

Evidence-based answers from the
Family Physicians Inquiries Network

CLINICAL INQUIRIES

Q/Which medications benefit patients with diastolic heart failure?

EVIDENCE-BASED ANSWER

A | ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs), PROPRANOLOL, STATINS, furosemide, and some angiotensin receptor blockers (ARBs) benefit patients. Medications that reduce mortality in diastolic heart failure include ACEIs (strength of recommendation [SOR]: C, 1 prospective cohort trial with matched controls), propranolol (SOR: B, 1 randomized controlled trial [RCT]), and statins (SOR: C, 1 prospective cohort trial).

Furosemide improves symptoms of heart failure and quality of life (SOR: C, 1 RCT, using cohort data).

ARBs show mixed results: candesartan decreases hospital admissions (SOR: B, 1 large RCT); losartan improves exercise duration and quality of life (SOR: B, 2 small RCTs); irbesartan doesn't improve heart failure symptoms or other outcomes (SOR: B, 1 large RCT).

Micah Crouse, MD;
David Flack, DO;
J. William Kerns, MD; Larisa
Martin, MD;
Daniel Pham, MD;
Ramashilpa Sudireddy, MD
Virginia Commonwealth
University-Shenandoah
Valley Family Practice
Residency, Front Royal, Va

Karen Knight, MSLS
University of Virginia
Health Sciences Library,
Charlottesville



ACE inhibitors, propranolol, and statins reduce mortality in patients with diastolic heart failure.

Evidence summary

Diastolic heart failure, defined as classic evidence of congestive heart failure with “preserved” or “normal” left ventricular ejection fraction (LVEF),¹ is often encountered in medical practice. Unfortunately, studies that address diastolic heart failure don't use a uniform ejection fraction to define preserved systolic function. Treatments for diastolic heart failure have included diuretics, ACEIs, ARBs, beta-blockers, calcium channel blockers, digoxin, and statins.

ACEIs decrease mortality

One small prospective study in France enrolled 358 subjects who were admitted for a first episode of heart failure but had ejection fractions $\geq 50\%$. Patients were separated into 2 groups based on whether or not they were prescribed an ACEI—lisinopril (32.3%), ramipril (25.6%), perindopril (23.8%), or enalapril (5.5%)—at discharge. The authors attempted to adjust for selection bias by developing a propensity score and comparing

matched controls.

Patients who had been prescribed ACEIs had a 10% reduction in 5-year mortality (number needed to treat [NNT]=10).²

ARBs produce mixed outcomes

Evidence regarding outcomes with ARBs is not clear cut. Candesartan was studied in the CHARM-Preserved Trial, which enrolled 3023 patients from 618 centers in 26 countries with New York Heart Association functional class II to class IV congestive heart failure of at least 4 weeks' duration and LVEF $>40\%$.³ The treatment group showed a significant decrease in hospital admission for congestive heart failure (NNT=30, covariate adjusted), but no improvement in mortality.

Losartan improved exercise duration and quality of life compared with placebo or hydrochlorothiazide in 2 small RCTs totaling 60 patients.^{4,5}

In the I-PRESERVE Trial, irbesartan didn't improve primary or secondary outcomes, including death from any cause or

TABLE

Treating the patient with heart failure and normal LVEF: Recommendations from the ACCF and AHA

Recommendation	Level of evidence
Control systolic and diastolic hypertension	Good supportive evidence
Control ventricular rate in patients with atrial fibrillation	Expert opinion/limited evidence
Use diuretics for pulmonary congestion and peripheral edema	Expert opinion/limited evidence
Perform coronary revascularization if ischemia is having an adverse effect	Expert opinion/limited evidence
Rhythm control in patients with atrial fibrillation may be useful	Expert opinion/limited evidence
Beta-adrenergic blocking agents, ACEIs, angiotensin II receptor blockers, or calcium antagonists may be effective	Expert opinion/limited evidence
Digitalis isn't clearly effective	Expert opinion/limited evidence

ACCF, American College of Cardiology Foundation; ACEIs, angiotensin-converting enzyme inhibitors; AHA, American Heart Association; LVEF, left ventricular ejection fraction.

Adapted from: Hunt SA et al. *J Am Coll Cardiol*. 2009.¹

>
Diuretics alone improved patients' quality of life.

hospitalization for a cardiovascular cause ($P=.35$), death or hospitalization from heart failure, or quality of life ($P=.44$).⁶ However, concomitant use of other medications could have been a factor because 39%, 28%, and 73% of patients in the irbesartan group and 40%, 29%, and 73% in the placebo group were taking an ACEI, spironolactone, or a beta-blocker, respectively.

Propranolol reduces mortality, but data on other beta-blockers are lacking

One prospective randomized trial of heart failure patients with LVEF $\geq 40\%$ already treated with an ACEI and a diuretic, found that propranolol reduced total mortality by 35% after 1 year of therapy (absolute risk reduction=20%; NNT=5).⁷ Studies of other beta-blockers haven't reported patient-oriented outcomes as an end point.

Diuretics alone outperform diuretics plus other meds

A study that randomized 150 elderly patients with symptomatic heart failure and LVEF $>45\%$ to diuretics alone (80% were given furo-

semide), diuretics plus irbesartan, or diuretics plus ramipril found that diuretics alone improved the quality of life score by 46% after 52 weeks and also improved symptoms of heart failure.⁸ No significant symptomatic or other benefit was noted with the addition of irbesartan or ramipril.

Statins are linked to lower mortality

A prospective cohort study followed 137 patients with heart failure and ejection fraction $>50\%$ for a mean of 21 months.⁹ After adjustment for differences in baseline clinical variables between groups, therapy with various statins (68% of patients were on atorvastatin) was associated with lower mortality (NNT=5).

Little evidence exists to support the use of calcium channel blockers, digoxin, or other vasodilators in diastolic heart failure.

Recommendations

The **TABLE** summarizes recommendations of the American College of Cardiology Foundation and the American Heart Association.¹ **JFP**

CONTINUED ON PAGE 108

CLINICAL INQUIRIES

CONTINUED FROM PAGE 102

References

- Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*. 2009;53:e1-e90.
- Tribouilloy C, Rusinaru D, Leborgne L, et al. Prognostic impact of angiotensin-converting enzyme inhibitor therapy in diastolic heart failure. *Am J Cardiol*. 2008;101:639-644.
- Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362:777-781.
- Little WC, Zile MR, Klein A, et al. Effect of losartan and hydrochlorothiazide on exercise tolerance in exertional hypertension and left ventricular diastolic dysfunction. *Am J Cardiol*. 2006;98:383-385.
- Warner JG Jr, Metzger DC, Kitzman DW, et al. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. *J Am Coll Cardiol*. 1999;33:1567-1572.
- Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456-2467.
- Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction $\geq 40\%$ treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol*. 1997;80:207-209.
- Yip GW, Wang M, Wang T, et al. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. *Heart*. 2008;94:573-580.
- Fukuta H, Sane DC, Brucks S, et al. Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. *Circulation*. 2005;112:357-363.

FREE
1.0 CME/CE
CREDIT

Protect Your Patients, Protect Your Practice

Practical risk assessment in the structuring of opioid therapy in chronic pain

This CME/CE supplement addresses key points in chronic pain treatment, including:

- The importance of a comprehensive medical review for the patient with chronic pain
- Available tools for assessing pain
- Ascertaining the risk of prescription opioid abuse—includes a clip-and-save clinical screening tool
- How best to prepare your practice for prescribing and managing opioid therapy

FACULTY

- >> Perry G. Fine, MD
- >> Thomas Finnegan, PhD
- >> Russell K. Portenoy, MD



Visit www.jfponline.com
and click on CME

This supplement to *The Journal of Family Practice* was supported by educational grants from Endo Pharmaceuticals and Ortho-McNeil-Janssen Pharmaceuticals. It has been edited and peer reviewed by *The Journal of Family Practice*.