Targeting success in heart failure

Evidence-based management

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Heart failure (HF) is a common condition in primary care with 1% of the population self-reporting this condition. Mortality is substantial, approaching 40% to 50% over 5 years. Heart failure is a complex syndrome in which abnormal heart function results in, or increases the subsequent risk of, clinical symptoms and signs of low cardiac output or pulmonary or systemic congestion.[1] This article will present some practical tips for managing HF.[2]

Case description

C.C. is a 67-year-old woman with a long history of dilated cardiomyopathy and chronic atrial fibrillation (since 1992), type 2 diabetes requiring insulin (since 1994), stage 3 chronic renal insufficiency (since 2005), and gastroesophageal reflux disease. She has an extensive list of medications: 160 mg of valsartan once daily; 10 mg of ramipril once daily; 40 mg of furosemide twice daily; 0.25 mg of digoxin once daily; 20 mg of atorvastatin once daily; 30 mg of nifedipine extended release once daily; 81 mg of acetylsalicylic acid once daily; 7.5 mg of warfarin once daily; 24 units of Novolin ge NPH in the morning, 30 units at supper; 10 units of Novolin ge Toronto in the morning, 5 units at night; 1000 mg of metformin twice daily; 150 mg of ranitidine once daily; 420 mg of magnesium oxide once daily; 500 mg of calcium carbonate once daily; and 300 mg of ferrous sulfate once daily.

After 16 years of stability, her lifestyle has deteriorated, with a poor diet and cessation of her cardiac rehabilitation exercise program. During 5 hospital admissions, 5 different cardiologists suggested differing treatment regimens, modifying doses or agents in the same class. Metabolic investigations reveal poor control of her diabetes, with a glycated hemoglobin A_{1c} of 8.1%. Results of complete blood count and electrolyte measurement are normal, but her creatinine level is 160 mmol/L (estimated creatinine clearance 40 mL/min). Cardiac investigations reveal new triple-vessel coronary artery disease. She declines revascularization and wishes to be treated medically. Her atrial fibrillation is well controlled. Echocardiography shows systolic dysfunction with an ejection fraction between 18% and 28%. The cardiothoracic surgeon indicates that cardiac pacing or an implanted cardioverter defibrillator are not options for C.C. Her treatment is challenged by the family medicine resident who questions potential inconsistencies between her treatment regimen and HF management guidelines. The patient's understanding of her condition is inadequate for her to comply effectively with lifestyle changes, and communication among her caregivers has been inadequate, given the complexity of her case.

Bringing evidence to practice

The management algorithm for chronic HF is summarized in **Figure 1**.[2] Both aggressive use of medication to target doses and patient education are required for effective management of HF[1]; however, the foundation for all HF therapy includes nonpharmacologic management (**Box 1**).[2]

Box 1. Nonpharmacologic management of heart failure

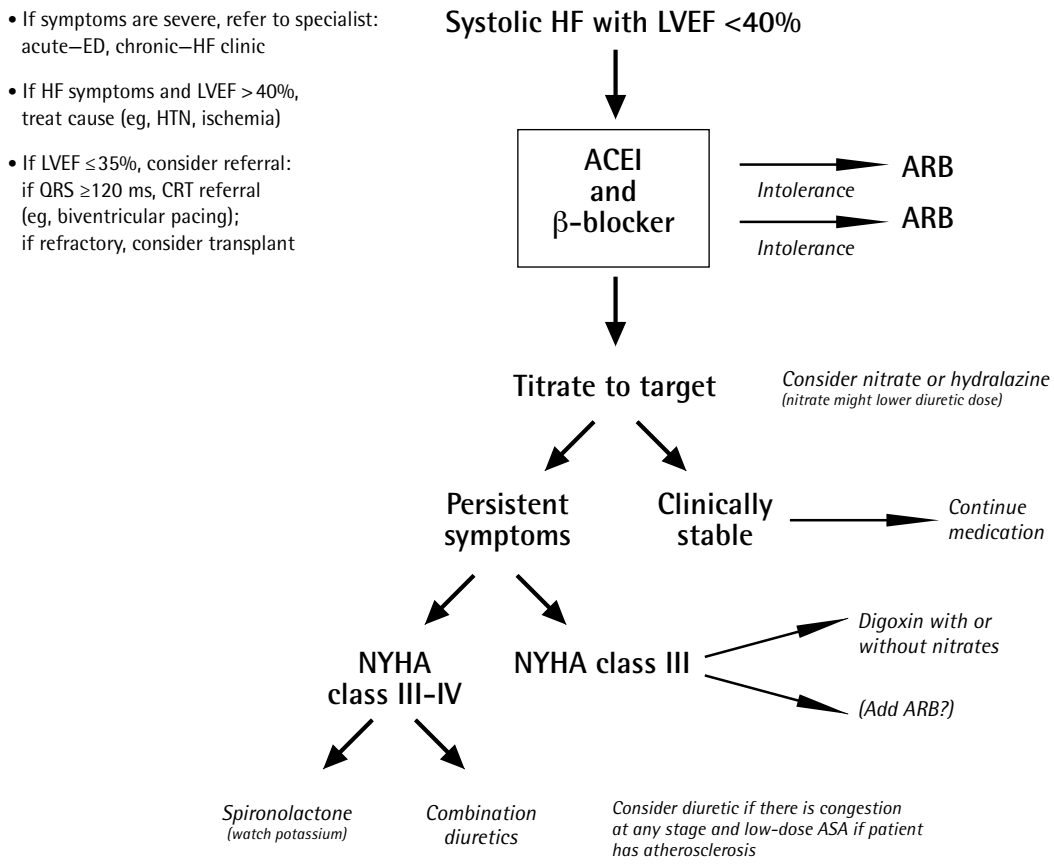
- Exercise (after stress test assessment)
- No-added-salt diet (2 to 3 g of salt per day)
  (6 g salt ≈ 1 tsp salt ≈ 2400 mg sodium)
- Daily morning weight (nude and after voiding)
- Fluid intake 1.5 to 2 L per day
- No more than 1 alcoholic drink per day
- Smoking cessation
- Influenza and pneumococcal vaccination

Data from Jin et al.[2]

Dietary, lifestyle, and over-the-counter nonsteroidal anti-inflammatory drug indiscretions are common sources of HF exacerbations.[2,3] Lifestyle measures facilitate HF management. Communicating information about exercise and salt and fluid intake to patients is essential for optimal management.

- The patient can exercise aerobically 3 to 5 times per week (30 to 40 minutes per session) for New York Heart Association class I to III HF.[4]
- All patients need to restrict salt intake to 2 to 3 g (0.5 tsp) per day. Patients with unremitting fluid retention or advanced cardiac failure (ejection fraction less than 35%) require restriction to less than 2 g (eg, approximately 0.25 tsp) of salt per day.
- Have patients report any weight gain of 2 lb (1 kg) in 1 to 2 days or 5 lb (2 kg) in 1 week. Selected patients might be suitable candidates to self-adjust their furosemide doses, doubling furosemide until normal weight is restored or holding furosemide if weight decreases by 1 kg.

Figure 1. Heart failure treatment overview



ACEI—angiotensin-converting enzyme inhibitor, ARB—angiotensin receptor blocker, ASA—acetylsalicylic acid, CRT—cardiac resynchronization therapy, ED—emergency department, HF—heart failure, HTN—hypertension, ICD—implantable cardioverter defibrillator, LVEF—left venticular ejection fraction, NYHA—New York Heart Association.
Data from Arnold et al[1] and Jin et al.[2]

- Patients, especially those with renal dysfunction or hyponatremia, should restrict fluid intake to 1.5 to 2.0 L per day.

Diuretics are useful in providing symptom relief, especially acutely, but do not prevent long-term mortality.[3] Overreliance on diuretics often results in hypotension and electrolyte abnormalities, limiting the use of other agents that reduce mortality.

- Loop diuretics are preferred for congestive symptoms. Once symptoms are relieved, use the lowest effective maintenance dose. Multiple daily dosing can be used to improve diuretic effect, especially if higher doses are needed.
- If persistent volume overload continues with optimal furosemide therapy, add a low-dose thiazide diuretic or metolazone (most effective if given 30 minutes before furosemide).[5] Remember to monitor daily weight and regularly measure creatinine, urea, potassium, and magnesium levels.
- Spironolactone (12.5 to 25 mg) should be considered for patients with an ejection fraction of less than 30% and symptoms of HF.[6] Although the target dose in the RALES (Randomized Aldactone Evaluation Study Investigators) trial was 50 mg, 25 mg daily was the average dose reached.[6] Remember to watch out for hyperkalemia.
- Isosorbide dinitrate or a nitroglycerin patch are additional options, especially for nocturnal dyspnea.

While diuretics help symptoms, β-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) have the best demonstrated evidence for mortality and morbidity outcomes in HF.[7-9]

- The maximum tolerated target dose of ACEI should be used in all HF patients with ejection fractions of less than 40%[1] (**Table 1**).[2,3,10-16]* If ACEI intolerance develops, an angiotensin receptor blocker (ARB) can be used.[13,17]
- Generally, ACEIs and ARBs should not be combined, as adverse effects increase with little extra benefit.

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*The full version of the RxFiles heart failure overview and treatment chart is available at www.cfp.ca. Go to the full text of the article online, then click on CFPlus in the menu at the top right-hand side of the page.

Table 1. Heart failure drugs overview comparison chart

CLASS	DRUG (BRAND NAME)	INITIAL ORAL DOSE (TARGET DOSE)	COST/MO FOR TARGET DOSE, $	USE AND COMMENTS
ACEIs	Ramipril (Altace)	1.25-2.5 mg twice daily (5 mg twice daily or 10 mg once daily)	43 or 29	• use in all patients as soon as safely possible after AMI and continue indefinitely in LVEF < 40% or if AHF complicated the AMI • use in all asymptomatic patients with LVEF < 35% and all patients with symptoms of HF and LVEF < 40% • good evidence for decreased mortality in HF; can use in combination with diuretic (if decreased weight or drop in BP occurs, hold or decrease diuretic dose and maintain ACEI dose) (ACEI vs placebo for trials up to 42 months' duration: all-cause mortality 15.8% vs 21.9%, NNT = 16; all-cause mortality or HF hospitalization 22.4% vs 32.6%, NNT = 10) • monitor: serum creatinine and potassium upon initiation and within 3-7 days of starting or adjusting dose (up to a 30% increase in serum creatinine and a potassium level up to 5.6 mmol/L might be reasonable)
	Lisinopril (Zestril)	2.5-5 mg daily (20-40 mg daily)	28-58	
	Perindopril (Coversyl)	2 mg daily (4 mg daily)	35	
	Enalapril (Vasotec)	1.25-2.5 mg twice daily (10 mg twice daily)	42	
	Captopril (Capoten)	6.25-12.5 mg 3 times daily (25-50 mg 3 times daily)	37-62	
	Trandolapril (Mavik)	0.5-1 mg daily (4 mg daily)	42	
BBs (Agents only listed if evidence of decreased mortality in HF; might not be a class effect)	Bisoprolol (Monocor)	1.25 mg daily (10 mg daily)	21	• use in all HF patients with LVEF ≤ 40%; if NYHA class IV symptoms, stabilize patient and congestion before initiation of a BB (eg, not for AHF) • BBs improve ventricular function, patient well-being, and survival; decrease hospitalizations; and treat atrial fibrillation • avoid abrupt withdrawal; if necessary, can titrate the dose down (by half) in AHF and titrate up once stabilized • bisoprolol and carvedilol have mortality benefit[10,11] (eg, bisoprolol vs placebo: all-cause mortality 11.8% vs 17.3%, NNT=19/1.3 years); for metoprolol, evidence stronger with tartrate salt (long-acting formulation) used in the United States[3,12]
	Carvedilol (Coreg)	3.125-6.25 mg twice daily (25 mg twice daily with food)	53	
	Metoprolol SR (Lopressor [succinate salt in Canada])	12.5-25 mg daily (200 mg SR daily)	21	
ARB (Only valsartan and candesartan have official HF indications)	Candesartan (Atacand)	4 mg daily (32 mg daily)	48	• use when ACEI not tolerated (eg, due to cough) • ARBs at high doses have shown similar outcome benefits to ACEIs[13,14] • ARBs and ACEIs sometimes, although not routinely, combined; adverse events with little extra benefit[15,16] • monitor: similar to ACEI (see above)
	Valsartan (Diovan)	40 mg twice daily (160 mg twice daily)	92	
	Losartan (Cozaar)	25-50 mg daily (≤ 150 mg daily)	74	
Aldosterone antagonists	Spironolactone (Aldactone)	12.5 mg daily (12.5-25 mg daily; maximum 50 mg daily)	9	• option for patients with LVEF < 30% and severe HF symptoms despite treatment optimization, or with AHF with LVEF < 30% • consider lowering or discontinue potassium supplements when starting; counsel regarding potassium; hold if diarrhea or vomiting
Vasodilators	Isosorbide dinitrate (Isordil)	20 mg 3 times a day before meals (40 mg 3 times a day before meals)	23	• combination ISDN and hydralazine useful in African Americans with systolic dysfunction (decrease mortality), patients unable to tolerate standard treatment, and chronic renal failure • ISDN or nitroglycerin patch also useful for nocturnal dyspnea; maintain a 12-hour nitro-free interval
	Hydralazine (Apresoline)	37.5 mg 3 times a day (75 mg 3 times a day)	48	
Diuretics	Furosemide	20-40 mg daily to twice daily	5	• furosemide useful for congestive symptom relief; once congestion resolves, reduce to lowest effective dose or stop so that agents with mortality evidence can be optimized; a second diuretic (thiazide or metolazone) might be useful to augment loop diuretic when necessary
	Hydrochlorothiazide	12.5-25 mg daily to twice daily	5	
	Metolazone (Zaroxolyn)	2.5-5 mg daily	10-17	
Cardiac glycoside	Digoxin	0.0625–0.125 mg daily for most (target low blood levels ≤ 1.3 nmol/L in HF, as higher levels are associated with harm)	15	• evidence for symptomatic and hospitalization benefit, but not mortality • might be useful for patients with both HF and atrial fibrillation when not controlled on BBs • many contraindications, drug interactions, and side effects

ACEI—angiotensin-converting enzyme inhibitor, AHF—acute heart failure, AMI—acute myocardial infarction, ARB—angiotensin receptor blocker, BB—β-blocker, BP—blood pressure, HF—heart failure, ISDN—isosorbide dinitrate, LVEF—left ventricle ejection fraction, NNT—number needed to treat, NYHA—New York Heart Association, SR—sustained release.

Data from Jin et al.[2]

Full version of the RxFiles heart failure overview and treatment chart is available on **CFPlus.***

Exceptions might include symptomatic patients with class III or IV HF on optimum ACEI and BB treatment, or those unable to tolerate BBs.[2] Blood pressure, serum creatinine, and potassium should be monitored.

- To titrate ACEIs or ARBs, start at low doses, then double the dose at 1- to 2-week intervals until the target dose is reached or until intolerable side effects persist. Trial evidence for best HF outcomes has been with relatively high doses.[14,18]
- β-Blockers have strong evidence for mortality reduction.[7] Initiate only if patients' HF is stable and euvolemic. Start at low doses and double the dose every 2 to 4 weeks. Warn patients to expect some symptom worsening, initially.
- When pursuing maximum tolerated doses of ACEIs or BBs, a heart rate as low as 50 beats per minute or a blood pressure as low as 80/50 mm Hg might not require any change in therapy, as long as the patient is not showing symptoms of hypotension (eg, dizziness and falls).

Other agents can help if symptoms persist after maximizing the most beneficial agents.

- Digoxin can be used to improve symptoms and decrease hospitalization if symptoms persist on optimal treatment, especially if the ejection fraction is less than 30% or for concomitant treatment of atrial fibrillation. The target blood level in HF is less than 1.3 nmol/L to prevent adverse events.[19]
- Combination isosorbide dinitrate and hydralazine should be considered in addition to standard therapy for African Americans with systolic dysfunction[20] and for HF patients unable to tolerate other standard treatment or who have chronic renal failure. A nitroglycerin patch can be substituted for oral nitrates. Remember to allow for a 12-hour nitrate-free period.

While patient dietary indiscretions often occur, we must also be aware of prescriber indiscretions that can exacerbate HF. Specifically, medications such as nonsteroidal anti-inflammatory drugs, antiarrhythmic agents, diltiazem, verapamil, stimulants, glitazones, corticosteroids, tumor necrosis factor blockers, and numerous cancer chemotherapeutic agents are implicated.[1,3]

Case resolution

Steps are taken to improve C.C.'s treatment regimen. The first step is communication with her HF clinic physician, who agrees to be the primary consultant for cardiac therapy changes. She participates in an intense educational program on HF. In the year after her therapy is changed, C.C. avoids any admission to the hospital for HF. Her medications are adjusted and better reflect the evidence-based treatment guidelines: 10 mg of ramipril once daily; 10 mg of bisoprolol once daily; 0.125 mg of digoxin once daily; 25 mg of spironolactone once daily; 80 mg of furosemide twice daily; 2.5 mg of metolazone on Monday, Wednesday, and Friday; 420 mg of magnesium oxide once daily; 60 mg of isosorbide mononitrate at bedtime; 600 mg of Slow K once daily; 5 mg of warfarin once daily; 40 mg of atorvastatin once daily; 81 mg of acetylsalicylic acid once daily; 40 units of Novolin ge NPH twice daily; 24 units of Novolin ge Toronto 3 times daily; 20 mg of rabeprazole once daily; 1000 IU of vitamin D once daily; 300 mg of ferrous sulfate once daily; and 500 mg of calcium carbonate once daily. Metformin, which had been held during periods of acute congestion, was restarted at 500 mg twice daily, in line with current recommendations.[3]

Important concepts in management of chronic HF are summarized in **Box 2**.[2] Educating patients on lifestyle measures supports medication management. Ensuring patients approach the maximal tolerated target doses for ACEIs and BBs improves mortality and morbidity. Adhering to the targets of treatment, combined with patient education and communication between family physicians, cardiologists, pharmacists, and dietitians, will lessen the burden of this disease on patients, caregivers, and the health care system.

Box 2. Pearls for decreased morbidity and mortality in HF

- Patient education is key (consider referral to an interprofessional HF clinic where available)
- Make sure all patients with reduced ejection fraction are on the maximum tolerated dose of BB and ACEI (or ARB)
- After HF is controlled, titrate BB dose gradually (every 2 to 4 weeks); patient will feel worse before feeling better; ACEI dose should be titrated every 1 to 2 weeks
- To optimize ACEI and BB dose, decrease dose of diuretics, nitrates, and other antihypertensives
- Consider adding a third drug (eg, spironolactone, digoxin, nitrate) if the patient is still symptomatic on ACEI and BB
- Ensure ongoing communication among health care providers

ACEI—angiotensin-converting enzyme inhibitor, ARB—angiotensin receptor blocker BB—β-blocker, HF—heart failure.
Data from Jin et al.[2]

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