

A Review of Heart Failure Treatment

GORDON H. GUYATT, M.D., M.Sc.^{1,2}, AND P.J. DEVEREAUX, M.D.¹

Abstract

Heart failure is a common and costly medical condition. Ischemic heart disease and hypertension account for most cases of heart failure in developed countries. Estimates of the one-year mortality rates for patients with New York Heart Association (NYHA) Class II, III, and IV are 10%, 20%, and 40%, respectively. Angiotensin-converting enzyme (ACE) inhibitors reduce mortality of heart failure patients by approximately 25% (odds ratio 0.77, 95% CI 0.67–0.88). Larger doses of ACE inhibitors are more effective in preventing hospitalization than are lower doses. Angiotensin II receptor blockers (ARBs) are an alternative for patients who cannot tolerate ACE inhibitors because of their side effects (e.g., cough). Evidence for benefits of using combination of ACE inhibitors and ARBs is encouraging, but requires further study. For patients who cannot tolerate either ACE inhibitors or ARBs, vasodilator therapy with hydralazine and nitrates will probably provide benefit. (Diuretic therapy, while a mainstay of heart failure treatment, is primarily used for symptom relief.) There is also evidence that spironolactone reduces mortality (relative risk reduction 30%, 95% CI 18–40%) for patients with NYHA class III and IV heart failure. When administering spironolactone to heart failure patients, monitoring for hyperkalemia is essential. After two centuries of use, randomized controlled trials have finally demonstrated that digoxin is effective in preventing hospitalizations (relative risk reduction 28%, 95% CI 21–34%). There is now overwhelming evidence that beta-blockers are safe for heart failure patients but that they reduce the risk of death for these patients by approximately 30%. In addition to these medical interventions, heart failure patients may also benefit from a number of non-pharmacological interventions.

Key Words: Heart failure, digitalis, beta-blockers, anti-arrhythmic agents, anticoagulation, ventricular assist device, exercise, randomized controlled trials.

FOLLOWING THE TENETS of evidence-based medicine (1), this paper will highlight results from randomized trials and insights from controlled trial methodology which guide us in managing patients with heart failure.

Epidemiology, Diagnosis, and Prognosis

Studies of heart failure incidence suffer from lack of agreement regarding definition, from variability in methods and criteria, and from a paucity of population-based studies. Estimates of heart failure incidence vary from

1.0–5.0 per thousand per annum, increasing substantially with age to a level as high as 40 cases per thousand in those older than 75 years of age (2). This corresponds to a prevalence of 1% in those 50–59, and 10% in those older than 80 (3). Only about 5% of symptomatic patients have severe heart failure (4).

In the more industrialized countries, ischemic coronary disease and hypertension account for most cases of heart failure (5, 6). Valvular disease and viral, idiopathic and alcoholic cardiomyopathy do occur with somewhat lesser frequency. On occasion, clinicians may see thyroid disease and hemochromatosis, which are treatable causes of heart failure. All told, multiple hospitalizations, the many medications, and the home care requirements result in a yearly cost of treating heart failure patients that may be as high as \$22,000 per person (7).

The classic heart failure symptoms of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea lack specificity — many patients with other conditions report identical symptoms (8). The same is true for the most easily detected

From the ¹Department of Medicine and ²Departments of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada.

Address all correspondence to Dr. P.J. Devereaux, McMaster University, Faculty of Health Sciences, Clinical Epidemiology and Biostatistics, Room 2C12, 1200 Main Street, West Hamilton, ON L8N 3Z5 Canada; email: philipj@mcmaster.ca

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physical sign, peripheral edema (5). This probably explains the findings of two studies that examined the accuracy of the diagnosis of heart failure by primary care physicians and found false positive rates of 47% (9) and 55% (10). Physical findings of a third heart sound, elevated jugular veins, and pulmonary crackles are more specific (11), though the last of these is prominent in one easily confused condition, pulmonary fibrosis. The diagnosis may be more difficult for older patients, of whom 30–40% with heart failure may have primarily diastolic dysfunction (11). The chest radiograph is helpful, despite the poor relationship between heart size and left ventricular function and between upper-lobe distension and pulmonary capillary wedge pressure (12). The limitations of history, physical examination, and chest radiographs lead experts to recommend routine echocardiography for patients suspected to have heart failure. B-natriuretic peptide shows promise as a laboratory test for differentiating between patients with and without left ventricular dysfunction, and may obviate the need for echocardiogram for some patients (13).

A clear picture of the prognosis for heart failure is also difficult, because while studies almost invariably classify patients according to the New York Heart Association (NYHA) functional classification, the between-observer agreement in NYHA class is poor (14). In any case, available evidence suggests that neither the incidence nor the prognosis of heart failure has changed dramatically over the last two decades (15). Despite limitations of the studies, one-year survival rates of older patients with severe heart failure are no higher than 60% (16). A recent population-based study found that one-year mortality of patients hospitalized with heart failure was greater than 30%, with even poorer prognosis for older patients with multiple comorbidity (17). Reasonable current estimates would suggest one-year mortalities for NYHA Class II, III and IV patients of 10%, 20% and 40%, respectively.

Management — Where to Look for Best Evidence

We offer our patients treatment for two reasons: to help them live longer and feel better. Uncontrolled observations, or observations from studies of weak design, may provide misleading estimates of treatment efficacy. Ten years ago, we were offering heart failure patients prophylactic anti-arrhythmic agents that

we now know led to premature death, while withholding beta blockers that would have helped them live both longer and better. The cardiology community was divided between vociferous advocates of digoxin and equally vociferous opponents. Only rigorously conducted, blinded, randomized controlled trials (RCTs) in which patient follow-up was complete and patients were analyzed in the groups to which they were randomized (18) have opened our eyes to the true benefits and harms of these interventions.

RCTs are inevitably limited by random error, and by the particular patient population and intervention that the investigators choose to study. Meta-analyses that pool results across RCTs provide a powerful tool to help deal with both of these limitations. To avoid bias, meta-analyses must themselves be rigorously conducted. For these systematic reviews, avoiding bias requires eligibility criteria that are both explicit and appropriate (appropriate, in that across the range of pooled patients, interventions, outcomes and methodologies, we expect more or less the same treatment effect), and a comprehensive and reproducible search for relevant studies (19). Furthermore, investigators must evaluate the methodological quality of the original studies; poorly designed studies will yield biased estimates, regardless of the rigor of the meta-analytic methods. Finally, meta-analysts must look carefully to see if study results are similar for different patients, interventions, measurements of outcome, and study methodologies (20). Our summary of the evidence shall, wherever possible, rely on systematic reviews that meet these criteria.

Judging the Magnitude of Treatment Effects

Because they must always trade off benefit and harm, clinicians cannot be satisfied with just knowing whether treatments work. They must attend also to the magnitude of the benefit patients can expect. The relative risk reduction (RRR) provides one way of expressing the extent to which treatments reduce the relative risk (RR) of an adverse outcome (for instance, they may cut the risk by $1/2$ or by $1/4$). The RRR may, however, be misleading. For patients with a 2% risk of dying, a treatment with an RRR of 50% will reduce the risk to 1%. The situation is very different when the patient's risk of dying is 40%, when the same treatment will cut the risk to 20%. Thus, the first patient experiences an absolute benefit of 1%, and the second of 20%. A compelling way to present such results uses

the number needed to treat (NNT), the number of patients we must treat over a particular time period to prevent an adverse outcome such as death, stroke, or myocardial infarction. We would need to treat 100 of the low-risk patients described to save one life, but only 5 of the high-risk patients (21).

Vasodilators

A rigorously conducted, systematic review of RCTs has examined the effect of angiotensin-converting enzyme (ACE) inhibitors for heart failure (22). The investigators found that ACE inhibitors reduce mortality by approximately 25% (odds ratio 0.77, 95% CI 0.67–0.88). The effect was consistent across all NYHA functional classes and all ACE inhibitors. This implies that clinicians would need to treat approximately 40 NYHA Class II patients and 10 Class IV patients for a year with ACE inhibitors in order to prolong a single life. Another meta-analysis of five trials that used individual data (23) showed a similar result (odds ratio 0.80, 95% CI 0.74–0.87) and also suggested lower rates of admission for heart failure (OR 0.67, 95% CI 0.61–0.74).

Clinicians can be confident of the applicability of these findings if they prescribe the relatively large daily doses of ACE inhibitors used in the RCTs (captopril 100–150 mg, enalapril 20 mg) (24). One large RCT (25) has compared the use of a very large dose of lisinopril to a very small dose, for patients with heart failure. The large dose was associated with a 12% reduction in the RR of death or hospitalization (95% CI 4–18%). These results support administration of high doses of ACE inhibitors for heart failure.

Some patients cannot tolerate ACE inhibitors (ACEIs), most commonly because of cough or renal failure with hyperkalemia. For such patients, what are the options? A systematic review of 17 RCTs of angiotensin II receptor blockers (ARBs) showed a trend toward decreased mortality (OR 0.68, 95% CI 0.38–1.22) and decreased hospitalization (OR 0.67, 95% CI 0.29–1.51) for the relatively small number of patients who participated in placebo-controlled trials of ARBs in comparison with background ACE inhibitor therapy. When compared directly with ACEIs, ARBs showed a weak trend toward increased mortality (OR 1.09, 95% CI 0.92–1.29) and an even weaker trend toward decreased hospitalization (OR 0.95, 95% CI 0.80–1.13) (26). In contrast, the combination therapy of ARBs and ACEIs was superior to ACEIs alone in reducing hospital-

ization (OR 0.74, 95% CI 0.64–0.86), but not mortality (OR 1.04, 95% CI 0.91–1.20). Subgroup analyses, however, have suggested that patients already on both ACEIs and beta-blockers may do less well when taking an ARB (26).

The combination of hydralazine and an oral nitrate represents another alternative to an ACEI. The evidence supporting this combination comes from a single RCT which reported a mortality rate of 34.3% for 273 placebo-treated heart failure patients and 25.6% for 186 patients treated with hydralazine and nitrates after two years of follow-up (27). The associated RRR of approximately one-third of those patients was on the borderline of conventional levels of statistical significance, and the usually preferable survival analysis failed to cross the conventional 0.05 boundary. A subsequent study demonstrated a mortality reduction when using an ACEI as compared to the hydralazine/nitrate combination (28).

Diuretics

Diuretics are a mainstay of treatment for heart failure patients, and their dramatic impact on symptoms has obviated the necessity for RCTs. Loop diuretics are usually required, though their effectiveness decreases as heart failure severity increases, particularly for patients with decreased renal function, (29, 30). When loop diuretic resistance becomes sufficiently severe, patients require the addition of a thiazide or spironolactone (31). Metolazone is popular in North America, though its continuous use tends to be associated with hyponatremia, hypochloremic alkalosis, and hypokalemia (32). Its best use may be as an intermittent treatment in response to weight gain caused by fluid retention.

A single trial involving 1663 patients with NYHA Class III and IV heart failure has suggested a possible mortality reduction with aldosterone-blocking therapy. Patients received 12.5–50 mg of spironolactone or matched placebo each day, depending on their serum potassium. The study, which was stopped early (mean follow-up of 24 months) because of evidence of benefit, showed an RRR of 30% (95% CI 18–40%). Symptomatic hyperkalemia was infrequent in the context of the trial, but may be more frequent in routine clinical practice.

Digoxin

After two centuries of digoxin use, RCTs have finally yielded a clear picture of the drug's

effect on heart failure patients in sinus rhythm. A large Digitalis Investigation Group (DIG) study (33) confirmed the findings of a meta-analysis of small RCTs conducted prior to 1990 (34) and two subsequent RCTs of digoxin withdrawal (35, 36), which suggested that digoxin can reduce the incidence of heart failure exacerbations. After enrolling more than 6,500 patients and achieving an average follow-up of 37 months, the DIG study group found nearly equal mortality among treated and control patients, but a reduction in heart failure hospitalizations with digoxin (26.8% vs. 34.7%, RR 0.72, 95% CI 0.66–0.79).

Previously hospitalized heart failure patients are at high risk of readmission. For instance, consistent with the DIG results, in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial that tested high- and low-dose lisinopril in 3,164 heart failure patients, more than 60% required hospitalization for a cardiovascular cause during an average follow-up of just under 4 years (37). If one were to consider a relatively low yearly risk of hospitalization of 10%, one would need to treat approximately 35 patients with digoxin for a year to prevent one hospitalization. The NNT would drop further for those with a higher hospitalization risk. Digoxin should be administered with caution to patients with renal dysfunction or AV nodal conduction abnormalities.

Beta-Blockers

The literature includes a profusion of meta-analyses of beta-blocker therapy for heart failure (38–43). While methods and results differ, all are sound and yield consistent findings. While increasing the ejection fraction, beta-blockers reduce the relative risk of dying by about 30%, with the lower boundary of the 95% CI of 10–15%. Patients with ischemic and non-ischemic cardiomyopathy can expect similar benefits. For patients with severe heart failure, of whom 40% might die in less than one year, the clinician must treat 8–9 patients with beta-blockers for one year to prolong one life; the number would be around 35 for lower risk NYHA Class II patients. Like digoxin, beta-blockers can exacerbate tendencies to bradycardia or increase the level of AV block in those with AV nodal disease.

One recent meta-analysis suggests the possibility that vasodilating beta-blockers have a larger impact on reducing mortality than do beta-blockers without vasodilating properties

(44). However, strong inferences regarding the relative effect of vasodilating and non-vasodilating beta-blockers must await head-to-head comparisons between the two subclasses.

Antiarrhythmic Agents

In the Framingham Heart Study, approximately 50% of all deaths of heart failure patients occurred within one hour of onset of symptoms (45), and sudden death continues to account for half the mortality in recent trials of pharmacologic therapy in heart failure (46).

In the past, cardiologists and internists often responded to Holter monitor findings of nonsustained ventricular tachycardia (NSVT) in patients with coronary artery disease or heart failure by prescribing Class I antiarrhythmic agents that include quinidine, procainamide, disopyramide, mexiletine, encainide, flecainide, and moricizine. Despite the ability of the last three drugs to obliterate nonlethal arrhythmias, individual trials paradoxically have shown that they are associated with a statistically significant increase in sudden death (47, 48). Moreover, a rigorously conducted meta-analysis of all 51 RCTs of Class I agents confirmed an increase in mortality (odds ratio 1.14, 95% CI 1.01–1.28) (49).

In 1997, the investigators of all 13 RCTs of amiodarone, a Class III agent, reported a meta-analysis that combined individual patient data from all of their trials (50). Of these studies, 5 were undertaken for heart failure patients and 8 for patients after myocardial infarction. Their pooled analysis showed an RRR for sudden death of 29% (95% CI 15–41%), and a total mortality of 15% (95% CI 2–29%), with consistent effects in the follow-up trials for myocardial infarction and heart failure. These results suggest that treating 100 NYHA Class II heart failure patients with nonsustained ventricular tachycardia would prolong the lives of 3 patients (NNT approximately 35) and similar treatment for 100 NYHA Class IV patients would prolong 12 lives (NNT approximately 8). However, in treating 100 patients, we would cause 6 patients to become hypothyroid, 1 to become hyperthyroid, 2 to develop bradycardia, and 1 to develop pulmonary infiltrates (49).

Anticoagulation

Most patients with heart failure and atrial fibrillation are likely to choose warfarin therapy to prevent stroke over aspirin therapy or no

treatment. A reasonable estimate of the one-year risk of having an embolic stroke for heart failure patients over 65 is 8% (51). A meta-analysis of five RCTs of the use of warfarin for patients with non-valvular atrial fibrillation showed a 68% relative risk reduction, with a CI of 50–79%. With conscientious monitoring of international normalized ratio (INR), the risk of serious gastrointestinal bleeding in the course of one year is likely to be 1% or less (52). Thus, for 100 patients treated for one year, 1 patient will have a serious bleed (number needed to harm 100) and 5–6 patients will avoid a stroke they would otherwise have suffered (NNT 18–20).

For patients in stable sinus rhythm, the decision regarding anticoagulation becomes more difficult. Reasons include the lower risk of thromboembolism and, more important, the lack of an RCT directly addressing this question (53). A decision to treat such patients therefore depends on observational studies and generalizations from trials for patients with atrial fibrillation. A decision analysis addressing this issue suggested that patients with severe heart failure, for whom taking warfarin is not problematic and whose bleeding risk is low, will benefit from anticoagulation (54). A conservative “do no harm” approach would withhold anticoagulants pending the conduct of an RCT directly addressing this issue.

Non-pharmacologic Therapy

Heart transplant provides a last resort option for some patients with severe heart failure. A randomized trial has shown that a ventricular assist device decreases mortality and improves quality of life over the period of one year, for patients with severe heart failure (55). Differences in survival between groups were no longer significant at 2 years.

The last decade has seen a growing interest in exercise rehabilitation for patients with heart failure. A systematic review of studies of exercise capacity identified 14 parallel group RCTs and 8 randomized cross-over studies. The results suggest short-term improvement in quality of life for heart failure patients participating in exercise programs (56). The participants, however, were not representative of most patients in the community, in that they were younger and had minimal co-morbidity. Much larger trials will be required to determine effects on hospitalizations or mortality.

Organizing care for a patient with severe heart failure is both challenging and crucial. A systematic review of randomized clinical trials of disease management programs for patients with heart failure identified 11 RCTs involving 2,067 patients with heart failure. Overall, the interventions reduced hospitalizations (RR 0.87, 95% CI 0.79–0.96), but not all-cause mortality (RR 0.94, 95% CI 0.75–1.19) (57). The results, however, differed across interventions. Specialized follow-up by a multidisciplinary team led to a substantial reduction in the risk of hospitalization (RR 0.77, 95% CI 0.68–0.86, $n=1,366$), whereas trials employing telephone contact and improved coordination of primary care services failed to find any benefit (RR 1.15, 95% CI 0.96–1.37, $n=646$). Disease management programs were cost saving in 7 of the 8 trials that reported cost data. An RCT of a nurse specialist program published subsequent to this systematic review showed consistent results, with a substantial reduction in a combined endpoint of death and hospitalization (hazard ratio 0.61, 95% CI 0.33–0.96) (58).

These results emphasize the importance of compliance-enhancing maneuvers and intensive follow-up for patients with congestive heart failure (CHF). A systematic review of 116 RCTs of compliance-enhancing maneuvers further reinforces the message (59). No single category of intervention was superior, but comprehensive interventions combining education (individual or group; oral, written, or audiovisual presentations), behavioral (packaging, mail or telephone reminders) and affective (home visits and family support) components were more effective than single-focus interventions.

Individualizing the Care of the Heart Failure Patient

In our discussion, we have placed great emphasis on RCTs and meta-analyses of RCTs. Yet, heterogeneity of patient response limits the usefulness of positive RCTs: is our patient a non-responder to an intervention that benefits only some of the target population? For interventions directed at evaluating and preventing distant events such as death or hospitalizations, an entire population must be treated since identifying individual responders and non-responders is never possible. However, when the question concerns symptomatic benefit or possible side effects, individualizing therapy becomes a possibility.

Clinicians traditionally respond to these latter situations with trials that institute, or withhold, therapy. Often, however, bias may intrude in deciding whether there is a causal connection between the intervention and the target outcome. Particularly when symptoms are the issue, natural history, expectations, placebo effects, and the patient's desire to please may all contribute to spurious inferences (60).

A methodology exists for making strong inferences about intervention effects for an individual patient (61). The approach, called "N of 1" RCT, involves pairs of treatment periods in which the patient receives active treatment during one period of each pair, and a matching placebo during the other period (Fig.). The treatment target, most often a symptom or group of symptoms, is monitored quantitatively during each period. Pairs of treatment periods are repeated, until both the patient and clinician become convinced of the treatment's effect or lack of effect. Utilizing the full methodology is challenging, but individual components can be more easily implemented. Repeatedly introducing and withdrawing a treatment, and quantitatively measuring patient symptoms, will strengthen inferences about the intervention's impact.

How might such an approach benefit patients with heart failure? Digoxin varies in its impact on symptoms; N of 1 trials can resolve the issue of symptomatic benefit for individual patients. For patients for whom one might hesitate to prescribe beta-blockers because of possible adverse effects on symptoms (such as patients with chronic airflow limitation or relative bradycardia), one can test the impact of the drug in an N of 1 RCT. For patients suffering from concomitant angina despite beta-blockers and

nitrates, one can use N of 1 methods to determine the symptomatic impact of adding a calcium-channel blocker, such as amlodopine, without negative cardiac effects in heart failure (62).

Conclusion

Heart failure patients who place a high value on prolonging life, and who have no contraindications, will wish to take both ACEI and beta-blockers, and may well choose to take spironolactone as well. Digoxin will benefit patients who wish to lower a high risk for hospital readmission. Patients interested in maximizing their quality of life will want to take advantage of exercise programs if they are offered in their community. If possible, a multidisciplinary team should co-ordinate the care of heart failure patients, with likely consequences of reduced hospitalization and reduction in costs.

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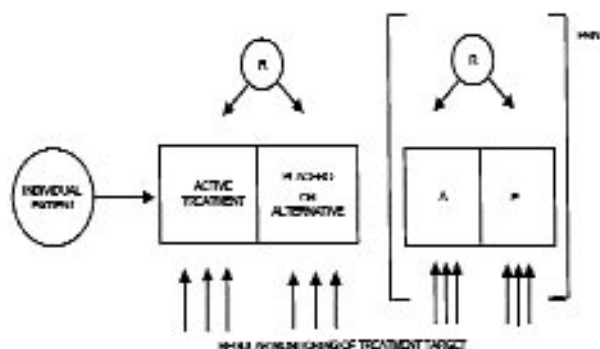


Fig. A schematic representation of an N of 1 randomized trial. The arrows represent measurements of the target outcome, generally patient's symptoms. The "PRN" represents the possibility of repeating the pairs of treatment periods until both patient and physician are satisfied that the patient does, or does not, benefit.

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