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Ultrafiltration in Heart Failure: A Rapid Review

Health Quality Ontario

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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 must be completed in a 2- to 4-week time frame. 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.

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. 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
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
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

The objective of this rapid review was to assess the effectiveness of ultrafiltration in patients with acute heart failure.

Clinical Need and Target Population

Heart failure is a complex syndrome, in which abnormal heart function is responsible for the failure of the heart to pump blood at the necessary rate for metabolizing tissues. (1) Common symptoms include shortness of breath; cough; sudden weight gain; bloating; loss of energy; loss or change in appetite; increased swelling of the ankles, feet, legs, sacrum (base of spine), or abdomen; and increased urination at night. (1) Leading causes of heart failure are coronary artery disease, hypertension, diabetes, heart valve disease, obesity, and excessive use of alcohol or drugs. (3)

Technology/Technique

Ultrafiltration is an alternative treatment for patients with acute heart failure who are not responding sufficiently to diuretic therapy. (4) An ultrafiltration device creates "a hydrostatic pressure gradient [that] triggers the mechanical removal of fluid across a filter membrane and isotonic plasma water is separated from blood without affecting serum electrolytes and other solutes." (4) A number of ultrafiltration devices have been licenced by Health Canada.

Both the Canadian Cardiovascular Society and the American Heart Association have made recommendations about the use of ultrafiltration in patients with heart failure:

- Canadian Cardiovascular Society (2012): Patients with persistent congestion despite diuretic therapy, with or without impaired renal function, may, under experienced supervision, receive continuous venovenous ultrafiltration. (5)
- American Heart Association (2009): Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy. (6)

Rapid Review

Research Question

What is the effectiveness of ultrafiltration compared to usual care in patients with acute heart failure?

Research Methods

Literature Search

Search Strategy

A literature search was performed on July 22, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, and EBM Reviews, for studies published from January 1, 2009, to July 22, 2014. (Appendix 1 provides details of the search strategies.) 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 publications
- published between January 1, 2009, and July 22, 2014
- systematic reviews and meta-analyses
- patients with acute heart failure admitted to hospital
- comparison of ultrafiltration to diuretic therapy

Exclusion Criteria

- non-systematic reviews
- patients whose main diagnosis was not heart failure

Outcomes of Interest

- fluid removal/weight loss
- adverse events

Expert Panel

In July 2014, the Episode of Care Expert Advisory Panel to Inform Quality-Based Funding for Congestive Heart Failure was reconvened to update the handbook. Members of the panel included health care providers, health care administrators and personnel from the Ministry of Health and Long-Term Care.

The role of the Expert Advisory Panel was to review the recommendations and the episode-of-care pathway they had developed in 2012 on acute heart failure. They were asked to identify any gaps in the original recommendations and confirm that the existing recommendations were still current and accurate. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of Expert Advisory Panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodological quality of systematic reviews. (7)

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (8) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials (RCTs) 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: the large magnitude of effect, the dose response gradient, and any residual confounding factors. (8) For more detailed information, please refer to the latest series of GRADE articles. (8)

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

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect.
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different.
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect.
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect.

Results of Rapid Review

The database search yielded 21 citations published between January 1, 2009, and July 22, 2014 (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.

One systematic review met the inclusion criteria. (9) Other systematic reviews were identified in the literature search, but the Wen et al review (9) was selected because of its high AMSTAR rating, recent publication date, and reporting of both outcomes of interest outlined above.

For each included study, the study design was identified and is summarized below in Table 1, a modified version of a hierarchy of study design by Goodman, 1996. (10)

Table 1: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCTs	
Systematic review of RCTs	1
Large RCT	
Small RCT	
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with non-contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	**1**

Abbreviations: RCT, randomized controlled trial

The 2013 systematic review by Wen et al (9) included 5 RCTs; the comparator group in all 5 was diuretic therapy.

Fluid Removal/Weight Loss

Three of the RCTs in the systematic review reported on fluid removal and weight loss. After 48 hours of treatment, there was a significantly higher rate of fluid removal ($P < 0.0001$) and weight loss ($P < 0.0002$) in patients receiving ultrafiltration than in those on diuretic therapy alone. The quality of the evidence for this outcome was low.

Adverse Events

The authors of the systematic review reported the results for a number of adverse events, including infection, renal function deterioration, cardiac arrest, anemia and hemorrhage, and worsening heart failure. Two RCTs in the systematic review reported on all of the adverse events reported. The authors of

the systematic review found no significant differences between ultrafiltration therapy and diuretic therapy for any of the adverse events reported. The quality of the evidence for this outcome was very low.

Limitations

The individual primary studies evaluated in the systematic review by Wen et al (9) were not critically appraised by Health Quality Ontario. Ultrafiltration is thought to be most potentially beneficial in patients who have not responded to diuretics, but it is unclear without looking at the individual reports whether the patients included in these studies had "failed" diuretic therapy prior to enrolling in the studies.

The duration of effect of ultrafiltration is unclear; Wen et al reported that after 48 hours of treatment, ultrafiltration led to significantly higher rates of fluid and weight loss, but it is not clear how long this difference is sustained. (9)

Wen et al acknowledged that their systematic review was based on a relatively small number of studies, and that data on hemodynamic parameters and adverse electrolytes were lacking. (9)

Conclusions

- Based on low quality evidence, there was a significant improvement in fluid removal and weight loss after 48 hours of treatment in patients with heart failure who received ultrafiltration compared to those who received diuretic therapy. However, the duration of effect was unclear.
- Based on very low quality evidence, there was no significant difference in the rate of adverse events in patients with heart failure who received ultrafiltration compared to those who received diuretic therapy.

Acknowledgements

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Kory Kingsbury	Cardiac Care Network	Chief Executive Officer

Appendices

Appendix 1: Literature Search Strategies

Search date: July 22, 2014
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, 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>, Ovid MEDLINE(R) <1946 to July Week 2 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 21, 2014>
Search Strategy:
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1 exp Heart Failure/ (92568)
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. (135768)
3 or/1-2 (162490)
4 exp Ultrafiltration/ (14721)
5 (ultrafiltrat* or ultra filtrat* or hemofiltrat*).mp. (23870)
6 or/4-5 (25135)
7 Meta Analysis.pt. (50365)
8 Meta-Analysis/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (72511)
9 (((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. (184826)
10 (meta analy* or metaanaly* or health technolog* assess*).mp. (133838)
11 or/7-10 (265019)
12 3 and 6 and 11 (29)
13 limit 12 to (english language and yr="2009 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained] (21)
14 remove duplicates from 13 (21)

Appendix 2: Evidence Quality Assessment

Table A1: AMSTAR Scores of Included Systematic Reviews

Author, Year	AMSTAR Score[a]	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
Wen et al, 2013 (9)	9/11	□	□	□	□	x	□	□	□	□	x	□

Abbreviation: AMSTAR, Assessment of Multiple Systematic Reviews.
[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al. (7)

Table A2: GRADE Evidence Profile for Comparison of Ultrafiltration and Diuretic Therapy

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Fluid Removal/Weight Loss							
3 (RCTs)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations	Likely (–1)[b]	None	⊕⊕ Low
Adverse Events							
2 (RCTs)	Serious limitations (–1)[a]	Serious limitations (–1)[c]	No serious limitations	No serious limitations	Likely (–1)[b]	None	⊕ Very Low

Abbreviation: RCT, randomized controlled trial.
[a]All of the studies had risk of bias limitations including allocation concealment, inconsistent blinding, and incomplete reporting of outcomes for all patients.
[b]Other systematic reviews on ultrafiltration have been published recently and have included more studies. The excluded studies are not listed.
[c]Inconsistencies in some of the adverse events reported. The studies were likely not powered to detect the differences in adverse events.

Table A3: Risk of Bias[a] Among Randomized Controlled Trials for the Comparison of Ultrafiltration and Diuretic Therapy

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Bart et al, 2005 (11)	Limitations[b]	No limitations	Limitations[c]	No limitations	No limitations
Costanzo et al, 2007 (12)	Limitations[b]	Limitations[d]	Limitations[c]	No limitations	No limitations
Rogers et al, 2008 (13)	Limitations[b]	Limitations[e]	Limitations[c]	No limitations	No limitations
Giglioli et al, 2011 (14)	Limitations[b]	Limitations[d]	Limitations[c]	No limitations	No limitations
Bart et al, 2012 (15)	Limitations[b]	Limitations[d]	Limitations[c]	No limitations	No limitations

[a]Risk of bias was taken directly from the systematic review by Wen et al (9); Health Quality Ontario did not conduct an additional critical appraisal.
[b]Unclear if allocation concealment was part of the study design.
[c]Incomplete accounting of patients.
[d]No blinding.
[e]Unclear if the study included blinding.

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