Effective Health Care

Inotropics for End-stage Heart Disease

Results of Topic Selection Process & Next Steps

The nominator, the American Academy of Hospice and Palliative Medicine (AAHPM), is interested in a new evidence review on the use of parenteral inotropic medications for patients with end-stage heart disease (ESHD) in home hospice care. Due to the large number of Americans living with heart failure, and the prevalence is projected to increase in the future, an evidence review may help demonstrate the value of inotropes in patients with ESHD and thus improve access to these therapies and potentially reduce suffering for these patients who are receiving hospice care.

Because limited original research addresses the nomination, a new review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Inotropics for End-stage Heart Disease (ESHD)

Nomination Date: 09/12/2018

Topic Brief Date: 01/12/2019

Authors
Laura Pincock

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

The prevalence of heart failure (HF) has continued to rise over time with the aging of the United States population. An estimated 6.2 million American adults ≥20 years of age had HF between 2013 and 2016 compared with an estimated 5.7 million between 2009 and 2012.[1] Many Americans prefer to spend the last weeks to months of their lives at home; however, repeated admissions near the end of life when patients are going through end-stage heart failure are common. Home hospice care provides the highest standard of end-of-life care and aims to minimize burdensome transfers to the inpatient setting, and to help patients realize the goal of remaining at home. However, heart failure guidelines do not specifically address inotrope management or decision-making at end-of-life.

Inotropic medications such as milrinone, dopamine, and dobutamine may be used for patients with advanced heart failure to palliate symptoms when other advanced therapies such as left-ventricular assist devices or cardiac surgery are not options.[2] However, the availability of inotropic infusions in the home setting is limited by high cost, lack of reimbursement, technical

complexity, and the need for strong caregiver support in the home. This may result in increasing readmissions for uncontrolled symptoms of advanced heart failure at the end-of-life.

There is little guidance on the risks and benefits of using inotropic medications and/or protocols for delivery in the hospice setting in patients with end-stage heart failure.[3,4] A 2019 survey indicated that hospice specialists report widely varied practice experiences for patients with heart failure receiving advanced therapies, including inotropes, with a low referral rate to palliative care or hospice.[4] A 2019 perspective published in the New England Journal of Medicine recently discussed several policy and systems-level changes that would facilitate the delivery of palliative inotropic medications for patients with heart failure.[5] Furthermore, a survey of hospice approaches has shown that just over half (57%) of the agencies surveyed could provide intravenous inotropic therapy.[6]

An evidence review may help demonstrate the value of inotropes in patients with ESHD and thus improve access to these therapies and potentially reduce suffering for patients with end-stage heart disease (ESHD) who are receiving hospice care.

Nominator and Stakeholder Engagement

The nominator, the American Academy of Hospice and Palliative Medicine (AAHPM), is interested in a new evidence review on the use of parenteral inotropic medications for patients with ESHD in home hospice care. Due to the large number of Americans living with heart failure, and the prevalence of HF is projected to increase in the future, AAHPM hopes that an evidence review of home inotrope infusions will help develop best practice policies for home health agencies, increase access to therapies, improve system management, and reduce burdensome hospital transfers for patients at the end of life. The nominator intends to use the report to inform guidelines for best practices for end of life care for ESHD patients.

Key Questions and PICOTS

The key questions for this nomination are:

1. How are inotropic medications being administered at home in hospice patients with ESHD?

2. What are the benefits and harms of inotropic medications in hospice patients with ESHD?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, outcomes, timing, and setting (PICOTS) of interest (Table 1).

Table 1. Key Questions and PICOTS

Key Questions	1. How are inotropic medications being administered at home in hospice patients with ESHD?	2. What are the benefits and harms of inotropic medications in hospice patients with ESHD?
Population	Hospice patients with ESHD	Hospice patients with ESHD
Interventions	Milrinone, dobutamine, or dopamine	Milrinone, dobutamine, or dopamine
Comparators	Usual care Inotropes Other care	Usual care Inotropes Other care

Key Questions	1. How are inotropic medications being administered at home in hospice patients with ESHD?	2. What are the benefits and harms of inotropic medications in hospice patients with ESHD?
Outcomes	• patient satisfaction • quality of life • improved care • reduced hospitalization • clinical outcomes • dyspnea score • pain score • patient fatigue • patient survival • caregiver burden • caregiver quality of life	• patient satisfaction • quality of life • improved care • reduced hospitalization • clinical outcomes • dyspnea score • pain score • patient fatigue • patient survival • caregiver burden • caregiver quality of life
Timing/Setting	Hospice	Hospice

Methods

We assessed the nomination "Inotropics for End-stage Heart Disease" for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last five years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.

Feasibility of New Evidence Review

We conducted a literature search in PubMed from January 2014 through January 2019. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

We reviewed all identified titles and abstracts for inclusion and classified identified studies by study design to assess the size and scope of a potential evidence review.

Results

See Appendix A for detailed assessments of all EPC selection criteria.

Appropriateness and Importance

This topic is both appropriate and important. This review potentially affects all patients who develop heart failure, a very large and growing proportion of the population.

Further assessment of key question 1 led to the conclusion that the majority of studies describing administration of inotropes were published over 10 years ago and are not specific to the home or hospice setting. The main interest lies in assessing the risks and benefits of home inotrope therapy in hospice patients with ESHD. Thus only key questions 2 was assessed further.

Desirability of New Review/Duplication

A new evidence review would not be duplicative of an existing evidence review. We found several general reviews of inotrope use in heart failure but they were not detailed on use in the hospice setting. We found two review articles of inotrope use in the home or hospice setting, but these did not appear to follow a rigorous systematic review methodology.

See Table 2, Duplication column for additional information.

Impact of a New Evidence Review

A new systematic review may have high impact. We also found two statements from a clinical professional society on advanced or end-stage heart failure that mention home continuous inotrope infusion and barriers.[13-14] However these were both consensus statements, and were based on a handful number of studies. The role of home inotropic infusion in patients with ESHD in hospice care is not clear.

Feasibility of a New Evidence Review

A new evidence review is not feasible. The majority of clinical studies describing administration of inotropes and the outcomes were published over 10 years ago and are not specific to the home or hospice setting. Our targeted literature search identified four retrospective studies or case studies of inotrope use in ESHD patients in hospice care.

See Table 2, Feasibility column for additional information

Table 2. Key Questions and Results for Duplication

Key Question	Duplication (1/2014-1/2019)	Feasibility (1/2014-1/2019)
KQ #2 (benefits and harms of home inotropic therapy)	Total number of identified systematic reviews: 7 • General treatment: 5 [3 7 8 9 10] • Hospice or home specific: 2 [11 12]	Size/scope of review Relevant Studies Identified: 4 o RCT: 0 o Case Study :1 [2] o Retrospective: 3 [15 16 17] Clinicaltrials.gov: 0

Abbreviations: KQ=Key Question; RCT=randomized controlled trial

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would not be duplicative of an existing product.
- Impact: A new systematic review has high potential.
- Feasibility: A new review is not feasible as there is limited primary research evaluating intotropic administration in the hospice/home care setting. The primary studies are all over 10 years old or are not specific to the home or hospice setting.

References

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019 Mar 5;139(10):e56-e528. doi: 10.1161/CIR.0000000000000659. PMID: 30700139.

2. Malotte K, Saguros A, Groninger H. Continuous Cardiac Inotropes in Patients With End-Stage Heart Failure: An Evolving Experience. J Pain Symptom Manage. 2018 Jan;55(1):159-63. doi: 10.1016/j.jpainsymman.2017.09.026. PMID: 29030210.

3. Francis GS, Bartos JA, Adatya S. Inotropes. J Am Coll Cardiol. 2014 May 27;63(20):2069-78. doi: 10.1016/j.jacc.2014.01.016. PMID: 24530672.

4. Groninger H, Gilhuly D, Walker KA. Getting to the Heart of the Matter: A Regional Survey of Current Hospice Practices Caring for Patients With Heart Failure Receiving Advanced Therapies. Am J Hosp Palliat Care. 2019 Jan;36(1):55-9. doi: 10.1177/1049909118789338. PMID: 30037272.

5. Warraich HJ, Rogers JG, Dunlay SM, et al. Top Ten Tips for Palliative Care Clinicians Caring for Heart Failure Patients. J Palliat Med. 2018 Nov;21(11):1646-50. doi: 10.1089/jpm.2018.0453. PMID: 30311835.

6. Lum HD, Horney C, Koets D, et al. Availability of Heart Failure Medications in Hospice Care. Am J Hosp Palliat Care. 2016 Dec;33(10):924-8. doi: 10.1177/1049909115603689. PMID: 26329799.

7. Habal MV, Garan AR. Long-term management of end-stage heart failure. Best Pract Res Clin Anaesthesiol. 2017 Jun;31(2):153-66. doi: 10.1016/j.bpa.2017.07.003. PMID: 29110789.

8. Ginwalla M, Tofovic DS. Current Status of Inotropes in Heart Failure. Heart Fail Clin. 2018 Oct;14(4):601-16. doi: 10.1016/j.hfc.2018.06.010. PMID: 30266368.

9. Katz JN, Waters SB, Hollis IB, et al. Advanced therapies for end-stage heart failure. Curr Cardiol Rev. 2015;11(1):63-72. PMID: 24251460.

10. Tariq S, Aronow WS. Use of Inotropic Agents in Treatment of Systolic Heart Failure. Int J Mol Sci. 2015 Dec 4;16(12):29060-8. doi: 10.3390/ijms161226147. PMID: 26690127.

11. Ciuksza MS, Hebert R, Sokos G. Use of home inotropes in patients near the end of life #283. J Palliat Med. 2014 Oct;17(10):1178-80. doi: 10.1089/jpm.2014.9403. PMID: 25302543.

12. Ginwalla M. Home Inotropes and Other Palliative Care. Heart Fail Clin. 2016 Jul;12(3):437-48. doi: 10.1016/j.hfc.2016.03.005. PMID: 27371519.

13. Whellan DJ, Goodlin SJ, Dickinson MG, et al. End-of-life care in patients with heart failure. J Card Fail. 2014 Feb;20(2):121-34. doi: 10.1016/j.cardfail.2013.12.003. PMID: 24556532.

14. Fang JC, Ewald GA, Allen LA, et al. Advanced (stage D) heart failure: a statement from the Heart Failure Society of America Guidelines Committee. J Card Fail. 2015 Jun;21(6):519-34. doi: 10.1016/j.cardfail.2015.04.013. PMID: 25953697.

15. Chernomordik F, Freimark D, Arad M, et al. Quality of life and long-term mortality in patients with advanced chronic heart failure treated with intermittent low-dose intravenous inotropes in an outpatient setting. ESC Heart Fail. 2017 May;4(2):122-9. doi: 10.1002/ehf2.12114. PMID: 28451448.

16. Martens P, Vercammen J, Ceyssens W, et al. Effects of intravenous home dobutamine in palliative end-stage heart failure on quality of life, heart failure hospitalization, and cost expenditure. ESC Heart Fail. 2018 Aug;5(4):562-9. doi: 10.1002/ehf2.12248. PMID: 29341466.
17. Hashim T, Sanam K, Revilla-Martinez M, et al. Clinical Characteristics and Outcomes of Intravenous Inotropic Therapy in Advanced Heart Failure. Circ Heart Fail. 2015 Sep;8(5):880-6. doi: 10.1161/CIRCHEARTFAILURE.114.001778. PMID: 26179184.
18. Go AS, Mozaffarian D, Roger VL, et al. Heart Disease and Stroke Statistics--2013 Update: A report from the American Heart Association. Circulation. 2013;217:e1-e240.
19. Teno JM, Gozalo PI, Bynum JPW, et al. Change in End-of-Life Care for Medicare Beneficiaries: Site of Death, Place of Care and Health Care Transitions in 2000, 2005, and 2009. JAMA. 2013;309(5):470-7.
20. Chuang E, Kim G, Blank AE, et al. 30-Day Readmission Rates in Patients Admitted for Heart Failure Exacerbation with and without Palliative Care Consultation: A Retrospective Cohort Study. J Palliat Med. 2016 Nov 08. doi: 10.1089/jpm.2016.0305. PMID: 27824514.
21. Francis GS, Bartos JA, Adatya S. Inotropes. Journal of the American College of Cardiology. 2014 2014/05/27/;63(20):2069-78. doi: https://doi.org/10.1016/j.jacc.2014.01.016.
22. Lopez-Candales AL, Carron C, Schwartz J. Need for hospice and palliative care services in patients with end-stage heart failure treated with intermittent infusion of inotropes. Clin Cardiol. 2004 Jan;27(1):23-8. doi: 10.1002/clc.4960270107. PMID: 14743852.

Appendix A. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Potentially affects all patients with heart disease, a very large and growing proportion of the population.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, costs can be high for home inotropic support but this may be offset by minimizing hospital admissions and helping the patients stay home.
2c. Represents important uncertainty for decision makers	Yes
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	No, it would not be redundant. We found two narrative reviews that addressed the use of inotropes in hospice setting. However one review was too old to be considered current (published in 2015); and both reviews did not appear to follow a rigorous systematic review methodology.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. We found a statement from the Heart Failure Society that outlined criteria for home inotrope infusion therapy. The evidence base was comprised of a handful of studies. However this statement was based on consensus.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	N/A
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	A systematic review is not feasible due to a lack of primary research studies. We found four studies addressing questions 2. Most primary studies are over 10 years old.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question;

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
CADTH (Canadian Agency for Drugs and Technologies in Health) https://www.cadth.ca/
DoPHER (Database of promoting health effectiveness reviews) http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9
ECRI institute https://www.ecri.org/Pages/default.aspx
Campbell Collaboration http://www.campbellcollaboration.org/
McMaster Health System Evidence https://www.healthsystemsevidence.org/
Robert Wood Johnson http://www.rwjf.org/
Systematic Reviews (Journal) : protocols and reviews http://systematicreviewsjournal.biomedcentral.com/
UBC Centre for Health Services and Policy Research http://chspr.ubc.ca/
WHO Health Evidence Network http://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/health-evidence-network-hen
CINAHL (EBSCO)

Appendix C. Search Strategy & Results (Feasibility)

((((((((((Inotropes[Title/Abstract]) OR Inotropics[Title/Abstract]) AND hospice) OR palliative)) AND heart failure[text word]AND "last 5 years"[PDat] AND Humans[Mesh])) AND "last 5 years"[PDat]) AND "last 5 years"[PDat] AND Humans[Mesh])):PubMed.gov (January 12, 2019)

460 studies found. 467studies reviewed. Additional studies added from bibliographies of studies and nominator recommendation

Clinicaltrials.gov (January 10, 2018)

https://clinicaltrials.gov/ct2/results?cond=End-stage+Heart+Failure

37 Studies found for: End Stage Heart Failure

https://clinicaltrials.gov/ct2/results?cond=End-stage+Heart+Disease

79 Studies found for: end-stage heart disease