OREGON DUR BOARD NEWSLETTER©

AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug_policy/newsletter

May 2008 Volume 12, Issue 3

The Challenges of Heart Failure Management

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Current heart failure (HF) treatment guidelines from the American College of Cardiology and American Heart Association[1] (ACC/AHA) recognize angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers (BBs), and aldosterone antagonists improve survival and clinical outcomes in HF.[1] Combination regimens with two or more of these drugs delay the progression of disease, the development of symptoms and improve survival without compromising patient safety. HF patients typically use 4 or 5 drugs for HF, along with several drugs for other medical conditions. This polypharmacy increases risk for side effects and decreases patient adherence. Challenges presented by the interplay of hemodynamic effects and side effects of drug combinations in patients with heart failure are renal insufficiency, electrolyte abnormalities, and hypotension.

Renal insufficiency

Renal dysfunction complicates treatment of HF and is one of the strongest risk factors for mortality. 33% to 50% of HF patients will present with renal disease (glomerular filtration rate < 60 ml/min/1.73^2), referred to as the cardiorenal syndrome.[2] Risk factors, such as older age, low ejection fraction, diabetes mellitus and hypertension, are associated with worsening renal function.[3] ACEIs and ARBs have both cardioprotective and renoprotective effects.[1] ARBs are reserved for those with ACEI- induced cough or other contraindications to ACEIs. ACEIs and ARBs can cause a transient decrease in GFR, with an increase in serum creatinine (SCr), within the first week of initiating therapy or with chronic therapy in an otherwise stable HF patient.[4-7] Elevated SCr levels usually return to baseline within 4-6 weeks. Hypotensive or volume depleted patients are at greater risk for this. Initiate therapy with a low dose of ACEI (see table 1) and then titrate over several weeks to a target dose. Typical daily doses are doubled every 2-4 weeks as tolerated or until target dose is reached. Some with renal dysfunction don't achieve full target doses. This is acceptable since the dose is logarithmic with the most benefit gained at a dose between the starting dose and target dose. In most patients ACEI can be continued safely if the rise in SCr is less than 30%. In the presence of fluid overload or diuretic resistance, the diuretic dose should be increased and/or one may add metolazone for diuretic resistance which further compromises the renal function. If this occurs, the dose of ACEI or ARB should be temporarily reduced or even discontinued, but once volume balance is restored, the ACEI or ARB should be re-titrated to target doses. NSAID should be discontinued before discontinuing ACEI.

Electrolyte Abnormalities

In HF, ACEIs and aldosterone antagonists both impair potassium excretion resulting in hyperkalemia. Adding spironolactone to an ACEI and BB further improves morbidity and mortality in patients with NYHA Class III or IV HF due to left ventricular systolic dysfunction(Table 2).[1] Aldosterone antagonists are typically initiated after an ACEI and BB are titrated to target or tolerated doses and the patient is on stable diuretic doses. They are not recommended if SCr >2.5mg/dL and potassium levels >5.5 (Table 3).[1] A recent study documented a large increase in the prescribing rate of spironolactone for heart failure, followed by a significant increase in deaths as a result of hyperkalemia.[8-9] Risk factors for hyperkalemia include older age, elevated SCr, and concomitant use of potassium supplements, salt substitutes, and ACEIs. Hypokalemia is commonly seen in patients with HF, possibly due to stimulation of renin-angiotensin-aldosterone system (RAAS) and aggressive loop diuretic therapy. According to Leier et al, maintaining potassium levels between 4.5-5.0mm/l in HF reduces the risk of arrhythmias.[10]

Some heart failure patients remain hypokalemic despite concurrent potassium sparing diuretics and/or ACEIs. In these patients, potassium supplements can be cautiously introduced. When starting a potassium supplement or an aldosterone antagonist, potassium levels and SCr should be assessed at 3 and 7 days after initiating therapy, and then at least monthly for the first three months.[1]

Hypotension

Hypertension is a major risk factor for development of HF. Thus, achieving optimal blood pressure (BP) control is important in HF prevention. Recently the AHA recommended even more stringent BP goals(<120/80mmHg) in patients with established left ventricular dysfunction (LVD).[11] However, it is not uncommon to see HF patients with a systolic BP of 80-90mm Hg in the outpatient setting. These patients may or may not report dizziness or other postural symptoms. Poor cardiac output may be a contributor to hypotension, as are the additive mechanisms of drugs used to treat heart failure. For example, volume depletion from high doses of diuretics can potentiate vasodilatory hypotensive effects of ACEI's. Optimizing drugs to target doses while avoiding worsening of hypotension can be a dilemma for the clinician.

Evaluation of fluid status is critical to successfully titrate ACEIs. Frequent assessment of volume status can identify patients who may not require high doses of diuretics. A subset of patients may benefit from flexible diuretic regimens based on their symptoms (e.g., patient is instructed to take diuretic doses when they experience increased shortness of breath or weight gain of more than 3 lbs in a day or over a week). Some patients who are on a twice daily regimen of diuretics may benefit from using lower doses of diuretics in the morning in combination with other vasodilators. This may help alleviate daytime fatigue and dizziness. NSAIDs can attenuate the effects of diuretics and should be discontinued. In hypotensive patients, an initial low dose of ACEI should be initiated and doses should be titrated no sooner than every two weeks. If, the patient is still symptomatically hypotensive then a long acting ACEI (e.g., lisinopril) may be given in divided doses. Patients should be encouraged to self monitor their weight and be advised on dietary choices that may prevent fluid retention and HF exacerbations.While BB use results in about 35% reduction in mortality,[1] not all BBs are approved for HF. The agents approved in the USA are metoprolol succinate, carvedilol and bisoprolol. Metoprolol succinate is a relatively cardioselective BB, while carvedilol is a mixed alpha-1, non-selective beta-blocker. The 2005 ACC/AHA guidelines indicate that patients do not have to be on high doses of an ACEI before initiating a BB (Table 2). The BB should be started early in the course of therapy once the patient is hemodynamically stable. Usually, if the patient has tolerated the starting dosage of the selected BB, the dose can be doubled every 2-4 weeks as tolerated, or until the target dose is reached. Although, side effects and patient tolerance are similar 'between BBs in most trials, metoprolol may be preferred in patients with hypotension or with complaints of dizziness. Conversely, carvedilol may be preferred in patients with inadequately controlled hypertension. Initiation of BB therapy can cause fluid retention so patients should be instructed to weigh themselves daily and have diuretics adjusted as appropriate. One may also consider splitting the dose of the BB. Another strategy is to give carvedilol with meals to slow the absorption and eventually blunt the vasodilitory affects of alpha blockage. It may not be unreasonable to discontinue other drugs, such as nitrates, to accommodate life-saving drugs. While polypharmacy is essentiall in the treatment of HF, the burden of multiple medication regimens, their side effects, and occasional lack of response, can lead to non-compliance. Diligent monitoring of side effects is critical to proper medical decision making and improving patient outcomes.

Guidelines for Initiation and Up-titration of Medications in Patients with Heart Failure

Table 1.

Drug	Initial dose	Max doses
Angiotensin Converting Enzyme Inhibitors		
Captopril	6.25mg TID	50 mg TID
Enalapril	2.5 mg BID	10-20 mg BID
Fosinopril	5-10 mg QD	10 -40mg QD
Lisinopril	2.5 mg- 5 mg QD	20-40mg QD
Perindopril	2 mg QD	8-16mg QD
Quinapril	5mg BID	10-20mg BID
Ramipril	1.25 -2.5 mg QD	10mg QD
Trandolopril	I mg QD	4 mg QD
Angiotensin II Receptor blockers		
Candesartan §	4-8 mg QD	32 mg QD
Valsartan §	20 -40 mg BID	160 BID
Losartan	25-50mg QD	50-100mg QD
Irbesartan	150-300 mg QD	300mg QD
Olmesartan	20-40mg QD	40 mg QD
Telmisartan	20-80mg QD	80 mg QD
Eprosartan	600-800mg QD or BID	800mg QD

§Only candesartan and valsartan are FDA approved for HF. Typical daily doses are doubled every 2-4 weeks as tolerated or until target dose reached. Before titrating, check for symptomatic hypotension, signs of renal impairment and hyperkalemia.Evaluate fluid status. If no signs and symptoms of congestion consider reducing diuretic doses. Consider decreasing doses or discontinuing drugs of concomitant medications which may affect BP such as calcium channel blockers or nitrates. In patients with renal impairment decrease doses, and if >30 % increase in SCr from baseline then discontinue ACEI's and reinstitute when renal function stabilizes. In hyperkalemia (K >5.5 mmol/L) discontinue potassium (K) supplements and stop NSAIDs. Monitor SCr, K and fluid status closely when increasing doses or adding new medications.

Table 2.

Aldosterone blockers*

Drug	Initial dose	Target dose
Spironolactone	6.25- 12.5 mg QD	25 mg QD
Eplerenone	25 mg QD	50 mg QD

* Not recommended in patients with potassium levels >5.0 mEq/L and SCr >2.5 mg/dL. Risk of hyperkalemia increases with concomitant use of ACE inhibitors, ARBs and potassium supplements. Serum K and SCr monitored in 3 days and 1 week after initiating therapy. New cycle of monitoring when increasing ACEI or ARB dose. Occasionally can be dosed on alternative days.

Table 3.

Beta blocker titration

Drug	Initial dose	Target dose
Metoprolol succinate	25 mg QD	200 mg QD
Carvedilol ❋	3.125 mg BID	25 mg BID
Bisoprolol	1.25 mg QD	10 mg QD

❋Hypotension is more common with carvedilol than metoprolol XL. Initiate low doses and titrate every 2 weeks or more and monitor closely for changes in vital signs and symptoms or worsening HF. Titration should be individualized based on patient symptoms. Risk of hypotension can be decreased by staggering all antihypertensive drugs throughout the day.
In volume depleted patients consider decreasing the diuretic dose.
Encourage patients to monitor BP, HR and weight daily when doses are increased. Inform the patients that clinical response takes 2-3 months to be apparent.

Reviewed by Greg Larsen, MD. Chief of Cardiology, VA Medical Center, Portland, OR and Wayne Kradjan, Pharm D. Dean, College of Pharmacy, OSU, Corvallis, OR.

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OSU Oregon State University
Oregon DUR Board Newsletter Produced by OSU COLLEGE of PHARMACY
DRUG USE RESEARCH & MANAGEMENT
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