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Vasodilators for Inhospital Heart Failure Management: A Rapid Review (Update)

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This report is an update of a rapid review of the same name published in January 2013.

Evidence Development and Standards Branch at Health Quality Ontario

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Conflict of Interest Statement

All authors in the Evidence Development and Standards branch at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Rapid reviews are completed in 2–4-week time frames. Clinical questions are developed by the Evidence Development and Standards branch 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. The methods prioritize systematic reviews, which, if found, are rated by AMSTAR to determine the methodological quality of the review. 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 in the systematic review are retrieved and the GRADE criteria are applied to 2 outcomes. If no systematic review is found, then RCTs or observational studies are included, and their risk of bias is assessed. All rapid reviews are developed and finalized in consultation with experts.

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Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—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.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also 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, the Evidence Development and Standards branch and its research partners review the available scientific literature, making every effort to consider all relevant national and international research; collaborate with partners across relevant government branches; consult with expert advisory panels, clinical and other external experts, and developers of health technologies; and solicit any necessary supplemental information.

In addition, Evidence Development and Standards 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 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.

Disclaimer

This rapid review is the work of the Evidence Development and Standards branch 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 as of the date of the literature search specified in the Research Methods section. Health Quality Ontario makes no representation that the literature search captured every publication that was or could be applicable to the subject matter of the report. 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.

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List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
ASCEND-HF	Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure
BUN	Blood urea nitrogen
CHF	Congestive heart failure
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
HF	Heart failure
QBP	Quality-based procedure
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 Procedures (QBP) 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 Procedures initiative, visit www.hqontario.ca.

Objective of Analysis

On the advice of the Expert Panel for the Update and Integration of the Acute Congestive Heart Failure (CHF) Quality-Based Procedure (QBP), a rapid review was published in 2013 that examined the risk of adverse events associated with vasodilators used for inhospital management of heart failure; in particular, what is the effect on renal function and risk of mortality for patients administered intravenous nitroglycerin or nesiritide in hospital? (1) Researchers found that one RCT comparing nesiritide with placebo met their inclusion criteria—the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF) study. (2)

The objective of the *current* analysis was to address a broader comparison, nesiritide with active vasodilators (e.g., dobutamine or nitroglycerin), to reflect real practice, and to do this by evaluating RCTs published since 2011.

Clinical Need and Target Population

Symptomatic Decompensation of Heart Failure

Patients with heart failure (HF) who are hospitalized for an acute decompensation may present with symptoms such as volume overload, pulmonary congestion, and dyspnoea. (3) Vasodilators, including nitroglycerin and nesiritide, may be administered to address volume overload in HF. (4)

Technique

Intravenous vasodilators as adjunctive therapy facilitate a number of beneficial hemodynamic effects, including: a reduction in pulmonary capillary wedge pressure, reduced myocardial oxygen consumption, a decrease in both systemic vascular resistance and ventricular workload, an increase in stroke volume, and improved cardiac output overall. (5) Surrogate endpoints have been the focus of studies to date, (6) assuming or lacking power to detect clinically relevant outcomes resulting from such physiological effects. (7, 8) Pooled data from small clinical trials have raised specific concerns, such as deleterious effects on renal function and increased risk of mortality. (9, 10)

Nitroglycerin is administered to facilitate prompt relief of pulmonary congestion. (11) As with other common pharmaceuticals for HF, despite the role of nitroglycerin as a cornerstone therapy there is a shortage of evidence, especially at the level of current regulatory and clinical standards for safety and efficacy. (12, 13) Nesiritide is a newer vasodilator approved by the Federal Drug Administration in the United States in 2001 for relief of dyspnoea in acutely decompensated HF. (14) Nesiritide was subsequently granted conditional marketing authorization from Health Canada in 2008, pending verification of promising early findings with further data. (15)

Rapid Review

Research Question

What is the effect of intravenous nesiritide compared with active vasodilators (e.g., dobutamine or nitroglycerin) on renal function and risk of mortality for heart failure inpatients?

Research Methods

Literature Search

The original literature search was revisited in light of an addition to the inclusion and exclusion criteria. The expert panel believed that instead of examining nesiritide compared with placebo, the studies should examine nesiritide compared with active vasodilators (e.g., dobutamine or nitroglycerin), to be representative of real practice. There was also a modification to the search dates that limited them to 2011 onwards (search dates from January 1, 2011, to July 2013).

Literature search strategies are presented in Appendix 1.

Inclusion Criteria

- English language full-text reports
- published between January 1, 2011 and July 2013
- health technology assessments, systematic reviews, and meta-analyses, RCTs
- studies comparing adult hospital inpatients with HF administered intravenous nesiritide or active vasodilators (e.g., dobutamine or nitroglycerin)

Exclusion Criteria

- observational studies, case reports, editorials

Outcomes of Interest

- renal function
- mortality

Expert Panel

In December 2013, an Expert Advisory Panel on Post-Acute, Community-Based Care for CHF Patients was struck. Members of the community-based panels included family physicians, physician specialists, community health care administrators, and allied health professionals.
The role of the expert advisory panel was to provide advice on primary CHF patient groupings; to review the evidence, guidance, and publications related to defined CHF patient populations; to identify and prioritize interventions and areas of community-based care; and to advise on the development of a care pathway model. The role of panel members was to provide advice on the scope of the project, the methods used, and the findings. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the expert panel members.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group criteria. (16) 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. 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 factors. (16) For more detailed information, please refer to the latest series of GRADE articles. (16)

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

Evidence quality assessment is presented in Appendix 2.

Results of Rapid Review

Literature Search Results

One RCT was identified and is discussed briefly in Table 1.

Table 1: Overview of Included RCT Assessing the effect of Nesiritide on the Treatment of Acute Decompensated Heart Failure (ADHF)

Author, Year	Study Design	Sample Size (Nesiritide/Nitroglycerin)	Intervention (Dose)	Outcomes
Chow et al., 2011 (17)	Randomized controlled trial	89 (45/44)	Nesiritide or nitroglycerin Nesiritide: 2 mcg/kg optional bolus + 0.01 mcg kg^{-1} min^{-1} infusion for at least 48 h Nitroglycerin: 10 mcg/min and titrated every 5–10 min until symptom relief[a]	Primary clinical outcomes: - changes in renal and neurohormonal markers Secondary clinical outcomes: - changes in serum creatinine, blood urea nitrogen (BUN), and creatinine clearance[b] at 24 and 48 h of infusion Tertiary clinical outcomes: - median length of stay, need for dialysis, and symptomatic hypotension - mortality and rehospitalization at 3 and 6 mo

[a]Symptom relief was defined as marked improvement in dyspnea, or both dyspnea and fatigue if symptoms were jointly present on admission.
[b]Estimated using the Cockcroft-Gault equation.

Outcomes of Interest

Renal Function

The markers obtained to measure renal function included serum creatinine, blood urea nitrogen (BUN), and creatinine clearance. Chow et al (17) identified no statistically significant differences (no *P* values provided) at baseline or during vasodilator therapy between the nesiritide and nitroglycerin groups. The duration of infusion of both nesiritide and nitroglycerin (24 vs 48 h) was also not associated with any changes in serum creatinine or creatinine clearances (Table 2).

Table 2: Renal Function Markers at Specified Time Points

Renal Function Marker	Baseline		24 h		48 h		Discharge	
	NTG	NES	NTG	NES	NTG	NES	NTG	NES
BUN (mg/dL)	27.5 ± 15.9	24.9 ± 8.9	28.6 ± 15.3	24.3 ± 10.6	28.4 ± 16.2	25.1 ± 9.3	29.6 ± 17.7	26.7 ± 9.7
sCr (mg/dL)	1.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4
CrCl (mL/min)	52.5 ± 25.5	51.5 ± 16.7	50.9 ± 25.4	50.3 ± 17.9	49.5 ± 26.0	49.7 ± 16.0	50.8 ± 23.4	49.1 ± 16.2

Abbreviations: BUN, blood urea nitrogen; CrCl, creatinine clearance; NES, nesiritide; NTG, nitroglycerin; sCr, serum creatinine.

Mortality

Chow et al (17) found no statistically significant differences between the nitroglycerin and nesiritide groups for mortality at 3 or 6 months post-discharge (Table 3).

Table 3: Mortality at 3 and 6 Months Post-discharge

Time Point	Intervention/Control		*P* Value
	NES (%)	NTG (%)	
3 mo	4 (9)	4 (9)	0.97
6 mo	7 (16)	7 (16)	0.96

Abbreviations: NES, nesiritide; NTG, nitroglycerin.

The study by Chow et al (17) was adequately powered to detect differences in serum creatinine based on observations from a previous study. However, the study was not specifically powered to assess the outcome of mortality.

The renal function outcome is measured differently in this study than it is in the ASCEND-HF (2) study examined in the previous rapid review. (1) Renal impairment was defined as a > 25% decrease in glomerular filtration rate from study-drug initiation through day 30. Chow et al (17) measured renal function through biomarkers serum creatinine, BUN, and creatinine clearance at baseline, 24 hours, 48 hours, and time of discharge. Also, the outcome of mortality was measured at different time points in both studies. In the ASCEND-HF (2) study, mortality was measured at 30 days. Chow et al (17) examined mortality at 3 and 6 months.

Conclusions

The following conclusions were drawn from the examination of 1 RCT comparing nesiritide versus nitroglycerin as part of the addendum to the rapid review:

- Based on moderate quality of evidence, there was no statistically significant difference in renal function biomarkers (at baseline, 24 hours, 48 hours, and discharge) among patients who received nesiritide versus nitroglycerin.
- Based on low quality of evidence, there was no statistically significant difference in mortality (at 3 or 6 months post-discharge) among patients who received nesiritide versus nitroglycerin.

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Appendices

Appendix 1: Literature Search Strategies

Search date: July 23, 2014
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase, All EBM Databases (see below)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2014>, EBM Reviews - ACP Journal Club <1991 to July 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <June 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <2nd Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2014>, Embase <1980 to 2014 Week 29>, Ovid MEDLINE(R) <1946 to July Week 2 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 22, 2014>
Search Strategy:
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1 exp Heart Failure/ (388287)
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. (307097)
3 or/1-2 (491633)
4 Vasodilator Agents/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Nitroglycerin/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed (50855)
5 Nesiritide/ use emez or Vasodilator Agent/ use emez or Coronary Vasodilating Agent/ use emez or glyceryl trinitrate/ use emez (55999)
6 (vasodilator* or (vasodilat* adj agent*)).ti,ab. (70358)
7 (nesiritide or natrecor or noratak or nitroglycerin*).mp. (31902)
8 or/4-7 (162842)
9 3 and 8 (20378)
10 (Meta Analysis or Controlled Clinical Trial).pt. (223588)
11 Meta-Analysis/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Meta-Analysis as Topic/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Technology Assessment, Biomedical/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed (72466)
12 Meta Analysis/ use emez or "Meta Analysis (Topic)"/ use emez or Biomedical Technology Assessment/ use emez (104716)
13 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab. (373125)
14 (meta analy* or metaanaly* or health technolog* assess*).mp. (261263)
15 exp Randomized Controlled Trial/ (725061)
16 exp Random Allocation/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Double-Blind Method/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Control Groups/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Placebos/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed (349383)
17 exp Randomization/ use emez or exp RANDOM SAMPLE/ use emez or Double Blind Procedure/ use emez or exp Triple Blind Procedure/ use emez or exp Control Group/ use emez or exp PLACEBO/ use emez (429271)
18 (random* or RCT or RCTs or placebo* or sham* or (control* adj2 clinical trial*)).ti,ab. (2318796)
19 or/10-18 (3206612)
20 9 and 19 (4685)
21 limit 20 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained] (4203)
22 limit 21 to yr="2011 -Current" [Limit not valid in DARE; records were retained] (656)
23 remove duplicates from 22 (552)

Appendix 2: Evidence Quality Assessment

Table A1: GRADE Evidence Profile for Comparison of Nesiritide and Nitroglycerin

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Mortality (death from any cause within 3 and 6 mo)							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected[c]	None	⊕⊕ Low
Renal function (measured by serum creatinine, BUN, and creatinine clearance)							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected[c]	None	⊕⊕⊕ Moderate

Abbreviations: BUN, blood urea nitrogen; RCT, randomized controlled trial.
[a]With all studies that are not blinded, bias from the knowledge of the treatment could affect the outcomes of the study.
[b]This study was not powered based on this outcome.
[c]Publication bias is nearly impossible to assess with a single study.

Table A2: Risk of Bias in the Randomized Controlled Trial Comparing Nesiritide and Nitroglycerin

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Chow et al, 2011 (17)	Limitations[a]	Limitations[b]	No limitations[c]	No limitations[d]	No limitations

[a]The authors state that participants were randomized but do not explain the method (e.g., computer generated etc).
[b]Participants or those conducting group assignment were not blinded. However, the treatment group assignment was blinded to the statisticians before and during statistical analysis.
[C]No loss to follow-up.
[d]Results for all prespecified outcomes were reported.

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