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Inotropic and Vasoactive Agents for In-Hospital Heart Failure Management: A Rapid Review

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Conflict of Interest Statement

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

Rapid Review Methodology

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

Disclaimer

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 This rapid review may be superseded by an updated publication on the same topic.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

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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.

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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.

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List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
CI	Confidence interval(s)
HF	Heart failure
M-H	Mantel-Haenszel test
NYHA	New York Heart Association
RCT	Randomized controlled trial
RR	Relative risk

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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 whether there was evidence of increased risk for heart failure (HF) patients who are administered inotropic and vasoactive agents in hospital—in particular, those administered dobutamine, milrinone, or nitroprusside.

Clinical Need and Target Population

Despite the availability of several effective medical therapies, many patients continue to require hospitalization for acute HF exacerbations. An estimated 10 to 15% of patients admitted for acute HF have more severe decompensation, including signs of reduced cardiac output and poor tissue perfusion, and potentially resulting in end-organ dysfunction. (1-3) In order to improve the prognosis for these patients, inotropic and vasoactive agents may be administered to restore hemodynamics, with the aim of promoting optimal patient outcomes.

Technique

Inotropic and vasoactive agents exert their effects of increased heart rate, vasodilation, or increased heart contractility via β-adrenergic agonism, α-receptor blockade, or phosphodiesterase inhibition, respectively. (4) However, these agents can also trigger atrial and ventricular arrhythmias, (5) myocardial ischemia, (6) and some randomized clinical trials (RCTs) have demonstrated a trend toward increased mortality with their use. (7) Given the lack of well-designed RCTs examining longer-term and substantive patient outcomes (8) and given that findings have been inconsistent across studies, (4) there is uncertainty about the safety of these agents, particularly with regard to mortality.

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Rapid Review

Research Question

Is there an increased risk of mortality for heart failure patients administered dobutamine, milrinone, or nitroprusside in hospital?

Research Methods

Literature Search

A literature search was performed on September 23, 2012, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2008, to September 23, 2012. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language full-reports
- published between January 1, 2008, and September 23, 2012
- health technology assessments, systematic reviews, and meta-analyses
- studies describing in-hospital treatment of HF patients with dobutamine, milrinone, or nitroprusside

Exclusion Criteria

- RCTs, observational studies, case reports, editorials, letters to the editor

Outcome of Interest

- mortality

Expert Panel

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

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

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Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) tool was used to assess the methodological quality of systematic reviews. (9)

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (10) 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—are then taken into account. Limitations in these areas result 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. (10) For more detailed information, please refer to the latest series of GRADE articles. (10)

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 that of 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

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Results of Literature Search

The database search yielded 121 citations published between January 1, 2008, and September 23, 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 studies were identified that examined the use of nitroprusside for in-hospital management of HF.

One Cochrane review by Amsallem et al (11) of phosphodiesterase-III inhibitors for HF included 2 RCTs on milrinone; however, it was unclear whether the study population was inpatient or outpatient. The oral administration of milrinone, the duration of treatment over several weeks to months, the dispensation of prepackaged medications, and the intermittent follow-up over several months indicated that this was not the intervention of interest, and these studies were excluded.

One meta-analysis of 14 RCTs (N = 673 patients) by Tacon et al (12) included studies of both inpatients and outpatients with HF and did not find an increased mortality risk with dobutamine compared with placebo or usual care (AMSTAR score was 9 out of 11). Five RCTs of HF inpatients (13-17) were extracted from the meta-analysis, but 2 (15;17) were excluded, as they were reported in abstract only and have not been subsequently published. Table 1 summarizes the 3 included studies of dobutamine versus placebo for HF inpatients. (13;14;16)

Table 1: Effect of Dobutamine on Mortality Compared to Placebo for In-Hospital HF Management

Author, Year	Study Design	Length of Follow-up	HF Severity, Study Population	Sample Size (Dobutamine/Placebo)
Adamopoulos et al., 2006 (13)	RCT	4 months	NYHA class III or IV	23/23
Bader et al., 2010 (14)	RCT	48 hours	NYHA class III or IV	43/47
Erlemeier et al., 1992 (16)	RCT	4 weeks	Treatment-resistant NYHA class IV	10/10

Abbreviations: CI, confidence interval; HF, heart failure; NYHA, New York Heart Association; RCT, randomized controlled trial.
Source: Tacon CL, McCaffrey J, Delaney A. Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials. Intensive Care Med. 2012;38(3):359-67. (12)

A meta-analysis was conducted using Review Manager Version 5. (18) The relative risk (RR) of mortality was calculated from the included RCTs comparing dobutamine against placebo for HF inpatients. The meta-analysis did not show a statistically significant increase in risk of mortality with dobutamine treatment (Figure 1).

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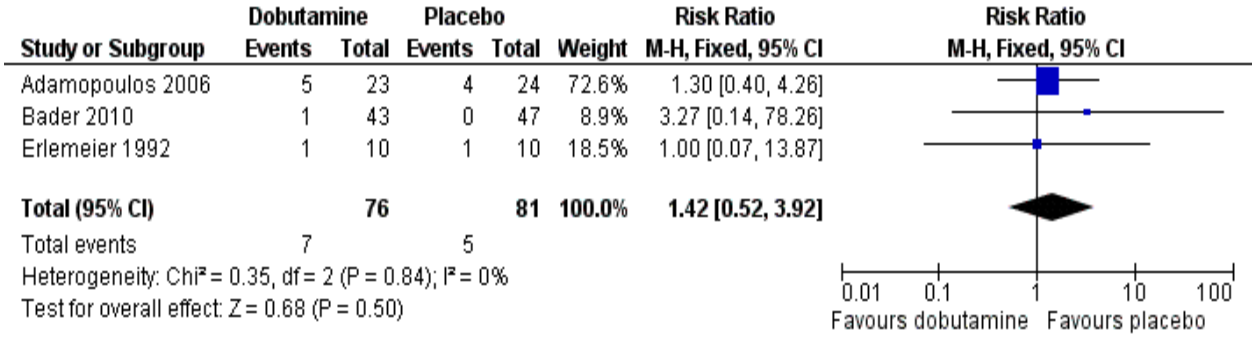

Figure 1. Meta-analysis of Dobutamine Versus Placebo on Mortality Risk

Abbreviations: CI, confidence interval; HF, heart failure; M-H, Mantel-Haenszel.

A fixed-effects analysis was used, as between-trial heterogeneity was not of concern. (19) To confirm findings, a random-effects model was also run, and the effect estimate was highly similar to that of the fixed-effects analysis (RR 1.38; 95% CI 0.50–3.83; *P* = 0.54).

Limitations

There are a number of challenges in formulating recommendations regarding the clinical utility of dobutamine for moderate to severe HF patients in hospital. Two of the 3 RCTs included in the meta-analysis were based on data from the early 1990s, predating the routine use of concomitant pharmacotherapies (e.g., β-blockers, angiotensin-converting enzyme inhibitors) that could conceivably affect the rate or nature of adverse events during in-hospital inotropic therapy. As well, the literature on dobutamine was focused on surrogate outcomes related to efficacy (e.g., hemodynamic indices), rather than on systemic patient outcomes. It is thought that the improvement of hemodynamics will lead to improvement in overall patient outcome, but there have been insufficient data to draw conclusions to any effect (GRADE quality of evidence: very low).

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Conclusions

- No studies were identified that examined in-hospital milrinone or nitroprusside therapy for the management of heart failure.
- In a meta-analysis of 3 identified RCTs, there was no evidence of a statistically significant increase in mortality risk compared with placebo for patients with moderate to severe heart failure who were administered dobutamine in hospital (GRADE quality of evidence: very low).
- Careful consideration is required in formulating recommendations regarding the clinical utility of dobutamine for moderate to severe heart failure decompensation in hospital, based on the quality of the body of evidence and the limitations of the component studies.

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Acknowledgements

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Dr. Susanna Mak	Cardiologist	University of Toronto, Department of Medicine, Division of Cardiology, Mount Sinai Hospital
Dr. Lisa Mielniczuk	Medical Director, Pulmonary Hypertension Clinic	University of Ottawa Heart Institute
Dr. Peter Liu	President, International Society of Cardiomyopathy and Heart Failure of the World Heart Federation Director, National C-CHANGE Program Scientific Director/VP Research, University of Ottawa Heart Institute Professor of Medicine	University of Ottawa Heart Institute
Dr. Robert McKelvie	Professor of Medicine, Cardiologist	McMaster University, Hamilton Health Sciences
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Appendices

Appendix 1: Literature Search Strategies

Search date: September 23, 2012
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Cochrane Library; CRD

Q: Inotropic therapy for Heart Failure management
Limits: 2008-current; English
Filters: health technology assessments, systematic reviews, and meta-analyses

Database: Ovid MEDLINE(R) <1946 to September Week 2 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 21, 2012>, Embase <1980 to 2012 Week 38>

Search Strategy:

#	Searches	Results
1	exp Heart Failure/	325037
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.	256438
3	or/1-2	414505
4	Cardiotonic Agents/ use mesz	12513
5	Inotropic Agent/ use emez	7039
6	(inotrop* or cardiotrop* or cardio-trop*).mp.	53712
7	(((cardiac or heart or myocardial or myocardium) adj (stimulant? or stimulat*)) or ((cardioactiv* or cardioprotect*) adj (agent? or substance?)) or cardiotonic*).ti.	3383
8	Dobutamine/	22774
9	(Dobutrex or dobutamin* or posiject or dobuject or dobucor or oxiken).ti,ab.	16356
10	(butamine or cardiject or dobumine or dobutamide or inotres or inotrex or inotrope or levdobutamine or levo-dobutamine).ti,ab.	1906
11	Milrinone/	6067
12	(milrinone or corotrop? or primacor or coritrope or corotrop? or corotrope or wincardin).ti,ab.	3301
13	Nitroprusside/ use mesz	10972
14	Nitroprusside Sodium/ use emez	22936
15	(nipride or nitroferricyanide or nitroprusside or nipruton or nitroprussiat? or ketostix or cyanonitrosylferrate or naniprus or nitropress or nitriate).ti,ab.	31274
16	(nipruss or nitan or nitrocyanoferrate or nitroferricyanide or nitroprusiato or nitroprussiat or nitrosylpentacyanoferrate).ti,ab.	55
17	or/4-16	127648
18	Meta Analysis.pt.	36333
19	Meta Analysis/ use emez	65909
20	Systematic Review/ use emez	53173
21	exp Technology Assessment, Biomedical/ use mesz	8837
22	Biomedical Technology Assessment/ use emez	11380
23	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	289646
24	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	3629
25	or/18-24	349304
26	3 and 17 and 25	467
27	limit 26 to english language	421
28	limit 27 to yr="2008 -Current"	132
29	remove duplicates from 28	117

.

Cochrane Library

Line #	Terms	Results
#1	MeSH descriptor: [Heart Failure] explode all trees	4860
#2	((cardia? or heart) next (decompensation or failure or incompetence or insufficiency)) or cardiac stand still or ((coronary or myocardial) next (failure or insufficiency)):ti,ab,kw (Word variations have been searched)	9323
#3	MeSH descriptor: [Cardiotonic Agents] this term only	871
#4	inotrop* or cardiotrop* or cardio-trop* (Word variations have been searched)	1484
#5	((cardiac or heart or myocardial or myocardium) next (stimulant? or stimulat*)) or ((cardioactiv* or cardioprotect*) next (agent? or substance?)) or cardiotonic* or cartonic*:ti (Word variations have been searched)	24
#6	MeSH descriptor: [Dobutamine] explode all trees	442
#7	Dobutrex or dobutamin* or posiject or dobuject or dobucor or oxiken:ti,ab,kw (Word variations have been searched)	738
#8	butamine or cardiject or dobumine or dobutamide or inotres or inotrex or inotrope or levdobutamine or levo-dobutamine:ti,ab,kw (Word variations have been searched)	111
#9	MeSH descriptor: [Milrinone] this term only	128
#10	milrinone or corotrop? or primacor or coritrope or corotrop? or corotrope or wincardin:ti,ab,kw (Word variations have been searched)	186
#11	MeSH descriptor: [Nitroprusside] explode all trees	488
#12	nipride or nitroferricyanide or nitroprusside or nipruton or nitroprussiat? or ketostix or cyanonitrosylferrate or naniprus or nitropress or nitriate:ti,ab,kw (Word variations have been searched)	878
#13	nipruss or nitan or nitrocyanoferrate or nitroferricyanide or nitroprusiato or nitroprussiat or nitrosylpentacyanoferrate:ti,ab,kw (Word variations have been searched)	3
#14	Enter terms for search(#1 or #2) and (#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)	106 from 2008 to 2012

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES	510
2	((((cardia? or heart) adj (decompensation or failure or incompetence or insufficiency)) or cardiac stand still or ((coronary or myocardial) adj (failure or insufficiency))):TI	308
3	#1 OR #2	543
4	MeSH DESCRIPTOR Cardiotonic Agents	33
5	(inotrop* OR cardiotrop* OR cardio-trop*) OR (((cardiac OR heart OR myocardial OR myocardium) ADJ (stimulant? OR stimulat*)) OR ((cardioactiv* OR cardioprotect*) ADJ (agent? OR substance?)) OR cardiotonic* OR cartonic):TI	86
6	MeSH DESCRIPTOR Dobutamine EXPLODE ALL TREES	13
7	(Dobutrex OR dobutamin* OR posiject OR dobuject OR dobucor OR oxiken OR butamine OR cardiject OR dobumine OR dobutamide OR inotres OR inotrex OR inotrope OR levdobutamine OR levo-dobutamine):TI	9
8	MeSH DESCRIPTOR Milrinone EXPLODE ALL TREES	3
9	(milrinone OR corotrop? OR primacor OR coritrope OR corotrop? OR corotrope OR wincardin):TI	5
10	MeSH DESCRIPTOR Nitroprusside EXPLODE ALL TREES	5
11	(nipride OR nitroferricyanide OR nitroprusside OR nipruton OR nitroprussiat? OR ketostix OR cyanonitrosylferrate OR naniprus OR nitropress OR nitriate):TI OR (nipruss OR nitan OR nitrocyanoferrate OR nitroferricyanide OR nitroprusiato OR nitroprussiat OR nitrosylpentacyanoferrate):TI	1
12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	123
13	#3 AND #12	26

Appendix 2: GRADE Tables

Table A1: GRADE Evidence Profile for Mortality in HF Patients Administered Dobutamine or Placebo in Hospital

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Mortality (all-cause, during treatment or follow-up time)							
3 (RCTs)	Very serious limitations (–2)[a]	No serious limitations[b]	No serious limitations	Serious limitations (–1)[c]	Undetected[d]	None	⊕ Very Low

Abbreviation: HF, heart failure; RCT, randomized controlled trial.

[a]The reporting quality of studies was lacking overall. No studies reported how the randomization sequence was generated or on how allocation to groups was concealed. One study (14) reported on loss to follow-up. No studies reported whether the primary results were based on intention-to-treat or per-protocol analysis. Two studies reported on at least 1 specific group being blinded: in 1 (16) both patients and care providers were blinded, and in the other (14) patients and care providers were blinded only for placebo—dobutamine was open-label. Bias due to lack of blinding is unlikely in the ascertainment of mortality as an outcome; however, the length of follow-up (range 48 hours to 4 months; mean 1.67 months) may not have been ideal to assess mortality, and all-cause mortality was reported as a direct attribution of death to the inotropic infusion.

[b]All effect estimates were in the same direction, there was no large variation in point estimates, and all findings were nonsignificant. Heterogeneity was not a concern $X^2 = 0.35$ ($P = 0.84$); $I^2 = 0\%$.

[c]There were small sample sizes and very small numbers of events in all RCTs and the meta-analysis. Adequate power is a concern, and the optimal information size criterion was not met.

[d]Publication bias is unlikely to be detected with only 3 RCTs. Of interest, 2 studies disclosed their source of support, with 1 (14) supported by Merrell Dow Pharmaceuticals Inc., and another (16) supported by the German Research Foundation (Deutsche Forschungsgemeinschaft; DFG). Multiple funding sources suggest that publication bias is not likely.

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