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CORE TRAINING FOR DOCTORS

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Pharmacological management of chronic heart failure: old drugs, new drugs and new indications

Heart failure affects 1–2% of the population in the developed world and remains an important cause of hospitalization. After stabilizing patients through the acute phase of their illness, their outcome in terms of mortality, morbidity and further hospitalization can be altered by treatment with appropriate disease-modifying drugs.

The hospital doctor plays a crucial role in restarting medications that were stopped during admission, titrating appropriate doses and initiating drugs with long-term benefits. This article gives an overview of the current drug options and the evidence to support their use in practice (*Figure 1*). The pharmacological therapy discussed focuses on evidence derived in patients with heart failure with impaired systolic function.

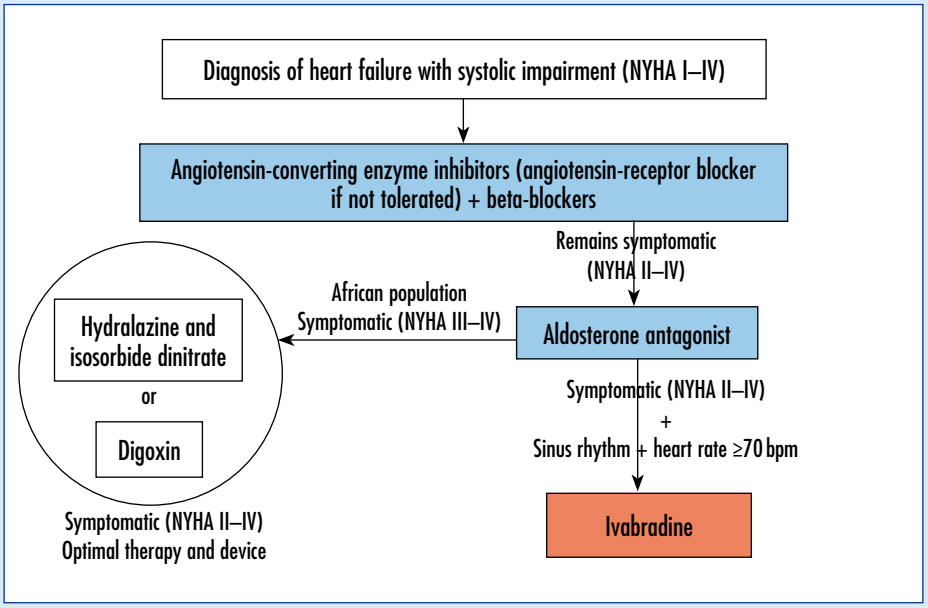
Old drugs

The neurohumoral axis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

The pathogenesis of heart failure is driven by two neurohumoral systems: the renin–angiotensin–aldosterone system and the sympathetic nervous system.

A decrease in cardiac output stimulates activation of these two systems in an attempt to compensate for cardiac dysfunction via vasoconstriction and augmenting cardiac output using the Frank–Starling mechanism. However, left unchecked, the increase pre-load and after-load causes worsening of cardiac function through adverse remodelling of the myocardium and vasculature. Current treatments counteract these adverse remodelling processes.

Figure 1. Pharmacological options for patients with heart failure with systolic impairment. NYHA = New York Heart Association.



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The CONSENSUS II study marked the beginning of angiotensin-converting enzyme inhibitors as the cornerstone in heart failure treatment. The study was terminated early with only 253 patients randomized to placebo or enalapril because there was a 40% reduction in death at 6 months in the treatment group (CONSENSUS Trial Study Group, 1987). These results were replicated by the SOLVD-Treatment trial that demonstrated mortality benefit and showed a 26% reduction in heart failure hospitalizations (SOLVD Investigators, 1991).

Although most patients diagnosed with heart failure are started on an angiotensin-converting enzyme inhibitor, few patients achieve the target dose. The ATLAS study (Packer et al, 1999) showed that patients on high-dose lisinopril (30 mg daily) had a 12% lower risk of re-hospitalization or death than patients treated with low-dose lisinopril (5 mg daily). It is thus essential that angiotensin-converting enzyme inhibitors are increased towards the target doses set out in guidelines and evaluated in study populations.

Most hospital doctors feel reluctant to uptitrate doses for fear of causing hypotension or renal deterioration. Angiotensin-converting enzyme inhibitors cause selective vasoconstriction of the afferent renal arteriole and vasodilatation of the efferent arteriole, resulting in reduced perfusion pressure at the glomerulus and hence reduced glomerular filtration rate. Thus, a change in renal function is almost universal and a 15–20% rise in creatinine is acceptable. Even if the rise in creatinine exceeds this, other causes (most notably excess diuretic dose) should be sought before reducing the angiotensin-converting enzyme inhibitor dose.

Recommended doses of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers from clinical trials are shown in *Table 1*.

In patients intolerant to angiotensin-converting enzyme inhibitors, angiotensin receptor blockers are an alternative. The CHARM-Alternative trial showed that candesartan reduced cardiovascular and heart failure hospitalization by 23% (Granger et al, 2003). The efficacy of angiotensin receptor blockers was further supported by the VALIANT study that demonstrated valsartan's non-inferiority to captopril (Pfeffer et al, 2003). As with angiotensin-converting enzyme inhibitors, high doses are more effective than low doses. In the HEAAL study (Konstam et al, 2009) there was a significant reduction in the combined end point of mortality or hospitalization in patients treated with high-dose (150 mg a day) compared to patients treated with low-dose (50 mg a day) losartan (hazard ratio 0·90, 95% confidence interval 0·82–0·99; P=0·027).

Angiotensin receptor blockers can also be used in addition to angiotensin-converting enzyme inhibitors. Evidence from the CHARM-Added trial showed a 17% and 16% reduction in heart failure hospitalization and cardiovascular death (McMurray et al, 2003).

A paradigm shift in thinking: beta-blockers and heart failure

For many years, conventional teaching was that beta-blockers were contraindicated in heart failure because of their negative inotropic effect. This misconception was dispelled following the first large randomized controlled trial which randomized over 1000 patients with mild, moderate or severe heart failure and ejection fraction <0.35 to placebo or carvedilol. The beta-blocker group had a 65% overall mortality reduction and a 27% reduction in cardiovascular hospitalization (Packer et al, 1996). This impressive finding propelled further beta-blocker trials that confirmed the results (*Table 2*).

Beta-blockers dampen the sympathetic response, decrease heart rate and myocardial oxygen demand through their negative chronotropic effect while mitigating the effects of myocardial remodelling by reducing renin secretion. Beta-blockers have reduced the incidence of sudden death in patients with heart failure and are effective across all heart failure subtypes. They also increase ejection fraction despite the negative inotropic effect inherent with these medications.

Table 1. Drugs, trials and dosages for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Drug		Key trials	Start dose	Target dose
Angiotensin-converting enzyme inhibitors	Captopril	SAVE (Pfeffer et al, 1992)	6.25 mg tds	50 mg tds
	Enalapril	CONSENSUS (CONSENSUS Trial Study Group, 1987), SOLVD-Treatment (SOLVD Investigators, 1991)	2.5 mg bd	20 mg bd
	Lisinopril	ATLAS (Packer et al, 1999)	2.5 mg od	35–40 mg od
	Ramipril	AIRE (AIRE Investigators, 1993)	1.25 mg bd	5 mg bd
	Trandolapril	TRACE (Køber et al, 1995)	0.5 mg od	4 mg od
Angiotensin receptor blockers	Candesartan	CHARM-Alternative/Added (McMurray et al, 2003)	4 mg od	32 mg od
	Losartan	ELITE (Pitt et al, 1997), HEALL (Konstam et al, 2009)	50 mg od	150 mg od
	Valsartan	Val-HeFT (Cohn et al, 2001), VALIANT (Pfeffer et al, 2003)	40 mg bd	160 mg bd

bd = twice a day; od = once a day; tds = three times a day

Table 2. Drugs, trials and dosages for beta-blockers

Drug	Key trials	Start dose	Target dose
Bisoprolol	CIBIS-II (CIBIS-II Investigators, 1999)	1.25 mg od	10 mg od
Carvedilol	COPERNICUS (Packer et al, 2001)	3.125 mg od	25–50 mg bd
Metoprolol	MERIT-HF (MERIT-HF Investigators, 1999)	12.25 mg od	200 mg od
Nebivolol	SENIORS (Flather et al, 2005)	1.25 mg od	10 mg od

bd = twice a day; od = once a day

Despite their benefits, the BEST study using bucindolol failed to show a significant mortality reduction (Beta-Blocker Evaluation of Survival Trial Investigators, 2001). The short-acting metoprolol tartrate was also found to be inferior to carvedilol in the COMET study (Poole-Wilson et al, 2003). These studies illustrate the importance of not assuming a class effect of drugs but adhering to the evidence derived from trials.

Beta-blockers remain underused by clinicians. They are often stopped in acute decompensation, not prescribed in patients with chronic obstructive pulmonary disease and used overcautiously in patients with low blood pressure. Evidence from randomized controlled trials shows that beta-blockers are safe to continue during episodes of decompensation although some required dose reduction. Chronic obstructive pulmonary disease by definition is a fixed airway obstruction and should not be affected by a beta-blocker. There is emerging evidence that patients with chronic obstructive pulmonary disease have a better prognosis when treated with beta-blockers (Short et al, 2011).

Initiation of beta-blockers should follow the 'start low, go slow' philosophy, with the dose gradually building up over no more than 2-weekly intervals toward the target dose.

New drugs

Breaking new ground: ivabradine in heart failure

For the last three decades, pharmacological therapy for heart failure was focused on refining neurohumoral antagonism. Ivabradine works on a hypothesis that heart rate is a mediator for progression of heart failure and controlling it would bring benefits.

Ivabradine acts on the I(f) channels in the sinoatrial node to lower heart rate. The SHIFT study tested this hypothesis by recruiting 6588 patients in New York Heart Association (NYHA) class II–IV, with ejection fraction < 35% and a starting heart rate of >70 bpm. It showed an 18% risk reduction in the composite end point of cardiovascular death or hospitalization for worsening heart failure. The results were mostly driven by a reduction in hospitalization (Swedberg et al, 2010).

The study required patients to already be on optimal therapy and although it boasted 90% compliance with a beta-blocker, it has been criticized as only 26% of the patients were on a target beta-blocker dose raising the question of whether ivabradine would still be effective if all patients in the trial were adequately treated with beta-blockers.

Nevertheless, the European Society of Cardiology gives ivabradine a class IIa recommendation for patients who are on optimal therapy with an adequate beta-blocker dose and a heart rate of > 70 bpm (McMurray et al, 2012). It has also been recommended that ivabradine is used in patients who cannot tolerate a beta-blocker. However, it is worth emphasizing that ivabradine's emergence is not a substitute for well-established beta-blocker treatment but rather an adjunct to the existing therapy. Ivabradine dosing should aim for a target dose of 7.5 mg twice per day.

New indications

Teaching an old dog new tricks: aldosterone antagonism

Spironolactone and eplenerone block the aldosterone receptor as part of the downstream pathway of the renin–angiotensin–aldosterone axis. Apart from the symptomatic benefit achieved through diuresis, aldosterone antagonism translates to mortality benefit by preventing adverse remodelling driven by the renin–angiotensin–aldosterone system (*Table 3*).

The benefit has been known since 1999 when the RALES study reported a 30% relative reduction in death and a 35% reduction in hospitalization when spironolactone was added to angiotensin-converting enzyme inhibitors and beta-blockers (Pitt et al, 1999).

However, the RALES trial was limited to patients with severe heart failure (NYHA class III–IV) and an ejection fraction <35%, leaving out a large proportion of patients with less severe heart failure. This changed following the publication of EMPHASIS-HF which recruited patients in NYHA class II with an ejection fraction <30%. They added two caveats to the inclusion criteria: cardiovascular hospitalization in the last 6 months and raised natriuretic peptide levels. The study demonstrated that eplenerone added to conventional therapy reduced death and hospitalization by 27% (Zannad et al, 2011).

Despite broadening the scope to include more patients, aldosterone antagonists can worsen renal function and cause hyperkalaemia when used in conjunction with an angiotensin-converting enzyme inhibitor. This can be problematic in clinical practice and serial assessment of renal function should be carried out following initiation of this treatment.

No one size fits all: hydralazine-isosorbide dinitrate

The benefits of hydralazine-isosorbide dinitrate were first demonstrated by the VHEFT-1 trial which compared hydralazine-isosorbide dinitrate, prazosin and placebo. Hydralazine-isosorbide dinitrate showed a trend in improving all-cause mortality and exercise tolerance (Cohn et al, 1986).

Hydralazine-isosorbide dinitrate fell out of favour following the V-HEFT2 trial which pitched hydralazine-isosorbide dinitrate against an angiotensin-converting enzyme inhibitor where it was proven to be inferior (Cohn et al, 1991). Two decades after the initial VHEFT-1 study, hydralazine-isosorbide dinitrate was rediscovered in the A-HEFT study where it was compared to placebo in a population of NYHA III–IV African American patients. This combination, when added on to conventional therapy, achieved a 43% reduction in mortality and a 33% improvement in quality of life (Taylor et al, 2004).

The Afro-Caribbean population tends to have a less active renin–angiotensin

Table 3. Drugs, trials and dosages for aldosterone antagonists

Drug	Key trials	Start dose	Target dose
Eplenerone	EMPHASIS-HF (Zannad et al, 2011)	25 mg once daily	50 mg once daily
Spironolactone	RALES (Pitt et al, 1999)	25 mg once daily	50 mg once daily

system and the remodelling process in this population is driven by endothelial dysfunction and oxidative stress. Hydralazine-isosorbide dinitrate prevents vascular and myocardial remodelling by serving as a nitric oxide donor and preventing nitric oxide degradation.

Although the randomized controlled trial indication is mainly in the Afro-Caribbean population, current European Society of Cardiology guidelines (McMurray et al, 2012) support the use of hydralazine-isosorbide dinitrate as an alternative in patients intolerant to angiotensin-converting enzyme inhibitors or angiotensin receptor blocker and in persistently symptomatic patients with ejection fraction <35% or <45% and a dilated left ventricle despite being established on optimal medical therapy. Hydralazine-isosorbide dinitrate should be given at an initial dose of 37.5 mg/20 mg three times per day, with a target dose of 75 mg/40 mg three times per day.

Miscellaneous

Symptomatic but non-prognostic: digoxin

Digoxin together with diuretics was the cornerstone of heart failure treatment in the pre-angiotensin-converting enzyme inhibitor era. Although it confers no prognostic benefit, digoxin has retained a role in the symptomatic management of patients. The DIG study randomized 6800 patients with NYHA class II–IV and ejection fraction <45% and in sinus rhythm to placebo or digoxin and found that, although digoxin did not alter all-cause mortality, there was a 28% reduction in hospitalization from worsening heart failure (Digitalis Investigation Group, 1997).

Digoxin can also be used to rate control patients with heart failure and atrial fibrillation. However, a more logical choice is a beta-blocker that confers a mortality benefit and provides better control of heart rate during exercise.

A work in progress: drugs in the pipeline

Aliskiren

Many of the drugs under development aim to exploit the success of neurohumoral antagonism. Aliskiren, a renin inhibitor, has thus far shown mixed results. The ALOFT study (McMurray et al, 2008) suggested that adding aliskiren to an angiotensin-converting enzyme inhibitor in chronic heart failure patients improved surrogate markers like NT-proBNP (N-terminal prohormone-B-type natriuretic peptide) and urinary aldosterone concentration. However, the ASPIRE study (Solomon et al, 2011) failed to demonstrate additional benefit on measures of left ventricular remodelling. It also caused hypotension and hyperkalaemia in patients who have poor left ventricular function and a recent myocardial infarction.

The jury is still out for aliskiren as both trials relied on surrogate markers and have not investigated mortality and morbidity. Two trials (ASTRONAUT and ATMOSPHERE) measuring cardiovascular deaths and heart failure hospitalization are underway to investigate whether further renin inhibition is suitable.

LCZ696

LCZ696 is an angiotensin receptor-neprilysin inhibitor. Neprilysin inhibitors prevent the degradation of atrial natriuretic peptides resulting in vasodilator and natriuretic effects. LCZ696 is currently being studied in the PARADIGM-HF trial in patients with heart failure and poor left ventricular function. The phase 2 PARAMOUNT study (Solomon et al, 2012) showed promise in patients with heart failure with preserved ejection fraction by reducing NT-proBNP levels. Similar to aliskerin, outcome data are awaited.

RLY5016

RLY5016 works by binding potassium to aid up-titration and optimization of existing therapy. The main concern with RLY5016 is that it causes hypokalaemia and hypomagnesaemia, which can be especially dangerous in cardiac patients. Clinical trials assessing the overall outcome in patients are awaited to determine its suitability in clinical practice.

Heart failure with preserved left ventricular function

Up to 50% of patients with clinical features of heart failure are found to have a normal left ventricular systolic function. These patients are often referred to as having diastolic dysfunction or heart failure with preserved left ventricular function. Despite advances in pharmacological development of heart failure medications, current medications have repeatedly failed to demonstrate survival benefit in this population.

Use of angiotensin receptor blockers has been suggested in these patients. The best evidence is from the CHARM-PRESERVE study (Yusuf et al, 2003) using candesartan. Candesartan prevented heart failure admissions but had no impact on cardiovascular death. On the other hand, the I-PRESERVE study (Massie et al, 2008) that looked at irbesartan had a neutral result.

The TOPCAT study that is underway investigates the role of spironolactone in this population. The rationale is that an aldosterone antagonist can help prevent fibrosis that is believed to be a key pathophysiological factor.

Currently, the management of these patients centres around treating the underlying cause, using diuretics to prevent fluid overload and initiating candesartan.

Conclusions

The aim of treatment in heart failure is to prevent deaths, avoid hospitalizations and relieve symptoms. Pharmacological therapy developed over the last three decades, based on the understanding of the driving pathophysiology, has revolutionized the outlook of heart failure patients.

In addition to pharmacological management, heart failure patients can further benefit from device therapy (cardiac resynchronization therapy, implantable cardiac defibrillators) and surgical interventions. However, these treatments require specialist input and patients who are already established on optimal medical therapy.

All doctors who come into contact with patients with heart failure can help to optimize their medical treatment and positively affect their outcome by ensuring that patients are on the appropriate medications and are titrated to the target dose. BJHM

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KEY POINTS

- All patients with heart failure (New York Heart Association I–IV) and left ventricular systolic dysfunction should be started on an angiotensin-converting enzyme inhibitor and a beta-blocker unless contraindicated.
- Optimal medical therapy consists of not only starting patients on the appropriate drugs but ensuring up-titration of the medication toward the target dose.
- Angiotensin-converting enzyme inhibitors and beta-blockers should be up-titrated. Asymptomatic hypotension is not a contraindication to increasing the dose.
- Aldosterone antagonists (eplenerone, spironolactone) are now indicated in symptomatic patients with left ventricular ejection fraction <35% as an add-on therapy.
- Ivabradine can be considered as an add-on to angiotensin-converting enzyme inhibitor plus beta-blocker plus aldosterone antagonist in patients who remain symptomatic and have a heart rate >70 bpm.
- Hydralazine/isosorbide dinitrate can be considered in Afro-Caribbean patients on optimal therapy in New York Heart Association class III–IV or all patients who remain symptomatic despite device and optimal medical therapy.