Review Article

Medical Therapy in Heart Failure – Is Polypharmacy Necessary?

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Abstract

The concept of heart failure has undergone several paradigm shifts in the past few decades. Therapeutic targets directed at the heart pump have shifted to circulatory haemodynamics to the current neurohormonal model. Consequently, therapeutic modalities have similarly evolved alongside clinical trials. Successive trials have tested newer drugs in addition to established therapies, resulting in evidence-based treatments necessitating polypharmacy. Optimal heart failure therapy has therefore become increasingly complex. It is only after understanding the precise modes of drug action, as well as the relevance of the design of clinical trials, will physicians hopefully be able to tailor the medical therapy optimally towards the individual patient with heart failure.

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Introduction

The clinical syndrome of heart failure is recognised by a characteristic pattern of haemodynamic, renal, neural and hormonal responses. Heart failure is the end-stage of all heart diseases. It is not a disease, but the common end of the cardiovascular continuum.[1] Epidemiological studies have documented improved survival of patients treated for heart failure over the past few decades.[2] Despite these improvements, overall survival remains poor, with the average heart failure patient showing 40% mortality in 5 years.

The Evolving Paradigms of Heart Failure

Until recently, management of congestive heart failure was based on a haemodynamic model. Based on this setting, the primary targets of treatment were to improve positive inotropism and peripheral unloading with vasodilation and diuresis. However, we now know the syndrome of heart failure involves activation of endogenous neurohormonal systems leading to ventricular remodelling.[3-6] This concept represents a new understanding of the "neurohormonal paradigm" of congestive heart failure.

Evolution of Heart Failure Trials

The first neurohormonal axis targeted was the renin-angiotensin pathway. Large clinical trials of angiotensin-converting enzyme (ACE) inhibitors in the 1980s and 1990s have firmly established the undisputed benefits of ACE-inhibition in the treatment of congestive heart failure. These trials demonstrated significant reductions in mortality and morbidity.[7-11]

The success of ACE-inhibition in congestive heart failure shifted attention to the sympathetic nervous system and its neurohormonal stimulation of the heart. As early as 1984, Cohn et al[12] have shown the deleterious effect of plasma norepinephrine in patients with heart failure. More recently, trials of beta-blockers have together demonstrated mortality and morbidity reductions with their use in heart failure patients of New York Heart Association (NYHA) functional classes II-IV.[13-16]

Low dose spironolactone, an aldosterone antagonist, was then shown to confer mortality benefits in patients with severe heart failure (NYHA class III-IV).[17] The focus further shifted to more selective aldosterone antagonists.

In the past few years, major drug trials in heart failure have turned the attention to angiotensin receptor blockers (ARBs), either as an alternative, or as an additional drug to ACE-inhibitors.[18-20] Such large-scale trials have yielded slightly differing results.

As a result of the design and chronology of these trials, the therapy of heart failure has led to the need for polypharmacy. Placebo-controlled trials were no longer ethically possible, leading to a proliferation of "add-on" therapeutic trials. With each "positive" trial showing

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beneficial effects, an additional drug would be added to the armamentarium of heart failure therapy. The following sections will deal with each class of drugs individually.

Treatment Targets

The therapeutic goals in heart failure management are: (1) to reduce symptoms, thereby improving quality of life, and (2) to improve survival. Table 1 summarises the current clinical evidence of various classes of drugs in achieving these aims. Presently available drugs for heart failure therapy can be classified into 2 groups, based on reduction in either morbidity or mortality.

Table 1. Summary of Current Clinical Evidence of Available Drugs for Heart Failure

Drug class	Reduce morbidity	Reduce mortality
ACE inhibitors	+	+
Beta-blockers	+	+
Aldosterone antagonists		
Spironolactone	+	+
Eplerenone	+	+
Digoxin	+	0
Loop diuretics	+	0
Hydralazine + Isosorbide dinitrate	+	+
ARBs		
Losartan	+	0
Valsartan	+	0
Candesartan	+	+

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker

Drugs Conferring Mortality Benefits

Drugs shown to reduce mortality in heart failure patients include the following:

Angiotensin-converting Enzyme Inhibitors

Over the past 20 years, the collective experience of ACE-inhibitors has established this class of drugs as the cornerstone of heart failure therapy. ACE-inhibitors alleviate symptoms, as well as improve survival in patients with heart failure. In addition, progression to heart failure in patients with asymptomatic left ventricular dysfunction is attenuated. From early studies with captopril and enalapril, to more recent studies with ramipril, ACE-inhibitors have consistently exhibited a beneficial "class-effect" in the treatment of heart failure. A meta-analysis by Garg and Yusuf[21] concluded there were no significant differences between several different agents.

When prescribed in the early post myocardial infarction setting, ramipril and captopril reduced mortality and recurrent event rates in patients with heart failure and asymptomatic left ventricular dysfunction, respectively.[9,10] In the prematurely terminated Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), patients with severe heart failure given enalapril had reduced mortality, as well as improved functional capacity.[7] The mortality benefit was maintained at 10-year follow-up.[22] The morbidity benefit of ACE-inhibitors was best demonstrated in the Effect of Enalapril on Mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions (SOLVD-prevention) study, where patients with asymptomatic left ventricular dysfunction given enalapril had less progression to heart failure and need for hospitalisation.[23] With such overwhelming burden of evidence, ACE-inhibitors should be considered the first-line drug of choice in heart failure therapy.

Major guidelines in the therapy of heart failure have stated or emphasised the importance of up-titrating ACE-inhibitors to those doses used in clinical trials.[24,25] This is supported by dose-ranging studies, such as the comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure (ATLAS) study, where lisinopril at higher doses is more efficacious.[26] However, in 2 studies with enalapril, there were no significant differences in efficacy at low versus high doses.[27,28]

Beta-Blockers

The use of beta-blockers appears counter-intuitive when viewed using the haemodynamic model. Beta-blockers are negatively inotropic and chronotropic, thereby leading to further reduction in cardiac output. However, we now know neurohormonal blockade of the sympathetic system results in beneficial effects in patients with heart failure.

Increased circulating plasma norepinephrine level is associated with worse prognosis in heart failure patients.[12] Using multivariate analysis, it has been found to be superior to haemodynamic measurements as an independent predictor of mortality.

Major consensus recommendations now advocate the use of beta-blockers in patients with symptomatic heart failure (NYHA class II-III). It began almost 30 years ago, when Waagstein and co-workers[29,30] showed that practolol, a beta-selective antagonist, was well tolerated in patients with heart failure. They later demonstrated the long-term benefits of another beta-blocker, metoprolol, in idiopathic dilated cardiomyopathy.[31] More recent studies have also shown that beta-blockers can reduce symptoms, improve left ventricular function and functional capacity in patients with heart failure.[32-38]

Large-scale clinical trials have demonstrated mortality benefits of beta-blockers. The US Carvedilol Heart Failure Study, which was terminated early, showed carvedilol

reducing overall mortality by 65%.[13] A meta-analysis of beta-blockade in heart failure by Lechat et al[39] showed all-cause mortality reduction of 32%. As if confirming this finding, the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[14] results reported identical all-cause mortality reduction of 32% by bisoprolol. This was followed a few months later with the publication of the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) results.[15] This trial showed metoprolol CR/XL reduced all-cause mortality by 34%. It is important to note that these trials demonstrated the benefits of beta-blockers when they were added to standard treatment with ACE-inhibitors and diuretics. In these trials, mortality reduction was achieved by reduction in sudden death, as well as progressive heart failure.

In advanced heart failure, only carvedilol has been shown to reduce mortality. The Effect of Carvedilol on Survival in Severe Chronic Heart Failure (COPERNICUS) trial enrolled patients in NYHA classes III and IV, where carvedilol reduced mortality by 35%.[16]

However, unlike ACE-inhibitors where a "class-effect" possibly exists, not all beta-blockers are beneficial in the treatment of heart failure. The Bucindolol in patients with Advanced Chronic Heart Failure (BEST) study showed that bucindolol, a third generation beta-blocker similar to carvedilol, did not reduce mortality in advanced heart failure.[40] In a head-to-head comparison trial of 2 beta-blockers, carvedilol was superior to metoprolol in reducing cardiac events.[41] However, the formulation of metoprolol used in this trial was different from the one approved for use in heart failure. There remains no clear evidence of superiority of any beta-blocker over another.

The selectivity of beta-blockers does not appear to influence their effect in heart failure. While carvedilol is a non-selective beta-blocker with $\alpha 1$ blockade, as well as antioxidant effects, bisoprolol and metoprolol are $\beta 1$-selective blockers with no ancillary properties. Perhaps the answer may lie in the lipophilic properties of the drugs. The evidence appears to favour lipophilic beta-blockers.

Whilst physicians should attempt using beta-blockers at doses comparable to those in clinical trials, we frequently find patients' bradycardia to be a limiting factor. Nevertheless, in up-titrating beta-blockers, the maxim "start low, go slow" remains quintessential.[42] Starting with high doses or up-titrating too quickly can precipitate decompensation in patients with heart failure.

Aldosterone Antagonists

Spironolactone, a non-selective aldosterone antagonist, was shown to reduce morbidity and mortality in patients with severe heart failure.[17] The low dosage (mean of 26 mg/day) employed in the trial suggested that the beneficial effect was mediated via the neurohormonal axis rather than via its diuretic effect. However, side effects of hyperkalaemia and gynaecomastia limit its wider use. The effects of spironolactone in patients with milder heart failure (NYHA classes I-II) remain unclear. In vitro studies demonstrating spironolactone's effect in reducing cardiac fibrosis may support its early use in patients with less severe heart failure.[43]

The selective aldosterone antagonist, eplerenone, was studied in the setting of heart failure early after myocardial infarction.[44] When added to optimal medical therapy, it was shown to reduce morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure. Hyperkalaemia was expectedly a frequent adverse event, whereas gynaecomastia was not more common than in the placebo group. However, the effects of eplerenone in chronic congestive heart failure are less clear.

When adding an aldosterone antagonist to any heart failure patient's treatment plan, frequent measurement of serum potassium is necessary, especially when there is concomitant renal dysfunction.

Angiotensin Receptor Blockers

The rationale for blockade of the renin-angiotensin axis arises from the deleterious effects of angiotensin II. Figure 1 shows the renin-angiotensin system and how it can be modulated. While there is strong and convincing evidence that ACE-inhibitors reduce mortality in heart failure, intolerance to ACE-inhibitors remains common. A high incidence of cough, particularly in Asians, has been reported.[45,46] This has been attributed to the accumulation

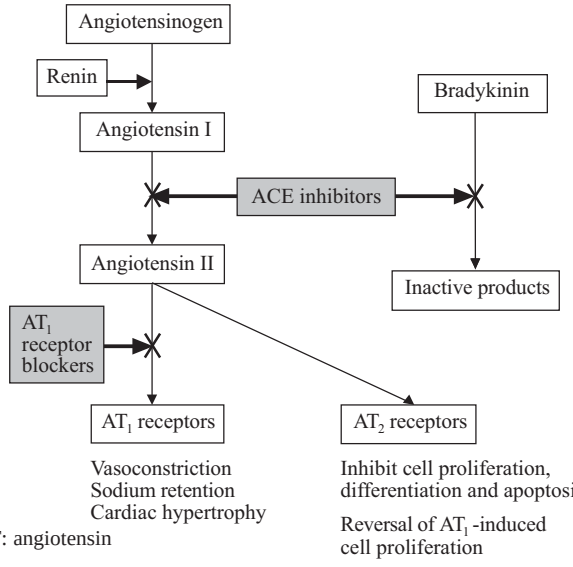


Fig. 1. Renin-angiotensin system and the sites of action of ACE-inhibitors and angiotensin receptor blockers.

of bradykinins. As a result, the attractiveness of ARBs is obvious. ARBs may provide more complete blockade of angiotensin II, without the accompanying buildup of bradykinin.

The Effect of Losartan Compared with Captopril on Mortality in patients with Symptomatic Heart Failure: Losartan Heart Failure Study (ELITE-II) is the first major published trial comparing an ARB to ACE-inhibitor.[18] Although losartan was shown not to be superior to captopril in improving survival, it was possibly equally effective and better tolerated. The Val-HeFT investigators reported that addition of valsartan to standard therapy in heart failure resulted in symptomatic improvement.[19] There was no significant impact on mortality.

The best results, by far, came from the CHARM programme.[20] In heart failure patients who are ACE-inhibitor intolerant, candesartan was shown to reduce morbidity and mortality.[47] When candesartan was added to patients already taking ACE-inhibitors, there was further reduction in cardiovascular events.[48] Therefore, whether used alone or in combination with ACE-inhibitors, candesartan showed beneficial results.

As the ARB trials showed differing results, ACE-inhibitors remain the cornerstone of heart failure therapy. The evidence currently supports the use of ARBs in ACE-inhibitor intolerant patients, and in patients who remain symptomatic despite the use of ACE-inhibitors. Routine combination use of ARBs with ACE-inhibitors should be discouraged as this combination will result in high rates of adverse events.

Hydralazine-Isosorbide Dinitrate Combination

An often forgotten but nevertheless effective combination therapy with hydralazine and isosorbide dinitrate was proven many years ago.[49] This combination, though shown to be inferior to ACE-inhibitors, is useful in patients unable to take ACE-inhibitors or ARBs (e.g. due to renal failure or hyperkalaemia).

Drugs Conferring Morbidity Benefits

Digoxin and diuretics have been used successfully by generations of physicians in the management of heart failure. However, there is a lack of scientific data in the form of randomised trials supporting their routine use.

Digoxin

Although commonly prescribed for many years, digoxin's role in the management of heart failure was only recently clarified. The DIG trial showed that digoxin did not reduce mortality. Its beneficial effect on morbidity is in the form of reduction in the rate of hospitalisation.[50] Its use should therefore be directed at symptomatic patients.

Diuretics

Many generations of physicians would attest to the efficacy of diuretics, particularly of loop diuretics, in the management of heart failure patients. In fact, it is unimaginable not to prescribe diuretics to a patient who is in an obvious state of fluid overload. Unfortunately, there are no randomised trials to prove its efficacy, and there will unlikely be any, due to ethical reasons.

Emerging Therapies on the Horizon

Several classes of agents are currently in various stages of investigative studies, to determine their roles, if any, in the management of heart failure.

Calcium Sensitisers

Levosimendan, a novel agent which increases the sensitivity of cardiac troponin C to calcium, thereby improving myocardial contractility without increasing adenosine triphosphate consumption.[51] Follath et al[52] showed that intravenous levosimendan was better than dobutamine in improving haemodynamics in severe, low-output heart failure. The benefit was also accompanied by lower mortality in the short- to mid-term. However, current calcium sensitisers also possess vasodilatory effects, which results in reflex increase in myocardial contractility and cardiac output. Hence, it is premature to conclude that calcium sensitisation is an effective mode of heart failure therapy.

Endothelin Receptor Blockers

The endothelin-1 (ET-1) isoform of endothelins possess potent vasoconstrictive effects. Blockade of ET-1 therefore attracted considerable attention in the treatment of pulmonary hypertension. Bosentan has been approved for use in primary pulmonary hypertension. However, studies of ET receptor blockers in heart failure have been disappointing. Although some studies have suggested benefit, larger studies have been neutral.[53-55] Further studies are needed to determine if dosing issues compounded previous trials.

Vasopeptidase Inhibitors

The vasopeptidase inhibitors are a new class of agents, which inhibit the activity of neutral endopeptidase, an enzyme that metabolises endogenous vasodilator peptides. This inhibition results in reduced production of the vasoconstrictor angiotensin II. Omapatrilat is the first vasopeptidase inhibitor to be studied in heart failure patients. The Comparison of Vasopeptidase Inhibitor, Omapatrilat, and Lisinopril on Exercise Tolerance and Morbidity in patients with Heart Failure (IMPRESS) trial did not live up to its name, where omapatrilat was found not to show any

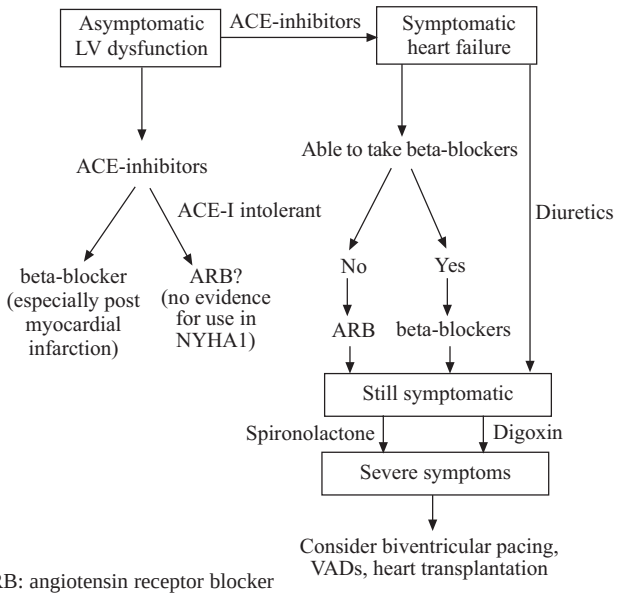
benefit over lisinopril on patients' exercise tolerance and morbidity.[56] Similarly, the Comparison of Omapatrilat and Enalapril in patients with Chronic Heart Failure: the Omapatrilat versus Enalapril Randomised Trial of Utility in Reducing Events (OVERTURE) trial showed no difference in the primary endpoint (death or hospitalisation) when omapatrilat was compared with enalapril.[57] Due to the higher incidence of adverse effects, especially angio-oedema, associated with omapatrilat, ACE-inhibitors remain undoubtedly the drug of choice.

Natriuretic Peptide

B-type natriuretic peptide is synthesised in ventricular myocardium, where its levels are increased in patients with heart failure. Nesiritide, a recombinant human B-type natriuretic peptide, is the first heart failure drug in 20 years to be approved by the Unites States Food and Drug Administration (FDA). When infused to patients with heart failure, it resulted in haemodynamic improvement.[58] Short-term studies with nesiritide did not show reduction in mortality, although it improved haemodynamics and patient symptoms more readily.[59] This drug is currently unavailable in Singapore.

Systolic versus Diastolic Heart Failure

In this present discussion, the author has deliberately limited the scope to heart failure caused by ventricular systolic dysfunction, and avoided the issue of diastolic dysfunction. Current diagnostic criteria for diastolic heart failure are both incomplete and imperfect.[60,61] In addition, there is lack of evidence-based approaches to its treatment.



ARB: angiotensin receptor blocker
NYHA: New York Heart Association
VAD: ventricular assist device

Fig. 2. Algorithm for medical management of chronic heart failure.

Haemodynamic studies have confirmed the theoretical advantage of beta-blockade in diastolic heart failure. However, clinical outcome trials are lacking. The only published trial on this area is CHARM-Preserved, which showed candesartan was able to reduce morbidity by preventing hospitalisations in heart failure patients with left ventricular ejection fraction of >40%.[62] Other on-going trials will hopefully shed more light on this subject.[63]

Tailored Therapy: A Little of Everything?

The optimal management of patients with heart failure is increasingly complex. The conventional approach to therapy targeting haemodynamic abnormalities of fluid retention or pulmonary congestion is inadequate. The complex neurohormonal milieu of the heart failure patient is only just being discovered. Treating the neurohormonal derangement in the heart failure patient is comparable to walking into a maze without a map.

The plethora of heart failure trials with positive outcomes results in evidence-based medicine dictating the use of multiple drugs. The combined use of drugs with mortality and morbidity benefits in heart failure invariably requires polypharmacy. Though it is tempting to up-titrate such drugs to doses used in clinical trials, the current consensus is to individualise and tailor pharmacological therapy accordingly. Combined use of low doses of several drugs is preferred to large doses of single agent. In Figure 2, the author offers a simplified algorithm to the pharmacological treatment of heart failure.

Hopefully, the future will allow determination of serum neurohormones, thereby allowing more precise titration of drugs to optimal, instead of maximal doses. This form of tailored therapy would be consistent with the current model of heart failure.

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