-effectiveness model. *Health Technol Assess.* 2017;21(40):1-150.
3. Tran DT, Ohinmaa A, Thanh NX, et al. The current and future financial burden of hospital admissions for heart failure in Canada: a cost analysis. *CMAJ Open.* 2016;4(3):E365-E370.
4. Heart disease in Canada: highlights from the Canadian Chronic Disease Surveillance System. Ottawa (ON): Public Health Agency of Canada; 2017: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/heart-disease-fact-sheet/heart-disease-factsheet-eng.pdf. Accessed 2019 Aug 19.
5. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 Comprehensive update of the Canadian Cardiovascular Society Guidelines for the management of heart failure. *Can J Cardiol.* 2017;33(11):1342-1433.
6. Pufulete M, Maishman R, Dabner L, et al. B-type natriuretic peptide-guided therapy for heart failure (HF): a systematic review and meta-analysis of individual participant data (IPD) and aggregate data. *Syst.* 2018;7(1):112.
7. McLellan J, Bankhead C. Natriuretic peptide guided therapy for management of patients with heart failure does not show improvement compared with usual medical therapy alone. *BMJ Evid Based Med.* 2018;23(2):74-75.
8. Troughton R, Michael Felker G, Januzzi JL, Jr. Natriuretic peptide-guided heart failure management. *Eur Heart J.* 2014;35(1):16-24.
9. Gamino-Arroyo AE, Prado-Galbarro FJ, Garcia-Perez S, Sanchez-Piedra C. Effectiveness of natriuretic peptide-guided treatment of chronic heart failure. A meta-analysis. *Arch Cardiol Mex.* 2018;88(3):171-177.
10. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 Aug 19.
11. Higgins JPT, Green S, editors. Figure 15.5.a: Drummond checklist (Drummond 1996). *Cochrane handbook for systematic reviews of interventions*. London (GB): The Cochrane Collaboration; 2011: http://handbook-5-1.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm. Accessed 2019 Aug 19.
12. Agree Next Steps Consortium. The AGREE II Instrument. Hamilton (ON): AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Aug 19.
13. Khan MS, Siddiqi TJ, Usman MS, et al. Does natriuretic peptide monitoring improve outcomes in heart failure patients? A systematic review and meta-analysis. *Int J Cardiol.* 2018;263:80-87.
14. CCS guidelines and position statements development procedures and policies version 2.6. Ottawa (ON): Canadian Cardiovascular Society; 2019: https://www.ccs.ca/images/Guidelines/Dev_proces/Gui-PS-development-Proc_policies.pdf. Accessed 2019 Aug 19.
15. Management of chronic heart failure: a national clinical guideline. *(SIGN publication no. 147)*. Edinburgh (GB): Scottish Intercollegiate Guidelines Network (SIGN); 2016: https://www.sign.ac.uk/assets/sign147.pdf Accessed 2019 Aug 19.
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
17. McMaster University Evidence-based Practice Center, Balion C, Don-Wauchope A, et al. Use of natriuretic peptide measurement in the management of heart failure. *(Comparative effectiveness review No. 126)*. Rockville (MD): Agency for Healthcare Research and Quality; 2013: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/heart-failure-natriuretic-peptide_research.pdf Accessed 2019 Aug 19.
18. SIGN. A guideline developer's handbook. *(SIGN publication no. 50)*. Edinburgh (GB): Scottish Intercollegiate Guidelines Network (SIGN); 2015: https://www.sign.ac.uk/assets/sign50_2015.pdf Accessed 2019 AUg 19.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Health Technology Assessment, Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Health Technology Assessment				
Pufulete,[2] 2017, UK	This HTA includes a systematic review on clinical effectiveness and an economic evaluation. The systematic review is not discussed in this current report as a more recent systematic review,[6] including additional studies was available from the same group and is discussed below. However, the economic evaluation is discussed in the economic sections (**Error! Not a valid result for table.**, , and) of this current report.			
Systematic reviews and meta-analyses				
Gamino-Arroyo,[9] 2018, Mexico	SR included 9 RCTs published between 2000 and 2011. Blinding was not mentioned. (countries of origin of the RCTs were not reported) Aim: To assess NP-guided therapy compared with clinically guided therapy	Patients with chronic HF N = 1914 (in the individual RCTs the numbers of patients ranged from 41 to 499) Age (mean ± SD) (years): 70.0 ± 4.8 % Male: 55.9% LVEF (mean) (%):ranged between 22% and 45% in 8 studies and was 81% in one study NYHA class: not reported	NP-guided therapy versus clinically guided therapy. NP includes BNP or NT-proBNP) Setting: Not reported	Overall mortality, HF-related mortality, overall hospitalization, and HF-related hospitalization Mean follow-up: 11.9 months
Khan,[13] 2018, USA	SR included 14 RCTs published between 2000 and 2017. Of the 14 RCTs, 2 RCTs were double-blind, 4 RCTs were single blind, 5 RCTs were open-label, and for 3 RCTs it was not specified. (countries of origin of the RCTs were not reported) This SR included 18 RCTs (14 RCTs on	Patients with HF N = Ranged between 41 and 894 in the individual RCTs Age (mean) (year): Ranged between 65 and 80 in the individual RCTs % Male: Ranged between 32% and 85% in the individual RCTs	NP-guided therapy versus conventional therapy (i.e,.guideline directed therapy). NP includes BNP or NT-proBNP) Setting: Interventions were provided mainly by specialists (such as HF clinic clinician, and cardiologists)	All-cause mortality, cardiovascular mortality, all-cause hospitalization, HF-related hospitalization, LVEF, symptomatic hypotension, renal dysfunction, change in NYHA class Mean follow-up: 3 months to 36 months

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	chronic HF and 4 RCTs on acute HF), only the RCTs relevant for the current report are included here) Aim: to assess NP-guided therapy compared with guideline-directed therapy in HF patients	LVEF (% of patients with HFrEF): 100% patients in 9 studies; 94% in one study; 75% in 3 studies; and 59% in one study NYHA class[a]: Class 1 to IV in 2 studies; Class I to III in 2 studies; class II to IV in 6 studies; class II to III in 2 studies; class III to IV in 2 studies		
Pufulete,[6] 2018, UK	SR included 14 RCTs (5 with IPD and 9 with aggregate data) published between 2000 and 2017. RCT blinding details were not reported. Of the 14 RCTs, 8 were conducted in Europe, 2 in New Zealand, three in US, and one in Israel. Aim: to assess BNP-guided therapy compared with symptom-guided therapy in HF patients	Adult patients who were being treated for HF in primary or secondary care. N = 3968 (ranged between 60 and 894 in the individual RCTs). Mean age (years): ranged between 60 and 80 in the individual RCTs. % Male: Ranged between 34% and 86% in the individual RCTs LVEF (median): ranged between 20% and 56% NYHA class[a]: Class 1 to IV in 4 studies;Class I to III in 3 studies; class II to IV in 2 study; class II to III in 1 studies; class III to IV in 1 study, majority class II in 1 study, and not reported in 2 studies.	NP-guided therapy versus symptom-guided therapy. (NP includes BNP or NT-proBNP) Setting: majority at HF clinic	All-cause mortality, cardiovascular death, all-cause hospitalization, HF hospitalization, adverse events, QoL Duration of follow-up: 4 months to 2.5 years
McLellan,[1] 2016, UK	SR included 18 RCTs published between 2000 and 2015. Of the 18 RCTs, 10 were conducted in Europe, 2	Adult patients who are being treated for HF	NP-guided therapy versus clinically guided therapy. (NP includes BNP or NT-proBNP)	All-cause mortality, HF mortality, HF admission, all-cause admission, QoL

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	in US, 2 in New Zealand, and 1 each in Canada, China, Israel and Russia. Aim: to assess NP-guided therapy compared with clinically guided therapy in HF patients (NP includes BNP or NT-proBNP)	N = 3660 (ranged between 41 and 499 in the individual RCTs). Mean age (years): ranged between 62 and 80 in the individual RCTs. % Male: ranged between 34% and 76% in the individual RCTs. Majority of the RCTs included > 60% male patients LVEF: One study did not report on LVEF, one study reported average LVEF of 56%, one study reported that 57% of the patients were <30% LVEF, and the remaining studies reported overall averages of LVEF ranging between 20% and 46% NYHA class[a] : Overall the patients ranged between class II and class IV	Setting: in hospital and out-of-hospital settings	Duration of follow-up: 1 month to 54 months

BNP = B-type natriuretic peptide; HF = heart failure; HFrEF = heart failure with reduced efection fraction; IPD = individual patient data; LVEF = left ventricular ejection fraction; NP = natriuretic peptide; NT-proBNP = N-terminal pro hormone BNP; NYHA = New York Heart Association; QoL = quality of life; RCT = randomized controlled trial; SD = standard deviation; SR = systematic review;

[a]NYHA class: Class 1 [no limitations, Class IV [severe limitations]

Table 3: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Pufulete,[2] 2017, UK	Cost-effectiveness analysis based on iNMB. A highly simplified two-state Markov model was used. Time horizon: Lifetime Health services perspective (UK NHS perspective)	To assess the cost-effectiveness of NP-guided therapy compared with symptom guided therapy in patients with HF, to assist clinicians and policy makers to decide on the best course of action .(NP includes BNP or NT-proBNP)	Patients with HF	BNP guided therapy versus symptom guided therapy (i.e., usual care) Setting: specialist-led treatment	A simplified two-state Markov model was used. Sensitivity analysis was conducted	Efficacy data from meta-analyses of RCT data. Resource use data were obtained from a cohort study. Cost data were obtained from CPRD-HES, DoH, or NICE	-Treatment effect derived from RCT participants were generalized to the patients with HF in the CPRD-HES-ONS linked data. -BNP-guided monitoring would cease after 18 months and the relative treatment effect would end after 4 years

BNP = B-type natriuretic peptide; CPRD = clinical Practice Research Datalink; DoH = Department of Health; HES = Hospital Episode Statistics; HF = heart failure; iNMB = incremental net monetary benefit; NHS = National Health Services (UK); NICE = National Institute for Health and Care Excellence;.

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Ezekowitz (CCS),[5] 2017, Canada						
Intended for clinicians, and	This document provides guidance with respect to	Mortality, hospitalization	Methods were not described. However it was	Recommendations were classified using GRADE.	Recommendations were based on consensus. At minimum, consensus	Externally reviewed; published in a

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
policy makers; target population: patients with heart failure	diagnosis, treatment and management of HF.		mentioned that it was based on the CCS guideline development procedures and policies[14] which requires a systematic literature review to be conducted	Strength of recommendation: strong or weak.[14] Strength of evidence very low, low, moderate, or high.[14]	must be based on two thirds majority of the voting panel. The GDG comprises individuals with expertise in the area and methodologists.	peer-reviewed journal
SIGN,[15] 2016, UK						
Intended for healthcare professionals involved in the management of patients with chronic HF, policy makers, patients and their carers. Target population: patients with chronic HF	This document provides guidance with respect to diagnosis; emotional well-being and health behavior change; pharmacological therapies (such as beta-blockers, angiotensin-converting enzyme inhibitors, ivabradine, NP-guided treatment); and interventional procedures.	Outcomes such as mortality, hospitalization, QoL, change in symptoms, and adverse events The focus is on the management of patients with stable HF rather than on in-hospital management of acute HF	Methods were based on the standard procedures used by SIGN for guideline development.[18] A systematic review was conducted to collect evidence.	Strength of evidence was graded as 1++, 1+. 1-, 2++, 2+, 2-, 3, 4. 1++ indicates evidence from high-quality meta-analyses, SR of RCTs, or RCTs with low risk of bias. (only the evidence level used for the recommendations relevant for the current report are described here). Strength of recommendation: strong or conditional For strong recommendation the term “should” is used. For conditional recommendations the term “considered” is used, and it indicates	Recommendations were based on consensus..[18] The GDG comprised individuals with relevant clinical expertise, pharmacist, nurse, scientist, health economist, and lay representative.	Externally reviewed.

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
				that the GDG is confident that the intervention will do more good than harm for most patients. However, the choice of intervention will depend on values and preferences, and entails discussion between clinician and patient.. (Only the evidence level and strength of recommendation used for the recommendations relevant for the current report are explained here).		

CCS = Canadian Cardiovascular Society; GDG = guideline development group; HF = heart failure; SIGN = Scottish Intercollegiate Guidelines Network

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[10]

Strengths	Limitations
Gamino-Arroyo (GreyLit 14),[9] 2018, Mexico	
• The objective was clearly stated • Multiple databases (MEDLINE, EMBASE, and Cochrane) were searched between 2000 and 2014 In addition, grey literature was searched. Also, reference lists of selected studies were searched. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Characteristics of the included studies were presented • Meta-analysis was conducted • Publication bias was explored using Funnel plots and Begg and Egger methods • The authors mentioned that there were no conflicts of interest	• A list of excluded studies was not provided • Quality assessment does not appear to have been performed
Khan,[13] 2018, USA	
• The objective was clearly stated • Multiple databases (MEDLINE, Scopus, and Cochrane CENTRAL) were searched from inception to December 2017. Also, reference lists of relevant reviews and editorials of major medical journals were searched. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was conducted using the Cochrane risk of bias tool. Generally, there was high risk of bias with respect to performance bias and reporting bias. Selection bias, attrition bias were either low or unclear. • Characteristics of the included studies were presented • Meta-analysis was conducted • Publication bias was explored using Funnel plots and publication bias seemed unlikely • The authors mentioned that there were no conflicts of interest	• A list of excluded studies was not provided
Pufulete,[6] 2018, UK	
• The objective was clearly stated • Multiple databases (MEDLINE, Embase, Cochrane library, and ISI Web of Science) were searched up to September 2016. Also, clinical trials registries and grey literature were	• A list of excluded studies was not provided • Not specifically mentioned that data extraction was done in duplicate, however as quality assessment was done in duplicate, it is possible that data extraction was done in duplicate

Strengths	Limitations
searched. In addition, reference lists of relevant articles were reviewed. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Article selection was done independently by two reviewers • Quality assessment was conducted independently by two reviewers using the Cochrane risk of bias tool. Of the 14 RCTs included, 11 RCTs were rated as having high risk of bias for at least one risk domain. The authors stated that the overall quality of the evidence for all outcomes varied between low and very low. • Characteristics of the included studies were presented • Meta-analysis was conducted • Publication bias was explored using Funnel plots and there appeared to be marked asymmetry suggesting publication bias seemed unlikely • The authors mentioned that there were no conflicts of interest	
McLellan,[1] 2016, UK	
• The objective was clearly stated • Multiple databases (MEDLINE, Embase, DARE, and NHSEED), Science citation index , and conference proceeding citations on Web of science were searched up to March 2016. In addition, authors of relevant studies and experts were contacted. • Study selection was described, and a flow chart was presented • A list of included studies was provided • A list of excluded studies was not provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was conducted independently by three reviewers using the Cochrane risk of bias tool and GRADE. The studies were judged to be of low or very low quality. • Characteristics of the included studies were presented • Meta-analysis was conducted • Publication bias was explored using Funnel plots when feasible • Conflicts of interest were declared. Of the 11 authors, 9 authors had no conflicts of interest, and two authors received funding from the National Institute of Health Research, UK.	• No major issues were apparent

RCTs = randomized controlled trials

Table 6: Strengths and Limitations of Economic Studies using the Drummond Checklist[11]

Strengths	Limitations
Pufulete,[2] 2017, UK	
• Objectives were stated. • The strategies compared were stated • Time horizon and perspective were stated • Clinical data sources were stated. • Cost data sources were stated • Time frame appeared to be adequate • Incremental analysis was reported. • Sensitivity analyses were conducted, both deterministic and probabilistic • Conclusions were consistent with the results reported. • Conflicts of interest were declared and of the 12 authors, one author had association with industry	• Indirect costs do not appear to have been considered. • Discounting was not mentioned

abb = abbreviation

Table 7: Strengths and Limitations of Guidelines using AGREE II[12]

Item	Guideline	
	Ezekowitz (CCS),[5] 2017, Canada	SIGN,[15] 2016, UK
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	y	y
2. The health question(s) covered by the guideline is (are) specifically described.	Not stated	y
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	y	y
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	y	y
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Not stated	y
6. The target users of the guideline are clearly defined.	y	y
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Details were not provided in the guideline document. However it was mentioned that the guideline document was prepared using the CCS guideline development	Details were not provided in the guideline document. However it was mentioned that the guideline document was prepared using the SIGN 50: A guideline developer's
8. The criteria for selecting the evidence are clearly described.		
9. The strengths and limitations of the body of evidence are clearly described.		
10. The methods for formulating the recommendations are clearly described.		
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.		

Item	Guideline	
	Ezekowitz (CCS),[5] 2017, Canada	SIGN,[15] 2016, UK
12. There is an explicit link between the recommendations and the supporting evidence.	procedures and policies;[14] the methods appear to be rigorous.	handbook.[18] the methods appear to be rigorous. It was also mentioned in the handbook that the methods are based on the criteria in AGREE II.
13. The guideline has been externally reviewed by experts prior to its publication.		
14. A procedure for updating the guideline is provided.		
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	y	y
16. The different options for management of the condition or health issue are clearly presented.	Details lacking	y
17. Key recommendations are easily identifiable.	y	y
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	Not stated	Not stated
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Not stated	Not stated
20. The potential resource implications of applying the recommendations have been considered.	Not stated	Not stated
21. The guideline presents monitoring and/or auditing criteria.	Not stated	Not stated
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Not stated	Not stated
23. Competing interests of guideline development group members have been recorded and addressed.	y, according to the CCS guideline development procedures and policies.[14]	y, according the SIGN 50: A guideline developer's handbook.[18]

CCS = Canadian Cardiovascular Society; SIGN = Scottish Intercollegiate Guidelines Network

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Gamino-Arroyo (GreyLit 14),[9] 2018, Mexico</td></tr>
<tr><td>Results for patients with chronic HF

<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>No. of patients</th><th>Effect with NP-guided treatment vs clinically-guided treatment. OR (95% CI)</th><th>Heterogeneity, I^2 (%)</th></tr>
<tr><td>Overall mortality</td><td>7</td><td>1711</td><td>0.73 (0.57 to 0.95)</td><td>0.0</td></tr>
<tr><td>HF-related mortality</td><td>3</td><td>529</td><td>0.70 (0.26 to 1.89)</td><td>42.5</td></tr>
<tr><td>Overall hospitalization</td><td>5</td><td>1097</td><td>0.80 (0.62 to 1.03)</td><td>0.0</td></tr>
<tr><td>HF-related hospitalization</td><td>4</td><td>699</td><td>0.53 (0.29 to 0.98)</td><td>67.1</td></tr>
</table></td><td>"NP-guided therapy seems to improve outcomes compared to clinically-guided therapy. However, heterogeneity found between interventions might reduce the generalization of these results. Specific interventions of the clinical trials should be examined when making recommendations regarding NP-guided therapy." (p.171)</td></tr>
<tr><td colspan="2">Khan,[13] 2018, USA</td></tr>
<tr><td>Results for patients with chronic HF

<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>Effect with NP-guided treatment vs clinically-guided treatment. RR (95% CI)</th><th>Heterogeneity, I^2 (%)</th></tr>
<tr><td>All-cause mortality</td><td>14</td><td>0.92 (0.81 to 1.04)</td><td>0</td></tr>
<tr><td>cardiovascular mortality</td><td>5</td><td>0.92 (0.73 to 1.16)</td><td>0</td></tr>
<tr><td>All-cause hospitalization</td><td>7</td><td>0.97 (0.89 to 1.06)</td><td>0</td></tr>
<tr><td>HF-related hospitalization</td><td>12</td><td>0.77 (0.60 to 1.00)</td><td>88</td></tr>
<tr><td>Symptomatic hypotension</td><td>5</td><td>2.03 (0.87 to 4.73)</td><td>32</td></tr>
<tr><td>Renal dysfunction</td><td>5</td><td>1.49 (0.71 to 3.11)</td><td>51</td></tr>
<tr><td>Change in LVEF</td><td>3</td><td>3.04 (2.13 to 3.96)</td><td>0</td></tr>
<tr><td>Change in NYHA class</td><td>5</td><td>-0.01 (-0.22 to 0.02)</td><td>50</td></tr>
</table></td><td>"This meta-analysis showed no significant reduction in mortality or HF-related hospitalizations with NP-guided therapy. The quality of evidence is affected by risk of bias in individual studies. NP-guided therapy should be further tested in a clinical trial which accounts for the current limitations." (p.86)</td></tr>
<tr><td colspan="2">Pufulete,[6] 2018, UK</td></tr>
<tr><td>Results for patients with HF</td><td>"BNP-guided therapy did not reduce mortality but reduced HF hospitalisation. The overall quality of the evidence varied from low to very low. The relevance of</td></tr>
</table>

Main Study Findings

Outcome	Data type	No. of RCTs (No. of patients)	Effect with BNP-guided treatment vs symptom-guided treatment.		Hetero-geneity, I^2 (%)
			Effect measure	Finding	
All-cause mortality	IPD	5 (983)	HR (95% CI)	0.96 (0.71 to 1.28)	0
	Agr	9 (2830)		0.84 (0.70 to 1.02)	8.7
	All	14 (3813)		0.87 (0.75 to1.01)	0
Cardiovascular mortality	Agr	5 (1909)	OR (95% CI)	0.88 (0.67 to 1.16)	0
All cause hospitalization	IPD	5 (984)	HR (95% CI)	0.96 (0.81 to 1.13)	0
	Agr	2 (622)		1.02 (0.75 to 1.38)	42.1
	All	7 (1606)		0.97 (0.85 to 1.10)	0
HF-related hospitalization	IPD	4 (852)	HR (95% CI)	0.91 (0.71 to 1.16)	0
	Agr	10 (2981)		0.77 (0.59 to 0.99)	61.8
	All	14 (3833)		0.81 (0.68 to 0.98)	46.2
Adverse events	Agr	5 (2055)	OR (95% CI)	1.29 (1.04 to 1.60)	0

Agr = aggregate; All = IPD & Agr; CI = confidence interval; HR = hazard ratio; IPD = individual patient data;

Adverse events:
Adverse events commonly reported included renal impairment, and hypotension.

QoL: 6 RCTs reported on QoL. Meta-analysis could not be performed as data were reported differently in the RCTs. The authors mentioned that the evidence was of very low quality, and there was uncertainty as to whether BNP-guided therapy improved QoL.

Subgroup analyses by age group:

Outcome	No. of RCTs	Subgroup by age	Effect with NP-guided treatment vs clinically-guided treatment. HR (95% CI)	Heterogeneity, I^2 (%)
All-cause mortality	6	<75 years	0.70 (0.53 to 0.92)	0
		≥75 years	1.07 (0.84 to 1.37)	3.1
All cause hospitalization	6	<75 years	0.82 (0.68 to0.99)	0
		≥75 years	1.08 (0.89 to 1.31)	0
HF-related hospitalization	5	<75 years	0.70 (0.49 to 1.00)	30.6
		≥75 years	0.92 (0.70 to 1.19)	0

Authors' Conclusion

these findings to unselected patients, particularly those managed by community generalists, are unclear." (p.1 of 21)

"The conclusions about the efficacy of BNP-guided therapy are uncertain because the findings are of borderline statistical significance and the overall quality of the evidence varied from low to very low. We could not identify an optimal BNP monitoring strategy and no group of researchers has defined one." (p18 of 21)

Main Study Findings	Authors' Conclusion

Subgroup analyses by NHYA class:

Outcome	No. of RCTs	Subgroup by NYHA class	Effect with NP-guided treatment vs clinically-guided treatment. HR (95% CI)	Heterogeneity, I^2 (%)
All-cause mortality	3	I/II	0.96 (0.48 to 1.95)	26.2
		III/IV	0.97 (0.51 to 1.84)	36.6
All cause hospitalization	4	I/II	1.03 (0.76 to 1.40)	20.9
		III/IV	1.01 (0.78 to 1.31)	0
HF-related hospitalization	4	I/II	0.89 (0.61 to 1.30)	0
		III/IV	1.02 (0.73 to 1.41)	0

Subgroup analyses by LVEF status:

Outcome	No. of RCTs	Subgroup by LVEF status	Effect with NP-guided treatment vs clinically-guided treatment. HR (95% CI)	Heterogeneity, I^2 (%)
All-cause mortality	11	HFrEF	0.84 (0.71 to 0.99)	0
		HFpEF	1.33 (0.82 to 2.11)	0
All cause hospitalization	5	HFrEF	0.91 (0.79 to 1.05)	0
		HFpEF	1.18 (0.82 to 1.72)	0
HF-related hospitalization	4	HFrEF	0.88 (0.77 to 1.01)	0.1
	3	HFpEF	1.07 (0.73 to 1.57)	0

Subgroup analyses by diabetes status:

Outcome	No. of RCTs	Subgroup	Effect with NP-guided treatment vs clinically-guided treatment. HR (95% CI)	Heterogeneity, I^2 (%)
All-cause mortality	5	Diabetic	0.89 (0.63 to 1.28)	10.3
		Non-diabetic	0.93(0.63 to 1.38)	
All cause hospitalization	5	Diabetic	0.94 (0.80 to 1.12)	0
		Non-diabetic	0.86 (0.67 to 1.10)	0
HF-related hospitalization	4	Diabetic	0.76 (0.58 to 0.98)	0
		Non-diabetic	0.93 (0.67 to 1.30)	0

Subgroup analyses by gender:

Outcome	No. of RCTs	Subgroup	Effect with NP-guided treatment vs clinically-guided treatment. HR (95% CI)	Heterogeneity, I^2 (%)
All-cause mortality	6	Men	0.84 (0.64 to 1.11)	0
		Women	0.88 (0.47 to 1.66)	26.3
All cause hospitalization	6	Men	0.94 (0.79 to 1.11)	0
		Women	0.98 (0.73 to 1.30)	20.5
HF-related hospitalization	5	Men	0.82 (0.68 to 1.01)	0
		Women	0.77 (0.55 to 1.10)	0

Main Study Findings	Authors' Conclusion

McLellan,[1] 2016, UK

Results for patients with HF

Outcome	No. of RCTs	No. of patients	Effect measure	Effect with NP-guided treatment vs clinically-guided treatment.	Hetero-geneity, I^2 (%)
All-cause mortality	15	3169	RR (95% CI)	0.87 (0.76 to 1.01)	16
HF-related mortality	6	853	RR (95% CI)	0.84 (0.54 to 1.30)	21
All-cause admission	6	1142	RR (95% CI)	0.93 (0.84 to 1.03)	0
HF-related admission	10	1928	RR (95% CI)	0.70 (0.61 to 0.80)	60
QoL	8	1812	MD (95% CI)	-0.03 (-1.18 to 1.13)	75

Subgroup analysis with studies which reported outcomes by age group

Outcome	Subgroup	No. of RCTs	No. of patients	Effect with NP-guided treatment vs clinically-guided treatment. RR (95% CI)	Hetero-geneity, I^2 (%)
All-cause mortality	Age < 75 years	3	410	0.73 (0.49 to 1.10)	58
	Age ≥ 75 years	3	420	1.23 (0.96 to 1.57)	58
HF-related admission	Age < 75 years	1	177	0.73 (0.45 to 1.17)	0
	Age ≥ 75 years	1	188	1.13 (0.77 to 1.64)	0

Cost

Four studies presented information on cost and results were conflicting.
In one study the total overall cost per intervention was reported as $20,949 for NT-proBNP guided treatment group and $23,928 for the symptom-guided treatment group.

In the second study, the overall cost for the duration of the study, was $35,262 for the NT-proBNP guided treatment group and $42,629 for the standard care group.
In the third study, it was reported that the NP-guided treatment was cost-effective and cheaper compared to the usual care group.

The fourth study, reported that cost per patient over a 18 month period, was $38,876 for the NP-guided treatment group, and $21,419 in the control group

"In patients with heart failure low-quality evidence showed a reduction in heart failure admission with NP-guided treatment while low-quality evidence showed uncertainty in the effect of NP-guided treatment for all-cause mortality, heart failure mortality, and all-cause admission. Uncertainty in the effect was further shown by very low-quality evidence for patient's quality of life. The evidence for adverse events and cost of treatment was low quality and we were unable to pool results." (p.2)

BNP = B-type natriuretic peptide; CI = confidence interval; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; LVEF = left ventricle ejection fraction; MD = mean difference; NP = natriuretic peptide; NYHA = New York Heart Association; OR = odd's ratio; QoL = quality of life; RCT = randomized controlled trial; RR = risk ratio

Table 9: Summary of Findings of Included Economic Evaluations

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Pufulete,[2] 2017, UK</td></tr>
<tr><td>
Results for patients with HF
For BNP-guided therapy compared with usual care (clinically-guided [CG-guided] therapy)

<u>Cost and QALY</u>
Based on deterministic analysis:
Patients (age < 75 years) and with any HF: for BNP, cost (£) = 64,777, QALY = 5.68; for CG, cost (£) = 58,139, QALY = 5.02

Patients (age ≥ 75 years) and with any HF: for BNP, cost (£) = 25,802, QALY = 2.23; for CG, cost (£) = 26,093, QALY = 2.20

<u>Incremental net monetary benefit (iNMB)</u>
Based on probabilistic analysis:

<table>
<tr><th colspan="2">Subgroup</th><th>iNMB (95% CI)[a] in £</th></tr>
<tr><th>By age</th><th>By condition</th><th></th></tr>
<tr><td rowspan="3"><75 years</td><td>All HF</td><td>6,426 (2,401 to 10,075)</td></tr>
<tr><td>HFrEF</td><td>5,424 (987 to 9,469)</td></tr>
<tr><td>HFpEF</td><td>3,155 (-10,307 to 11,613</td></tr>
<tr><td rowspan="2">≥75 years</td><td>All HF</td><td>869 (-2,814 to 4,606)</td></tr>
<tr><td>HFrEF</td><td>2,267 (-1,524 to 6,074)</td></tr>
</table>

<u>Results of sensitivity analysis for all HF patients <75 years of age</u>
Based on probabilistic analysis:

<table>
<tr><th>Sensitivity analysis using</th><th>iNMB (95% CI)[a] in £</th></tr>
<tr><td>Survival based on the Weibull distribution</td><td>6,838 (2,512 to 10,8235)</td></tr>
<tr><td>Survival based on the Kaplan-Meier curve from a published study</td><td>6,914 (2,632 to 10,847)</td></tr>
<tr><td>The relative treatment effect and cost of NP-guided monitoring ceases at 2 years</td><td>3,395 (1,137 to 5,368)</td></tr>
<tr><td>The relative treatment effect and cost of NP-guided monitoring continues for lifetime</td><td>15,033 (4,330 to 26,556)</td></tr>
<tr><td>BNP test cost low (£12.50)</td><td>6,438 (2,391 to 10,142)</td></tr>
<tr><td>BNP test cost high (£37.50)</td><td>6,358 (2,319 to 10,027)</td></tr>
<tr><td colspan="2">[a]Wllingness to pay threshold (λ) considered was £20, 000 per QALY.
iNMB = (λ x [incremental effectiveness]) – (incremental cost) i.e,.
iNMB = (λ x [$QALY_{BNP}$ -$QALY_{CG}$]) – ($Cost_{BNP}$ – $Cost_{CG}$);
iNMB < 0 indicates that the intervention is cost-effective</td></tr>
</table>
</td><td>"This study has shown that BNP-guided therapy, as implemented in RCTs in specialist HF clinics, appears to be efficacious and cost-effective in patients who have predominantly been recruited to the RCTs, namely those who are < 75 years of age and with HFrEF. The conclusions about the efficacy of BNP-guided therapy are uncertain because the findings are of borderline statistical significance, and the majority of trials contributing to the findings were judged to have high risk of bias." (p.121)</td></tr>
</table>

BNP = B-type natriuretic peptide; CG = standard clinically-guided group; CI = confidence interval; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; iNMB = incremental net monetary benefit; QALY = quality adjusted life years

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Ezekowitz (CCS),[5] 2017, Canada	
Guidance related to management **Evidence 1:** Evidence was obtained from multiple small RCTs, most of which found benefit, and three meta-analyses, which showed benefit. It was also mentioned that an ongoing RCT is likely to affect this recommendation. Further details were not reported	**Strength of Evidence 1:** Moderate quality
Recommendation 1: "We suggest, in ambulatory patients with HFrEF, measurement of BNP or NT-proBNP to guide management should be considered to decrease HFrelated hospitalizations and potentially reduce mortality. The benefit is uncertain in individuals older than 75 years of age (Weak Recommendation; Moderate-Quality Evidence)." (p.	**Strength of Recommendation 1**: Weak
Guidance related to prognosis **Evidence 2:** Three studies showed that there was an association between NP levels and risk of mortality and/ or hospitalization	**Strength of Evidence 2**: High quality
Recommendation 2: "We recommend that measurement of BNP/NTproBNP levels be considered in patients with an established diagnosis of HFrEF for prognostic stratification, in view of optimizing medical therapy (Strong Recommendation; High-Quality Evidence)." (p.1351)	**Strength of Recommendation 2**: Strong
Evidence 3: Evidence is from multiple small RCTs, all of which found an association with clinical outcomes. Further details were not reported	**Strength of Evidence 3:** Moderate quality
Recommendation 3: "We suggest that measurement of BNP or NTproBNP in patients hospitalized for HF should be considered before discharge, because of the prognostic value of these biomarkers in predicting rehospitalization and mortality (Strong Recommendation; Moderate-Quality Evidence)."	**Strength of Recommendation 3**: Strong
SIGN,[15] 2016, UK	
Evidence: Evidence was based on two systematic reviews with meta-analyses, published in 2013. One systematic review showed that there was reduction in all-cause mortality with NP-monitoring compared to standard care. It also reported that HF-related hospitalization was significantly reduced in younger (less than 75 years) patients and or in those with higher baseline BNP. Another systematic review showed that there was no significant reduction in in BNP-guided therapy, but all-cause mortality was significantly reduced with NT-proBNP guided therapy. It also reported that combined mortality and HF-related hospitalization was significantly reduced in patients of age less than 75 years compared to patients of age 75 years or older.	**Strength of Evidence**: 1++ **Strength of Recommendation**: Not reported
Recommendation: "NT-proBNP-guided treatment may be considered in patients with heart failure aged less than 75 years, especially in the presence of higher baseline NT-proBNP levels (>2,114 pg/ml)." (p.24)	

BNP = B-type natriuretic peptide; CCS = Canadian Cardiovascular Society; HFrEF = heart failure with reduced ejection fraction; NT-proBNP = N-terminal proBNP; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network

Appendix 5: Overlap between Included Systematic Reviews

Table 11: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation, Study name	Systematic Review Citation			
	Gamiño-A-Arroyo,[9] 2018, Mexico	Khan[a],[13] 2018, US	Pufulete,[6] 2018, UK	McLellan, [1] 2016, UK
Anguita 2010	x	x	x	x
Beck -da Silva 2005	x	x		x
Berger 2010, Vienna		x	x	x
Eurlings 2010, PRIMA	x	x	x	x
Felker 2017, GUIDE-IT		x	x	
Gaggin 2011, PROTECT		x		
Januzzi 2011, PROTECT	x		x	x
Jourdain 2007, STARS-BNP	x	x	x	x
Karlstrom 2011, UPSTEP	x	x	x	x
Krupika 2010 (abstracts & contact w/ author)				x
Lainchbury 2010, BATTLESCARRED		x	x	x
Li 2015				x
Persson 2010, SIGNAL-HF	x	x	x	x
Pfisterer 2009, TIME-CHF	x	x	x	x
Maeder 2013, TIME-CHF		x	x	x
Schou 2013,, Northstar		x	x	x
Shah 2011, STARBRITE			x	x
Shochat 2011 (abs)/Schochat 2012 (abstract and/or contact w/ author)			x	x
Skvortsov 2015				x
Troughton 2000, Christchurch pilot	x	x	x	x

[a] This systematic review included studies involving both chronic and acute heart failure patients. Only the studies involving chronic HF which were relevant for this current report are listed here