Ontario
Health Quality Ontario
Qualité des services
de santé Ontario

Vasodilators for Inhospital Heart Failure Management: A Rapid Review

A Schaink

January 2013

Vasodilators for Inhospital Heart Failure Management: A Rapid Review. January 2013; pp. 1–21.

Suggested Citation

This report should be cited as follows:

Schaink A. Vasodilators for inhospital heart failure management: a rapid review. Toronto, ON: Health Quality Ontario; 2013 Jan. 21 p. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews.

Conflict of Interest Statement

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

Rapid Review Methodology

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

Disclaimer

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

About Health Quality Ontario

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

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

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

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

About Health Quality Ontario Publications

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

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

Permission Requests

How to Obtain Rapid Reviews From Health Quality Ontario

All rapid reviews are freely available in PDF format at the following URL:
http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews.

Table of Contents

List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
CI	Confidence interval(s)
CV	Cardiovascular
HF	Heart failure
HQO	Health Quality Ontario
RCT	Randomized controlled trial
RR	Relative risk

Background

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

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

Objective of Analysis

The objective of this analysis was to determine the 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?

Clinical Need and Target Population

Symptomatic Decompensation of Heart Failure

Heart failure (HF) patients who are hospitalized for an acute decompensation may present with symptoms such as volume overload, pulmonary congestion, and dyspnoea. (1) Vasodilators, including nitroglycerin and nesiritide, may be administered to address volume overload in HF. (2)

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. (3) Surrogate endpoints have been the focus of studies to date, (4) assuming or lacking power to detect clinically relevant outcomes resulting from such physiological effects. (5;6) Pooled data from small clinical trials have raised specific concerns, such as deleterious effects on renal function and increased risk of mortality. (7;8)

Nitroglycerin is administered to facilitate prompt relief of pulmonary congestion. (9) 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. (10;11) 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. (12) Nesiritide was subsequently granted conditional marketing authorization from Health Canada in 2008, pending verification of promising early findings with further data. (13)

Rapid Review

Research Question

What is the effect of intravenous nitroglycerin or nesiritide on renal function and risk of mortality for heart failure inpatients?

Research Methods

Literature Search

A literature search was performed on November 1, 2012, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2011, until November 1, 2012. The date limit for this search was set to reduce the number of citations for feasibility within the rapid review timeline, and with consideration to a seminal randomized controlled trial (RCT) on nesiritide published in 2011. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language full-text reports
- published between January 1, 2011 and November 1, 2012
- health technology assessments, systematic reviews, and meta-analyses, RCTs and guidelines
- studies of adult hospital inpatients with heart failure administered intravenous nitroglycerin or nesiritide compared to placebo

Exclusion Criteria

- observational studies, case reports, editorials
- studies of vasodilators other than nitroglycerin or nesiritide and/or comparison therapies other than placebo

Outcomes of Interest

- renal function
- mortality

Expert Panel

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

The role of the Expert Advisory Panel on Congestive Heart Failure Episode of Care was to contextualize the evidence produced by HQO and provide advice on the components of a high-quality episode of care

for heart failure patients presenting to an acute care hospital. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of Advisory Panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) tool is used to assess the methodological quality of systematic reviews. (14)

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (15) 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. (15) For more detailed information, please refer to the latest series of GRADE articles. (15)

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

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

Results of Literature Search

The database search yielded 708 citations published between January 1, 2011, and November 1, 2012 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

No systematic reviews, meta-analyses, or health technology assessments were identified which met the predetermined inclusion criteria on either nitroglycerin or nesiritide. Thus, in accordance with the HQO Evidence Development and Standards Rapid Review Methodology, RCTs were taken as the next level of evidence.

There were no RCTs assessing the safety of nitroglycerin identified. One RCT comparing nesiritide with placebo met the inclusion criteria. (16) Two other RCTs were also identified. However, both were excluded as the comparator was nitroglycerin and, thus, did not meet the prespecified inclusion criteria. An overview of the RCT by O'Connor et al (16) is provided in Table 1.

Table 1: Overview of Included RCT Assessing the Safety and Effectiveness of Nesiritide for the Treatment of Acute Decompensated Heart Failure (ASCEND-HF)

Author, Year	Study Design (Methods)	Sample Size (Intervention/Control)	Intervention (Dose)	Outcomes (Through Day 30)
O'Connor et al, 2011 (16)	RCT (398 sites)	7141 (3496/3511)	Nesiritide or Placebo (2µg/kg bolus + infusion of 0.010 µg/kg/min for 24h – 7 days)	Coprimary clinical outcomes: -self-reported dyspnoea at 6h and 24h -composite of death from any cause or rehospitalization for HF Secondary clinical outcomes: -self-reported well-being at 6h and 4h -rehospitalization for or death from CV causes -persistent/worsening HF or death from any cause -days alive and out of hospital Safety outcomes: -death from any cause -renal impairment -hypotension (symptomatic and asymptomatic)

Abbreviations: CI, confidence intervals; CV, cardiovascular; h, hours; HF, heart failure; RCT, randomized controlled trial.
Source: O'Connor et al, 2011 (16)

The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial (16) was purposefully designed to answer outstanding questions regarding effectiveness and safety. This international, multicentre, double-blind, randomized trial was conducted between May 2007 and August 2010. Adults presenting to the emergency department or admitted to hospital within 24 hours for acute decompensated heart failure were eligible for enrollment. Patients were randomized to receive an intravenous infusion of either nesiritide or matching placebo in addition to standard therapies as required (e.g., diuretics, morphine, and other vasoactive medications).

Patients were followed-up with for 30 days after randomization during which time several important clinical and safety outcomes were assessed (see Table 1). Among the important safety outcomes were death from any cause and renal impairment. Table 2 summarizes the relative risk of 30-day all-cause mortality and renal impairment for patients treated with nesiritide compared with placebo. No statistically significant differences in rates of death or renal impairment were found between groups. Within the 30-day period, 126 (3.6%) and 141 (4.0%) deaths occurred in the nesiritide and placebo groups, respectively. The occurrence of renal impairment events was 1032 (31.4%) among patients administered nesiritide and 968 (29.5%) among those who received placebo.

Table 2: Effect of Nesiritide on Mortality and Renal Dysfunction Compared with Placebo

Outcome	Definition	Events/Sample Size		Effect Estimate Risk Ratio[a] (95% CI)	*P* value
		Intervention	Control		
Mortality	Death from any cause within 30 days	126/3490	141/3499	0.90 (0.71–1.13)	0.36
Renal impairment	> 25% decrease in glomerular filtration rate from study-drug initiation through day 30[b]	1032/3298	968/3278	1.06 (0.99–1.14)	0.10

Abbreviations: CI, confidence intervals.
[a]Mantel-Haenszel risk ratio.
[b]Calculated by simplified Modification of Diet in Renal Dysfunction equation.
Source: O'Connor et al, 2011 (16)

The ASCEND-HF was the largest RCT to date on nesiritide, and was powered adequately to address safety questions. However, it was a single study. The pragmatic trial design included a broad range of HF patients. This may increase the generalizability of the findings as HF is a highly heterogeneous syndrome due to variations in underlying pathophysiology. (12) The study was designed to ascertain rates of death or rehospitalization within 30 days based on predicted event rates in the groups of 11% to 14%. However, the true event rates were lower and, thus, the study did not reach its intended power of 89% for this outcome. (16) Prespecified subgroup analyses by geographical, sociodemographic, and clinical characteristics provide support for homogeneity of the findings across several potential subpopulations within HF. Given the lack of statistically significant findings despite the large sample size and stringently set statistical significance levels, this trial may be considered quite robust.

Detail on the assessment of the quality of this RCT can be found in the GRADE tables in Appendix 2.

Conclusions

No systematic reviews, meta-analyses, or health technology assessments on the safety and effectiveness of nitroglycerin or nesiritide were identified in the literature search. No RCTs were identified evaluating the safety of nitroglycerin.

One large multicentre RCT addressed these questions with regard to nesiritide. (16) No statistically significant increase in risk of mortality (GRADE: moderate) or renal dysfunction (GRADE: high) was found, compared to placebo.

Acknowledgements

Editorial Staff
Pierre Lachaine

Medical Information Services
Corinne Holubowich, Bed, MLIS
Kellee Kaulback, BA(H), MISt

Expert Panel for Health Quality Ontario: Episode of Care for Congestive Heart Failure

Name	Title	Organization
Dr. David Alter	Senior Scientist	Institute for Clinical Evaluative Sciences Research Program Director and Associate Staff, The Cardiac and Secondary Prevention Program at the Toronto Rehabilitation Institute-UHN; Associate Professor of Medicine, University of Toronto
Dr. Douglas Lee	Scientist	Institute for Clinical Evaluative Sciences
Dr. Catherine Demers	Associate Professor	Division of Cardiology, Department of Medicine McMaster University
Dr. Susanna Mak	Cardiologist	University of Toronto: Department of Medicine, Division of Cardiology, Mount Sinai Hospital
Dr. Lisa Mielniczuk	Medical Director, Pulmonary Hypertension Clinic	University of Ottawa Heart Institute
Dr. Peter Liu	President, International Society of Cardiomyopathy and Heart Failure of the World Heart Federation / Director, National C-CHANGE Program Scientific Director/VP Research, University of Ottawa Heart Institute / Professor of Medicine,	University of Ottawa Heart Institute
Dr. Robert McKelvie	Professor of Medicine, Cardiologist	McMaster University, Hamilton Health Sciences
Dr. Malcolm Arnold	Professor of Medicine	Western University, London Health Sciences Centre
Dr. Stuart Smith	Chief of Cardiovascular Services Director, Heart Failure Program	St. Mary's General Hospital
Dr. Atilio Costa Vitali	Assistant Professor of medicine – Division of Clinical Science	Sudbury Regional Hospital
Dr. Jennifer Everson	Physician Lead	Hamilton Niagara Haldimand Brant Local Health Integration Network
Dr. Lee Donohue	Family Physician	Ottawa
Linda Belford	Nurse Practitioner, Practice Leader PMCC	University Health Network
Jane MacIver	Nurse Practitioner Heart Failure/Heart Transplant	University Health Network
Sharon Yamashita	Clinical Coordinator, Critical Care	Sunnybrook Health Sciences Centre
Claudia Bucci	Clinical Coordinator, Cardiovascular Diseases	Sunnybrook Health Sciences Centre
Andrea Rawn	Evidence Based Care Program Coordinator	Grey Bruce Health Network
Darlene Wilson	Registered Nurse	Heart Function Clinic, Trillium Health Centre
Kari Kostiw	Clinical Coordinator	Health Sciences North Ramsey Lake Health Centre
Janet Parr	CHF Patient	
Heather Sherrard	Vice President, Clinical Services	University of Ottawa Heart Institute
Sue Wojdylo	Manager, Case Costing	Lakeridge Health

Name	Title	Organization
Jane Chen	Manager of Case Costing	University Health Network
Nancy Hunter	LHIN Liaison & Business Development	Cardiac Care Network of Ontario
Ministry Representatives		
Gary Coleridge	Senior Program Consultant	Ministry of Health and Long-Term Care
Louie Luo	Senior Methodologist	Ministry of Health and Long-Term Care

Appendices

Appendix 1: Literature Search Strategies

Search date: November 1, 2012
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Cochrane Library; CRD

Q: Vasodilators for Heart Failure management
Limits: 2011-current; English
Filters: health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and guidelines

Database: Ovid MEDLINE(R) <1946 to October Week 4 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 31, 2012>, Embase <1980 to 2012 Week 43>
Search Strategy:

Search Strategy:

#	Searches	Results
1	exp Heart Failure/	328766
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.	259357
3	or/1-2	418837
4	Vasodilator Agents/ use mesz	37031
5	Natriuretic Agents/ use mesz	851
6	Natriuretic Peptide, Brain/ use mesz	8484
7	Nitroglycerin/ use mesz	11369
8	Vasodilator Agent/ use emez	25558
9	Coronary Vasodilating Agent/ use emez	441
10	Nesiritide/ use emez	1227
11	Natriuretic Factor/ use emez	3528
12	Brain Natriuretic Peptide/ use emez	13952
13	Glyceryl Trinitrate/ use emez	31492
14	(vasodilator* or (vasodilat* adj agent*)).ti,ab.	65896
15	(nesiritide or natrecor or noratak).mp.	1795
16	nitroglycerin*.mp.	27006
17	or/4-16	176380
18	Meta Analysis.pt.	37256
19	Meta Analysis/ use emez	66797
20	Systematic Review/ use emez	54209
21	exp Technology Assessment, Biomedical/ use mesz	8883
22	Biomedical Technology Assessment/ use emez	11403
23	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or	294823

	published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	
24	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	3795
25	exp Random Allocation/ use mesz	76290
26	exp Double-Blind Method/ use mesz	117930
27	exp Control Groups/ use mesz	1380
28	exp Placebos/ use mesz	31496
29	Randomized Controlled Trial/ use emez	331618
30	exp Randomization/ use emez	59833
31	exp Random Sample/ use emez	4276
32	Double Blind Procedure/ use emez	111601
33	exp Triple Blind Procedure/ use emez	35
34	exp Control Group/ use emez	38869
35	exp Placebo/ use emez	207241
36	(random* or RCT).ti,ab.	1390337
37	(placebo* or sham*).ti,ab.	449991
38	(control* adj2 clinical trial*).ti,ab.	38520
39	exp Practice Guideline/ use emez	279866
40	exp Professional Standard/ use emez	270060
41	exp Standard of Care/ use mesz	593
42	exp Guideline/ use mesz	23206
43	exp Guidelines as Topic/ use mesz	102801
44	(guideline* or guidance or consensus statement* or standard or standards).ti.	220135
45	(controlled clinical trial or meta analysis or randomized controlled trial).pt.	458049
46	or/18-45	2988938
47	3 and 17 and 46	6378
48	limit 47 to english language	5751
49	limit 48 to yr="2011 -Current"	792
50	remove duplicates from 49	700

Cochrane Library

Line #	Terms	Results
#1	MeSH descriptor: [Heart Failure] explode all trees	4873
#2	((cardia? or heart) next (decompensation or failure or incompetence or insufficiency)) or cardiac stand still or ((coronary or myocardial) next (failure or insufficiency)):ti,ab,kw (Word variations have been searched)	9337
#3	Enter terms for search #1 or #2	9342
#4	MeSH descriptor: [Vasodilator Agents] this term only	3211
#5	MeSH descriptor: [Natriuretic Agents] this term only	53
#6	MeSH descriptor: [Natriuretic Peptide, Brain] explode all trees	696
#7	MeSH descriptor: [Nitroglycerin] this term only	1619
#8	vasodilator* or (vasodilat* next agent*):ti,ab,kw or nesiritide or natrecor or noratak or nitroglycerin* (Word variations have been searched)	7134
#9	#4 or #5 or #6 or #7 or #8	7741
#10	#3 and #9 from 2011 to 2012	60

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES IN DARE,HTA	345
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 IN DARE, HTA FROM 2008 TO 2012	118
3	#1 OR #2	362
4	MeSH DESCRIPTOR Vasodilator Agents IN DARE,HTA	63
5	MeSH DESCRIPTOR Natriuretic Agents IN DARE,HTA	4
6	MeSH DESCRIPTOR Natriuretic Peptide, Brain EXPLODE ALL TREES IN DARE,HTA	59
7	MeSH DESCRIPTOR Nitroglycerin EXPLODE ALL TREES IN DARE,HTA	16
8	(vasodilator* OR (vasodilat* ADJ agent*)):TI OR (nesiritide OR natrecor OR noratak) OR (nitroglycerin*) IN DARE, HTA FROM 2008 TO 2012	31
9	#4 OR #5 OR #6 OR #7 OR #8	148
10	#3 AND #9	42
11	(#10) FROM 2011 TO 2012	6

Appendix 2: GRADE Tables

Table A2-1: GRADE Evidence Profile for Comparison of Nesiritide and Placebo

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Mortality (death from any cause within 30 days)							
1 (RCT)	No serious limitations[a]	No serious limitations[b]	No serious limitations	Serious limitations (-1)[c]	Undetected[d]	None	⊕⊕⊕ Moderate
Renal Impairment (≥ 25% decrease in glomerular filtration rate from study-drug initiation through day 30)							
1 (RCT)	No serious limitations[e]	No serious limitations[b]	No serious limitations	No serious limitations	Undetected[d]	None	⊕⊕⊕⊕ High

Abbreviations: No., number; RCT, randomized controlled trial.

[a]Data management activities and analyses were conducted by a consortium of academic research organizations. Fatal events were reviewed and categorized by an independent, blinded committee.

[b]Two analysis plans were employed to satisfy regulatory needs of both Europe and the United States and the results from both analyses support the same conclusions.

[c]The optimal information size (OIS) criteria was met, however, event rates were much lower than predicted during a priori sample size calculation (11-14% predicted vs. 3.6-4% observed). The width of the confidence interval (CI) is relatively narrow, however, the lower limit of the CI indicates a potential 29% mortality benefit with nesiritide, which may be appreciable.

[d]Publication bias is nearly impossible to assess with a single study. Despite sponsorship by the pharmaceutical, the publication of such a large RCT with null results suggests that publication bias is unlikely.

[e]Presence or absence of renal impairment was calculated using a standardized formula (simplified Modification of Diet in Renal Dysfunction equation).

Table A2-2: Risk of Bias in the Randomized Controlled Trial Comparing Nesiritide and Placebo

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
O'Connor et al, 2011 (16)	No limitations[a]	No limitations[b]	No limitations[c]	No limitations[d]	No limitations

[a]A centralized randomization procedure with a computer-generated randomization schedule was used to assign subject number and treatment code. Medication code numbers were preprinted on the study drug labels prior to distribution to sites.

[b]Study drug compounds appeared and were packaged identically with labels containing pertinent clinical information (e.g., directions for use) and identifying information (e.g., subject number) but not drug identity. Certain laboratory tests (e.g., serum BNP) were not permitted during the treatment phase to prevent breaking the blind of the clinician. Mortality was assessed by an independent, blinded clinical events committee, and renal impairment through a standardized formula based on laboratory test results (i.e., serum creatinine).

[C]98% of randomized patients were included in the analysis. Similar numbers withdrew consent from the treatment and placebo groups (16 and 14, respectively) and 4 were lost to follow-up in each group.

[d]Results for all prespecified outcomes were reported, including individual components of composite outcomes.

References

(1) Didomenico RJ, Park HY, Southworth MR, Eyrich HM, Lewis RK, Finley JM, et al. Guidelines for acute decompensated heart failure treatment. Ann Pharmacother. 2004 Apr;38(4):649-60.

(2) Arnold JM, Liu P, Demers C, Dorian P, Giannetti N, Haddad H, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. Can J Cardiol. 2006 Jan;22(1):23-45.

(3) Fonarow GC. Pharmacologic therapies for acutely decompensated heart failure. Rev Cardiovasc Med. 2002;3 Suppl 4:S18-S27.

(4) Topol EJ. Nesiritide - not verified. N Engl J Med. 2005 Jul 14;353(2):113-6.

(5) Salzberg SP. In patients hospitalised with acute heart failure, nesiritide, compared with placebo, is not associated with improvements in dyspnoea or 30-day rehospitalisation or mortality. Evid Based Med. 2012 Apr;17(2):53-4.

(6) Topol EJ. The lost decade of nesiritide. N Engl J Med. 2011 Jul 7;365(1):81-2.

(7) Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA. 2005 Apr 20;293(15):1900-5.

(8) Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation. 2005 Mar 29;111(12):1487-91.

(9) Coons JC, McGraw M, Murali S. Pharmacotherapy for acute heart failure syndromes. Am J Health Syst Pharm. 2011 Jan 1;68(1):21-35.

(10) Konstam MA, Pang PS, Gheorghiade M. Seeking new heights in acute heart failure syndromes: lessons from ASCEND and EVEREST. Eur Heart J. 2011 Aug 6.

(11) Nesiritide in Acute Decompensated Heart Failure. N Engl J Med. 2011 Oct 19;365(16):1547.

(12) Kociol RD, Konstam MA. Nesiritide ASCENDs the ranks of unproven treatments for acute heart failure. Am J Kidney Dis. 2012 Jul;60(1):8-11.

(13) Health Canada. Conditional Marketing Authorization of NATRECOR: Fact Sheet. 2008 [cited 2012 Nov 5]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/natrecor_fs_fd_111760-eng.php

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

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

(16) O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011 Jul 7;365(1):32-43.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca