

## Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

Medwave 2016;16(2):e6426 doi: 10.5867/medwave.2016.6426

# Continuous infusion or bolus injection of loop diuretics for congestive heart failure?

**Authors:** Patricio Zepeda[1,3], Carmen Rain[1,3], Paola Sepúlveda[1,2,3]

### Affiliation:

[1] Programa de Salud Basada en Evidencia, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

[2] Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

[3] Proyecto Epistemonikos, Santiago, Chile

**E-mail:** [pasepulveda@med.puc.cl](mailto:pasepulveda@med.puc.cl)

**Citation:** Zepeda P, Rain C, Sepúlveda P. Continuous infusion or bolus injection of loop diuretics for congestive heart failure?. *Medwave* 2016;16(2):e6426 doi: 10.5867/medwave.2016.6426

**Publication date:** 22/4/2016

## Abstract

Loop diuretics are widely used in acute heart failure. However, there is controversy about the superiority of continuous infusion over bolus administration. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified four systematic reviews including 11 pertinent randomized controlled trials overall. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded continuous administration of loop diuretics probably reduces mortality and length of stay compared to intermittent administration in patients with acute heart failure.

### Problem

The management of patients with acute heart failure is largely based on the use of loop diuretics. However, they may be administered as intermittent bolus or continuous infusion.

While bolus administration of furosemide is associated with lower costs, it could increase adverse effects as a consequence of changes in volume which would increase plasma concentration of the drug. Moreover, high doses administered intermittently may produce acute tolerance to diuretics by compensatory renal retention after their effect has subsided. Continuous administration of furosemide has been proposed as a solution to these problems but there is controversy about the clinical effects of both approaches.

### Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

### Key messages

- Continuous administration of loop diuretics probably reduces mortality and length of stay compared to intermittent administration in patients with acute heart failure.
- Risk/benefit and cost/benefit probably favor continuous administration.

### About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found four systematic reviews [1],[2],[3],[4], including 11 randomized controlled trials reported in 12 articles [5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16].
What types of patients were included	All studies included adults with acute heart failure with an average age ranging from 53 to 74 years.  Four studies included patients with functional capacity between III and IV [8],[11],[15], two studies included patients with functional capacity between II and III [5],[10] while the remaining studies did not describe functional capacity.  Regarding renal function, all studies included patients with creatinine $\leq 2$ mg/dL.
What types of interventions were included	Regarding continuous infusion of loop diuretics, one study used torsemide [10] and the remaining ten used furosemide; of these, four [7],[11],[14],[15] used a loading dose of 40 mg followed by continuous infusion at variable rate. One study did not report doses and only reported it was determined by the attending physician.  All studies compared against bolus injection. Two studies [8],[10] administered bolus injection once a day, seven [5],[6],[7],[9],[11],[14],[15] twice a day and one used three boluses per day. Daily doses of furosemide ranged from 120 mg/day to 2000 mg/day in the continuous infusion group and from 90 mg/day to 2000 mg/day in the bolus injection group.
What types of outcomes were measured	All-cause mortality, cardiac death, length of stay, electrolyte disturbances, changes in serum creatinine, adverse effects (hair loss and tinnitus), body weight, urine output, and urinary sodium excretion.

### Summary of findings

Information on the effects of continuous loop diuretics compared to bolus injection for congestive heart failure is based on 11 randomized trials including 622 patients. Four studies reported overall mortality and four studies reported length of stay.

- Continuous administration of loop diuretics probably reduces mortality compared to intermittent administration in patients with acute heart failure. The certainty of the evidence is moderate.
- Continuous administration of loop diuretics probably reduces length of stay compared to intermittent administration in patients with acute heart failure. The certainty of the evidence is moderate.

Continuous infusion versus bolus injection of loop diuretics for acute heart failure				
<b>Patients</b>		Acute heart failure		
<b>Intervention</b>		Continuous infusion of loop diuretics		
<b>Comparison</b>		Bolus injection of loop diuretics		
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH bolus injection	WITH continuous infusion		
	Difference: patients per 1000			
<b>All cause mortality</b>	260 per 1000	179 per 1000	RR 0.69 (0.52 to 0.92)	⊕⊕⊕ <sup>1</sup> Moderate
	Difference: 81 patients less per 1000 (Margin of error: 21 to 125 less)			
<b>Hospital length of stay (days)</b>	7 days	5.41 days	MD -1.59 (-2.23 to -0.96)	⊕⊕⊕ <sup>1</sup> Moderate
	Difference: 1.59 less (Margin of error: 0.96 to 2.23 less)			

Margin of error = 95% confidence interval (CI).  
 RR: Relative risk.  
 MD: Mean difference.  
 GRADE: evidence grades of the GRADE Working Group (see later in this article).

\* The risks **WITH bolus injection** are based on the risk in the control group of the studies for mortality, and an approximate average risk in the control group for hospital stay. The risk **WITH continuous infusion** (and its margin of error) is calculated from the relative effect (and its margin of error).

<sup>1</sup> The certainty of the evidence was downgraded in one level because studies have serious limitations, mainly for lack of blinding.

### About the certainty of the evidence (GRADE)\*

⊕⊕⊕⊕

**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕○

**Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕○○

**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕○○○

**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

\*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

---

## Other considerations for decision-making

---

### To whom this evidence does and does not apply

---

- The information in this summary applies to adult patients with decompensated acute heart failure from any cause, with renal function close to normality (serum creatinine  $\leq 2$  mg/dL)
  - It is important to note in clinical practice is frequent to use larger boluses of loop diuretics than described in most studies.
- 

### About the outcomes included in this summary

---

- The outcomes presented are those considered critical for decision making in the opinion of the authors of the summary and coincide with those reported by the systematic reviews identified [1],[2],[3],[4].
- 

### Balance between benefits and risks, and certainty of the evidence

---

- Continuous infusion of furosemide confers a benefit on mortality and length of stay with moderate certainty. While there is a greater degree of uncertainty concerning some outcomes as hypokalemia and hypomagnesemia (RR 0.78 [95% CI 0.39 to 1.56], very low certainty of the evidence) or increase in serum creatinine (MD -0.45 [95% CI -0.42 to -0.47]), these outcomes are relatively less important than the former, so the balance is clearly in favor of using continuous infusion.
- 

### Resource considerations

---

- The total amount of diuretics used in both groups of the studies analyzed was similar.
  - Since it is a relatively low-cost intervention, and has an impact on mortality and length of stay, it would be a cost/effective intervention.
  - In relation to the direct cost, while some cost items may vary between the two options (cost of the pump and staff needed to use it in continuous infusion; cost of fluids and personnel to administer the bolus for intermittent injection), probably these differences are of little relevance for decision-making. Moreover, there may be savings from reduced length of stay and extra costs resulting from adverse effects.
- 

### Differences between this summary and other sources

---

- The systematic reviews identified disagree in their conclusions regarding the effect on mortality and length of stay. Our summary is consistent with one of them [3], while the other two [1],[2] conclude there are no differences.
  - Two of the three main clinical guidelines on this topic [17],[18],[19],[20] address the question of this summary, presenting recommendations discordant with our findings. One [19] mentions it is not clear what is the optimal form of administration, and there might be no difference between both alternatives. While in the other guideline [20] both forms of administration are recommended indistinctly.
- 

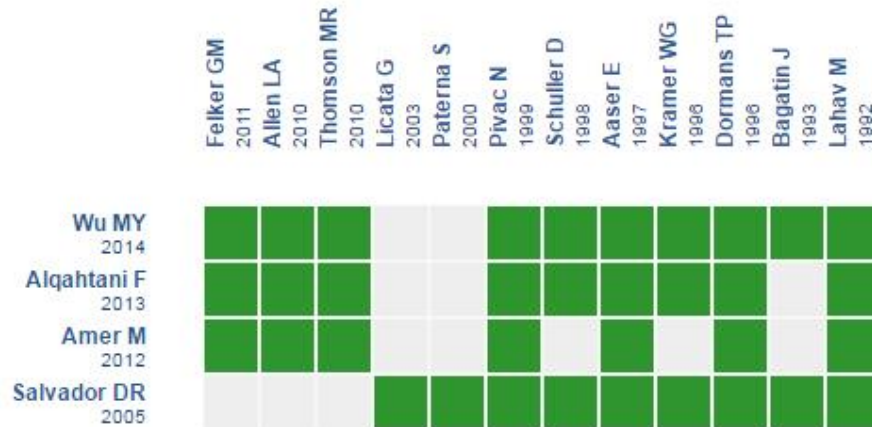
### Could this evidence change in the future?

---

- The likelihood of future evidence changing the conclusions of this summary is low due to the certainty of the evidence.
  - We did not identify ongoing studies that may increase the certainty of this evidence in the future.
-

## How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.

The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.

The rows represent systematic reviews that share at least one primary study, and columns display the studies.

The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version** [Continuous infusion versus bolus injection of loop diuretics for heart failure](#)

## Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here <http://dx.doi.org/10.5867/medwave.2014.06.5997>.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database ([www.epistemonikos.org](http://www.epistemonikos.org)).

These summaries follow a rigorous process of internal peer review.

## Conflicts of interest

The authors do not have relevant interests to declare.

## Referencias

1. Alqahtani F, Koulouridis I, Susantitaphong P, Dahal K, Jaber BL. A meta-analysis of continuous vs intermittent infusion of loop diuretics in hospitalized patients. *J Crit Care.* 2014 Feb;29(1):10-7. | [CrossRef](#) | [PubMed](#) |
2. Wu MY, Chang NC, Su CL, Hsu YH, Chen TW, Lin YF, et al. Loop diuretic strategies in patients with acute decompensated heart failure: a meta-analysis of randomized controlled trials. *J Crit Care.* 2014 Feb;29(1):2-9. | [CrossRef](#) | [PubMed](#) |
3. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane Database Syst Rev.* 2005 Jul 20;(3):CD003178. | [PubMed](#) |
4. Amer M, Adomaityte J, Qayyum R. Continuous infusion versus intermittent bolus furosemide in ADHF: an updated meta-analysis of randomized control trials. *J Hosp Med.* 2012 Mar;7(3):270-5. | [CrossRef](#) | [PubMed](#) |
5. Aaser E, Gullestad L, Tølløfsrud S, Lundberg J, Hall C, Djøseland O, et al. Effect of bolus injection versus

- continuous infusion of furosemide on diuresis and neurohormonal activation in patients with severe congestive heart failure. *Scand J Clin Lab Invest.* 1997 Jul;57(4):361-7 | [PubMed](#) |
6. Allen LA, Turer AT, Dewald T, Stough WG, Cotter G, O'Connor CM. Continuous versus bolus dosing of Furosemide for patients hospitalized for heart failure. *Am J Cardiol.* 2010 Jun 15;105(12):1794- | [CrossRef](#) | [PubMed](#) |
  7. Bagatin J, Sardelic S, Gancevic I. Diuretic efficiency of furosemide in continuous intravenous infusion vs. bolus injection in congestive heart failure: results of a pilot study. *Pharmaca.* 1993;31:279-86.
  8. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol.* 1996 Aug;28(2):376-82. | [PubMed](#) |
  9. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med.* 2011 Mar 3;364(9):797-805. | [CrossRef](#) | [PubMed](#) |
  10. Kramer WG, Smith WB, Ferguson J, Serpas T, Grant AG 3rd, Black PK, et al. Pharmacodynamics of torsemide administered as an intravenous injection and as a continuous infusion to patients with congestive heart failure. *J Clin Pharmacol.* 1996 Mar;36(3):265-70. | [PubMed](#) |
  11. Lahav M, Regev A, Ra'anani P, Theodor E. Intermittent administration of furosemide vs continuous infusion preceded by a loading dose for congestive heart failure. *Chest.* 1992 Sep;102(3):725-31. | [PubMed](#) |
  12. Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J.* 2003 Mar;145(3):459-66. | [PubMed](#) |
  13. Paterna S, Di Pasquale P, Parrinello G, Amato P, Cardinale A, Follone G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail.* 2000 Sep;2(3):305-13. | [PubMed](#) |
  14. Pivac N, Rumboldt Z, Sardelic S, Bagatin J, Polić S, Ljutić D, et al. Diuretic effects of furosemide infusion versus bolus injection in congestive heart failure. *Int J Clin Pharmacol Res.* 1998;18(3):121-8. | [PubMed](#) |
  15. Schuller D, Lynch JP, Fine D. Protocol-guided diuretic management: comparison of furosemide by continuous infusion and intermittent bolus. *Crit Care Med.* 1997 Dec;25(12):1969-75. | [PubMed](#) |
  16. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB. Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. *J Card Fail.* 2010 Mar;16(3):188-93. | [CrossRef](#) | [PubMed](#) |
  17. Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail.* 2010 Jun;16(6):e1-194. | [CrossRef](#) | [PubMed](#) |
  18. Moe GW, Ezekowitz JA, O'Meara E, Lepage S, Howlett JG, Fries S, et al. The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update: anemia, biomarkers, and recent therapeutic trial implications. *Can J Cardiol.* 2015 Jan;31(1):3-16. | [CrossRef](#) | [PubMed](#) |
  19. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2012 Aug;14(8):803-69. | [CrossRef](#) | [PubMed](#) |
  20. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013 Oct 15;62(16):e147-239. | [CrossRef](#) | [PubMed](#) |

**Author address:**

[1] Facultad de Medicina  
Pontificia Universidad Católica de Chile  
Lira 63  
Santiago Centro  
Chile



Esta obra de Medwave está bajo una licencia Creative Commons Atribución-No Comercial 3.0 Unported. Esta licencia permite el uso, distribución y reproducción del artículo en cualquier medio, siempre y cuando se otorgue el crédito correspondiente al autor del artículo y al medio en que se publica, en este caso, Medwave.