

2006 CE Series — Lesson One

Updates and Current Recommendations in the Treatment of Heart Failure

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Goals:

- 1) To review the current approach to the management of heart failure.
- 2) To acquaint the community pharmacist with new models of assessing and categorizing the degree of heart failure.
- 3) To review the pharmacologic basis of currently recommended drugs for heart failure.

Objectives: Following completion of this topic, the community pharmacist should be able to

- 1) understand the current terminologies used when discussing heart failure,
- 2) identify drugs appropriate for individual patients, determined by their degree of disease, and
- 3) educate the patient and fellow health care providers on the pharmacologic basis for efficacy of selected drug therapies.

Introduction

While many advances in medical therapy involving 1) diagnosis and early detection of disease, 2) advanced drug therapy and monitoring the efficacy thereof, and 3) improved education of patients on the importance of diet and exercise has resulted in decreases in many cardiovascular disease states, heart failure remains a major contributor to death rates in this country. In fact, while all other cardiovascular disease rates have decreased in recent years, heart failure is the only one to show an increase in incidence. This may be due, in large part, to the increase in longevity that has resulted from the aforementioned advances and the added years of work that is required of the heart as an organ. This is supported by epidemiological evidence which indicates that heart failure is present in roughly 2-3% of persons aged 65, while amongst persons aged greater than 80 years the incidence skyrockets to 80%.

The current state of heart failure in patients has prompted clinicians to examine closely their approaches to the disease. This examination has focused on the early detection and diagnosis of heart failure, attempts to decrease predisposing risk factors, and plans to optimize both pharmacologic and non-pharmacologic therapy. The goals of therapy include reductions in office visits and hospitalizations secondary to the disease, improved quality of life, and of course a delayed morbidity. The results, published in September 2005, represent the latest approaches to the treatment of heart failure, including a new classification scheme designed to quantify the clinical presentation of the disease, proper pharmacologic therapy for each classification, and consideration of when specific therapies are appropriate or not. Since the community pharmacist is a key member of the health care team, his understanding of current terms is important in

understanding the level of care a patient may require. Additionally, since the pharmacist is central in drug therapy and potential benefit and/or complications that may arise from it; this article will focus on a comparison of the new scheme with older methods of classification and the pharmacologic recommendations for treatment, with a review of their pharmacodynamic bases of efficacy.

Progression of Heart Failure and Its Classification

There are numerous risk factors that may predispose a patient to heart failure, including, but not limited to, hypertension, coronary artery (or atherosclerotic) disease, diabetes mellitus, obesity, metabolic syndrome, and the use of cardiotoxins such as excessive ethanol intake and smoking. Additionally, structural damage ultimately causing heart failure may arise from myocardial infarction or other injuries to the myocardium directly or indirectly. Disease states and dietary deficiencies (such as hyperthyroidism and beri-beri) may also cause a progressive cardiac failure characterized by a high cardiac output. Once the myocardium is damaged, either through chronic insult from the aforementioned risk factors or some cardiac event, a progressive decline in cardiac function is observed.

In the earliest stages of heart failure, the patient is often asymptomatic and the reduction in cardiac output may be minimal. However, as the cardiac output continues to decline, decreases in blood pressure and renal perfusion will cause compensatory actions designed to increase cardiac function. These reflex actions include stimulation of the cardioacceleratory centre of the CNS, causing increased sympathetic tone to both the heart and the vasculature. This adrenergic-mediated action will have positive chronotropic and inotropic effects (increased heart rate and force of contraction) as well as vasoconstricting effects. Concurrently, the kidney responds by initiating the renin-angiotensin-aldosterone system, prompting the retention of sodium and water in an attempt to correct the perceived decrease in blood volume and pressure. This phase of the disease has historically been referred to as compensated heart failure. A relatively new term, used to describe these changes in cardiac structure and function, is remodeling. These changes are thought to be due to a combination of increased sodium, increased actions of noradrenaline, and increased aldosterone acting at specific cellular sites and receptors within the heart itself. It is well recognized that the added workload on the heart, a combination of increased sympathetic tone and increased afterload secondary to water retention, will cause the progression of the disease to the uncompensated or decompensated phase, in which structural changes in the heart are evident, including thinning and loss of contractility and elasticity of the ventricular wall. Typically, during this decompensated phase, the patient begins to exhibit the classic signs of heart failure including pulmonary edema (dyspnea, orthopnea), pitting edema, ascites, and fatigue (depending upon whether the failure is predominantly right or left sided) and the term congestive heart failure was used to describe this (it is currently recommended to simply refer to the disease as heart failure, since the congestion does not appear early nor in every patient).

For many years, this concept of pre-existing heart disease, compensated failure following initial structural damage to the heart, and subsequent decompensated failure served as the standard when discussing heart failure. Since fatigue and dyspnea are such prominent symptoms of heart failure, the New York Heart Association published a Heart Failure Symptom Classification

System based upon these, labeled NYHA I-IV, to assess patients and determine their treatment options. In this system, NYHA I patients are not limited in their physical activity by fatigue or dyspnea. NYHA II patients are somewhat limited in their ordinary physical activities by these symptoms. NYHA III patients will experience fatigue and/or dyspnea upon even less activity, and NYHA IV patients will suffer from fatigue/dyspnea at rest or following very little exertion. Therefore, the NYHA scheme represents a progressive classification which follows the progression of the disease.

The new classification scheme, published in September 2005 by the American College of Cardiology and the American Heart Association (ACC/AHA), is similar to both of these older systems, but includes those patients at risk of developing heart failure and is based upon a combination of risk, structural damage, and symptomatology. The ACC/AHA Classification of Chronic Heart Failure uses the designators A, B, C, and D. Stage A includes all patients who are at risk of developing heart failure, but do not present with structural damage or symptoms of heart failure. Stage B, sometimes labeled asymptomatic heart failure, includes those patients with structural damage but who do not present with symptoms of heart failure. Stage C or symptomatic failure includes patients with structural damage who currently exhibit symptoms of heart failure or have a prior history of symptoms. Stage D represents refractory or end-stage heart failure. There is some degree of overlap between these three systems, as summarized in Table 1.

Approaches to Therapy – New Classification System

In addition to the new classification scheme for heart failure itself, the ACC/AHA have revised the classification system of therapeutic options in heart failure, in an attempt to provide a systematic, literature-based approach to optimizing care. Included in this scheme are many non-pharmacologic and pharmacologic therapies. The system is divided into three ranks, labeled I, II, and III, with subdivisions by A, B, and C. Class I treatment options are those for which evidence and general agreement indicate that the treatment is beneficial, useful, and effective in attaining the goals of heart failure therapy. Class II represents treatments for which there is conflicting evidence supporting their use and it is divided into Class IIa and Class IIb. Class IIa treatments are those where evidence and opinion indicate usefulness and efficacy while for Class IIb the evidence is less well established. Class III treatments are considered inappropriate, based upon evidence that they are not useful or beneficial and/or may be harmful. These are summarized in Table 2, indicating the relative risk:benefit ratio for each. The determination of weight of evidence used in this classification scheme was based upon available literature and was ranked A, B, or C, depending upon the study design, statistical analysis, randomization of patients, and consensus opinions of experts in the field. Any further discussion of the methods used is beyond the scope of this article.

As far as pharmacotherapy is concerned, the most significant changes by these new guidelines are the shifts of some drugs to higher or lower classifications. Specifically, the angiotensin converting enzyme inhibitors (ACEIs), long considered a first line drug of choice, were shifted from a Class I treatment option to Class IIa for patients in Stage A heart failure. Additionally, for Stage C patients, aldosterone inhibitors (such as spironolactone and eplerenone) have been

upgraded to a Class I treatment, while digoxin has been downgraded to a Class IIa recommendation.

A summary of these most current recommendations, based upon the stage of heart failure, may be found in Table 3 with specific choices made based upon the history and needs of the individual patient.

Pharmacodynamic Basis for Drug Efficacy in Heart Failure

Each of the drug classes that are currently used for various stages of heart failure are included for specific effects that help the clinician meet his goals of therapy – decreasing disease-related office visits and/or hospitalizations, improving quality of life, or delaying disease progression and decreasing the morbidity/mortality for as long as possible, depending upon the stage of disease. Below is a brief summary of why these classes of drugs are effective and used during specific stages of heart failure. While the complete drug profile (pharmacokinetics, adverse drug reactions and toxicities, drug interactions, dosing, etc.) is important, these drugs are familiar to pharmacists and no new drugs have been introduced within the past two years. Therefore, these summaries will focus only on the pharmacodynamic basis for their efficacy.

Diuretics – The thiazide (hydrochlorothiazide, metolazone, etc.), loop (furosemide, bumetanide), and potassium sparing (amiloride, triamterene, etc.) diuretics are all used in heart failure. As indicated in Table 3, their use is certainly appropriate in Stage C heart failure, but they are most often started in Stage A, as a treatment for hypertension in attempts to minimize risk for developing heart failure. Regardless of the specific mechanisms involved for each class, their overall pharmacodynamic effect is to decrease total body water volume and blood volume and therefore decrease total peripheral resistance. By decreasing afterload, the heart does not have to pump as hard to eject blood and peripheral perfusion is improved. Additionally, since the theory that excess sodium may play a role in the remodeling of the heart, the direct natriuretic effects of the diuretics may also be beneficial in slowing the progression of failure.

Aldosterone Antagonists – While spironolactone and eplerenone are potassium sparing diuretics, and thus beneficial for the reasons stated above, they may also be beneficial in heart failure due to extra-renal actions as well. Recall that during remodeling, it is proposed that aldosterone, acting at receptors directly in the heart, may contribute to the structural and physiological changes that lead to decompensated failure. It is currently thought that blocking these cardiac effects of aldosterone with specific antagonists will slow the remodeling, thus slowing the progression of the disease.

Angiotensin Antagonists – There are two classes of angiotensin antagonists available for use, viz the angiotensin receptor antagonists (drugs such as losartan, valsartan, candesartan, etc) and those that inhibit the synthesis of angiotensin (the ACEIs such as lisinopril, enalapril, captopril, etc). Pharmacodynamically, these drugs actually have a dual response that is beneficial in treating heart failure. Recall that the renin-angiotensin-aldosterone system is responsible for correcting drops in blood pressure and volume. Angiotensin has a direct vasopressor effect, causing contraction of vascular smooth muscle with subsequent vasoconstriction. It also prompts

the release of aldosterone, which in turn is responsible for sodium retention (and the subsequent release of anti-diuretic hormone, causing water retention) and the direct cardiac remodeling effects noted above. By blocking the actions of angiotensin, these drugs will 1) prevent vasoconstriction directly (thus reducing afterload and improving cardiac performance) and 2) prevent the actions of aldosterone indirectly. This second effect will produce a diuretic like response, which also reduces total peripheral resistance as noted above and prevent the sodium- and aldosterone-mediated remodeling. Therefore, the angiotensin antagonists are acting as vasodilating, potassium-sparing diuretic, and anti-remodeling drugs.

Vasodilators – Similar to the diuretics, there are many pharmacologic classes of vasodilators that have been and are currently used in patients with heart failure. These may be categorized broadly as venodilators and arteriodilators and they may act by different mechanisms. Their common pharmacodynamic effects, however, are to cause relaxation of vascular smooth muscle (or prevent the contraction of vascular smooth muscle), thus reducing total peripheral resistance and blood pressure. While the venodilators predominantly cause a reduction in preload (the amount of blood returning to the heart) and the arteriodilators focus more on reducing afterload (the pressure the heart has to pump against), both of these actions will reduce cardiac workload and allow the remaining functionality of the heart to pump more efficiently and maintain peripheral perfusion. Two specific vasodilators, hydralazine and isosorbide dinitrate, have been the target of extensive clinical research and are being recommended more in the recent guidelines, both alone and in combination. Marketed in combination, under the trade name BiDil®, it is specifically targeted for males of African descent, in whom it has demonstrated very good clinical responses in heart failure. Other vasodilators that may be considered are the alpha-adrenergic antagonists (prazosin, terazosin, etc.), additional organic nitrates, and nesiritide (a parenteral only drug that is used in severe heart failure).

Beta-adrenergic antagonists (blockers) – For many years, these drugs were contraindicated in heart failure patients due to their negative inotropic effects. However, following clinical trials indicating efficacy, they were approved for use in patients during the NYHA II and III stages of failure. Pharmacodynamically, they are beneficial because of their ability to block sympathetic input into the heart. Recall that during the compensated phase of heart failure, increased sympathetic tone will increase both the rate and force of contraction of the heart. In a heart with structural damage, this will ultimately cause further damage. Therefore, while immediately the increased sympathetic tone may increase cardiac output, chronically this will hasten the failure of the organ, and is part of the remodeling that occurs during compensated failure. These drugs are effective because they block this increased sympathetic tone and thus slow the progression of the disease. It is generally regarded that these drugs do not immediately improve quality of life, nor do they lessen the symptoms of failure. However, they will delay the progression and therefore will decrease heart failure related office visits, hospitalizations, and complications in the middle phases of the disease as well as delaying the refractory phase of the disease. They should not be used in NYHA IV or ACC/AHA Stage D (refractory) heart failure patients, since the negative inotropic effects in those stages would become markedly evident and cardiac output would suffer. Although all blockers may be used, carvedilol and labetalol have some preference over

others in the class. In addition to their antagonism, these drugs also block adrenergic receptors and therefore have some vasodilating properties as well, thus providing two beneficial pharmacodynamic effects.

Positive Inotropes – This group of drugs (digoxin, the beta adrenergic agonists such as dobutamine, and the phosphodiesterase 3 inhibitors such as milrinone) all act to increase the force of contraction of the heart. The latter two are parenteral only, have limitations to their usefulness, and are only used in emergency cases where cardiac output is so low that the life of the patient is in imminent danger. Pharmacodynamically, all positive inotropes are effective by increasing myocardial contractility and thus increasing cardiac output. In general, this will improve peripheral perfusion and reduce the fatigue and edema that accompanies heart failure. However, the increased workload on the heart may cause the failure to progress more rapidly. Therefore, while they may improve quality of life, they may also worsen the morbidity and mortality. Digoxin, in particular, is of interest, given that it is extensively used in the latter stages (NYHA IV and ACC/AHA Stage C) of heart failure. The Digitalis Investigation Group Trial (2003) indicated that higher levels of digoxin have been associated with a greater risk of mortality while lower concentrations are beneficial. Additionally, this effect has been shown to be more pronounced in female patients. Therefore, the current recommendations for digoxin use involve lower doses of the drug and lower target serum levels than previously used (with target levels for females lower than male target levels). Additionally, there is some evidence that even lower doses of digoxin (lower than that required to produce a positive inotropic effect or traditionally what would have been considered a subtherapeutic dose) may have beneficial effects. This proposed beneficial effect is thought to be due to a decrease in cardiac remodeling (thus, again, delaying the progression of the disease), rather than increasing cardiac function.

Summary and Conclusion

This overview has provided the pharmacist with the latest clinical approach to heart failure treatment. As noted, the drugs that are being used and the rationale behind their use are basically traditional, but new understanding of the progression of the disease and improved clinical studies, have resulted in slight modifications in how these drugs are used. In understanding these new classification schemes and pharmacologic options, the pharmacist can be a more well informed and useful member of the health care team.

References available upon request.

**Table 1
Comparison of Heart Failure Classification Schemes**

Stage or Phase of Heart Failure	Historical Classification	NYHA Classification	2005 ACC/AHA Classification
At Risk			A
Cardiac Damage, no symptoms	Compensated	I	B

Mild Symptoms	Compensated (remodeling)	II	B/C
Moderate Symptoms	Compensated/Decompensated (remodeling)	III	C
Severe Symptoms	Decompensated	IV	C/D

**Table 2
Summary of Treatment Classification Schemes**

Class I	Class IIa	Class IIb	Class III
Benefit >>> Risk	Benefit >> Risk	Benefit \approx Risk	Benefit $\#$ Risk
Well Supported	Additional Studies Needed	Additional Studies Needed	Well Documented
Treatment SHOULD be used	Treatment is REASONABLE	Treatment MAY BE CONSIDERED	Treatment should NOT be used

**Table 3
General Drug Treatment Recommendations, Based upon Stage of Heart Failure**

Stage A	Stage B	Stage C	Stage D
Treatment of underlying risk factors (antihypertensives, antihyperlipidæemics, antianginals, antidiabetics, etc. – to continue through all stages) ACEI or Angiotensin Receptor Antagonists	ACEI Angiotensin antagonists Beta adrenergic antagonists	Routine Diuretics ACEI Beta blockers Selected Patients Aldosterone antagonists Angiotensin antagonists Vasodilators Digoxin	Chronic positive inotropic drugs, including continuous infusion devices.