

Does furosemide decrease morbidity or mortality for patients with diastolic or systolic dysfunction?

■ Evidence-Based Answer

No large-scale randomized, placebo-controlled trials evaluate furosemide's effect on mortality and long-term morbidity in diastolic or systolic dysfunction. In short-term studies, furosemide reduces edema, reduces hospitalizations, and improves exercise capacity in the setting of systolic dysfunction (strength of recommendation [SOR]: **B**, based upon low-quality randomized controlled trials). Furosemide and other diuretics reduce symptomatic volume overload in diastolic and systolic dysfunction (SOR: **C**, based on expert opinion).

There is potential morbidity with the use of high-dose loop diuretics (volume contraction, electrolyte disturbances, and neuroendocrine activation).¹⁻³ Use of high-dose loop diuretics for systolic dysfunction is associated with increased mortality, sudden death, and pump failure death (SOR: **B**, based on retrospective analyses of large-scale randomized controlled trials). However, diuretic resistance or disease severity may explain these latter findings.

■ Evidence Summary

Faris et al⁴ conducted a meta-analysis of randomized controlled trials that used diuretics (peritane, furosemide, furosemide-hydrochlorothiazide) in congestive heart failure (**TABLE**).⁴ Of the 18 trials, 8 were placebo-controlled and 10 used active controls (diuretics vs angiotensin-converting enzyme [ACE] inhibitors, digoxin, or ibopamine, a dopamine agonist). Three placebo-controlled trials (N=221) showed an absolute risk reduction in death of 8% in diuretic-treated patients (number needed to treat [NNT]=12.5). Four placebo-controlled trials (N=448) showed a significantly lower rate of admissions for worsening failure among diuretic-treated patients (NNT=8.5), and 4 of the active-controlled trials (N=150) showed a nonsignificant trend toward decreased admissions. Six active-controlled studies (N=174) showed significantly increased exercise capacity for patients on diuretics. One of these

latter trials also assessed quality of life, edema, and New York Heart Association (NYHA) class, and demonstrated no change in these outcomes in the treatment and placebo groups.⁵

The studies used in this meta-analysis had numerous shortcomings: the individual trials had small numbers of patients (N=14-139), short follow-up periods (typically 4-8 weeks), and inadequate statistical power to clearly demonstrate morbidity/mortality reductions. There was significant heterogeneity between studies. Crossover studies were included, some studies did not clearly report masking and assessment of outcome measures, and assessment of study validity was not clear. Studies employed a variety of diuretic types and doses, used different controls, and did not clarify whether patients' congestive heart failure was caused primarily by diastolic or systolic dysfunction.

It is worth noting that diuretic use also carries some risk. One large retrospective study evaluated 6796 patients using potassium-sparing diuretics vs non-potassium-sparing diuretics in the Studies of Left Ventricular Dysfunction (SOLVD) trial.⁶ Rates of hospitalization or death from worsening congestive heart failure were significantly higher in the non-potassium-sparing diuretic population than in the nondiuretic population (relative risk [RR]=1.31, 95% confidence interval [CI], 1.09-1.57; number needed to harm=5.78). This increased risk was not found for patients taking potassium-sparing diuretics (RR=0.99; 95% CI, 0.76-1.30).

Another retrospective study of SOLVD patients found a significant and independent association with increased risk of arrhythmic death among patients taking non-potassium-sparing diuretics (RR=1.33; 95% CI, 1.05-1.69).⁷

A retrospective study of 1153 patients with NYHA Class III to IV heart failure, who were enrolled in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE), found high diuretic doses to be independently associated with mortality (adjusted hazard ratio [HR]=1.37; $P=.004$), sudden death (HR=1.39; $P=.042$), and pump failure death (HR=1.51; $P=.034$).⁸

The authors caution that there is no proof of causation between furosemide and death; diuretic resistance may explain the poor outcomes, or the use of loop diuretics at high doses may be proxy of more severe illness, and thus poorer outcome.

TABLE

Clinical effects of diuretics in congestive heart failure

OUTCOME	TRIAL DESCRIPTION	N	RESULTS (REPORTED AS OR)	95% CI	P VALUE	NNT
Death	3 placebo-controlled	221	0.25	0.07–0.84	.03	12.5
Admissions	4 placebo-controlled	448	0.31	0.15–0.62	.001	8.5
	4 active-controlled	150	0.34	0.10–1.21	.10	12.8
Exercise capacity	6 active-controlled	174	0.37	0.10–0.64	.007	*

*Unable to calculate NNT due to lack of uniform reporting of exercise times.
OR, odds ratio; CI, confidence interval; NNT, number needed to treat.
Source: Faris et al, *Int J Cardiol* 2002.⁴

Recommendations from Others

The American College of Cardiology recommends using diuretics in the setting of left ventricular systolic dysfunction and fluid retention (level of evidence [LOE]: A), and recommends using diuretics in diastolic dysfunction to control pulmonary congestion and peripheral edema (LOE: C).⁹

The European Society of Cardiology notes that no randomized controlled trials have assessed survival effects of diuretics in congestive heart failure, but recommends using diuretics for symptomatic treatment of volume overload (LOE: A). This society also cites evidence that diuretic use improves exercise tolerance (LOE: B). They recommend that diuretics be used always in addition to an ACE inhibitor, that loop diuretics be used if symptoms are more than mild and if glomerular filtration rate (GFR) <30 cc/min, and that thiazide diuretics can be used with loop diuretics for synergistic effects in severe congestive heart failure.¹⁰

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Clinical Commentary
Helpful in the acute setting, diuretics shouldn't be used alone chronically

Furosemide and the other loop diuretics are very satisfying to use clinically. The patient in heart failure arrives at the hospital dyspneic, cyanotic, and terrified. After a single large dose of medication, the patient diureses and begins to feel good again quite quickly.

The practitioner, however, needs to be wary of the resulting impression that diuretics are “good” for heart failure. ACE inhibitors, beta blockers, and (in severe cases) spironolactone are “good” for heart failure because they prolong lives. One must not allow diuretic therapy—started for acute decompensation—to prevent use of more important long-term medications by causing dehydration, hypotension, or electrolyte disturbances.

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What is the best treatment for gastroesophageal reflux and vomiting in infants?

■ Evidence-Based Answer

The literature on pediatric reflux can be divided into studies addressing clinically apparent reflux (vomiting or regurgitation) and reflux as measured by pH probe or other methods (**TABLES 1 AND 2**). Sodium alginate reduces vomiting and improves parents' assessment of symptoms (strength of recommendation [SOR]: **B**, small randomized controlled trial [RCT]). Formula thickened with rice cereal decreases the number of postprandial emesis episodes in infants with gastroesophageal reflux disease (GERD) (SOR: **B**, small RCT).

There are conflicting data on the effect of carob bean gum as a formula thickener and its effect on regurgitation frequency (SOR: **B**, small RCTs). Metoclopramide does not affect vomiting or regurgitation, but is associated with greater weight gain in infants over 3 months with reflux (SOR: **B**, low-quality RCTs).

Carob bean gum used as a formula thickener decreases reflux as measured by intraluminal impedance but not as measured by pH probe (SOR: **B**, RCT). Omeprazole and metoclopramide each improve the reflux index as measured by esophageal pH probe (SOR: **B**, RCT).

Evidence is conflicting for other commonly used conservative measures (such as positional changes) or other medications for symptomatic relief of infant GERD. There is very limited evidence or expert opinion regarding breastfed infants, particularly with regard to preservation of breastfeeding during therapy.

■ Evidence Summary

Regurgitation ("spitting up") and gastroesophageal reflux are common in infants. In a cross-sectional survey of 948 parents of healthy infants aged 0 to 13 months, regurgitation occurred daily in half of infants from birth to 3 months old, peaked to 67% at age 4 months, and was absent in 95% by age 12 months.¹ Gastroesophageal disease (GERD) is characterized by refractory symptoms or complications (pain, irritability, vomiting, failure to thrive, dysphagia, respiratory symptoms, or

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