

CARVEDILOL FOR HEART FAILURE

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Renewed Interest in Beta Blockers

The idea of using beta blockers (BB's) to treat heart failure seems counterintuitive:

- They lower blood pressure, and many patients with congestive heart failure (CHF) are already hypotensive.
- They have a negative inotropic effect which should worsen the already depressed left ventricular (LV) systolic function of the CHF patient.

Nonetheless, BB's, once contraindicated in CHF, are gaining acceptance as part of the treatment regimen. This has occurred largely for two reasons:

- 1) The focus of treatment has moved from the edema of CHF to afterload reduction and to the neurohumoral responses that occur in the setting of depressed LV function and the resultant impaired tissue perfusion.
- 2) Two recent clinical trials^{1 2} have found that carvedilol (Coreg) reduces mortality and morbidity when added to an angiotension-converting enzyme inhibitor, a diuretic and digoxin. It may also slow progression of heart failure and has the potential to produce significant cost savings by reduced hospital admissions and reduced length of stays.

Why Use A Beta Blocker?

- 1) Short-term activation of the sympathetic nervous system promotes circulatory homeostasis in response to the impaired tissue perfusion in CHF patients. Prolonged stimulation of these systems in patients with

LV dysfunction can produce deleterious effects that may accelerate the progression of CHF.³ Interference with these adverse effects provides the principal basis for considering the use of BB's for the treatment of chronic CHF.⁴

- 2) Conventional therapy for CHF now includes:⁵
 - Angiotensin-converting enzyme inhibitors, as first line drugs
 - Diuretics, to relieve volume overload and edema, thus decreasing symptoms.
 - Digoxin, which is inotropic and has some neurohormonal antagonizing actions and also helps to decrease symptoms.
 - Dietary salt restriction (4 gm. Na)
 - Treatment of underlying etiologic or precipitating cause if possible
 - Patient education, to assure compliance with treatment.

However, even with this treatment, the morbidity and mortality rates in CHF remain extremely high (50-80% of patients die within 2-5 years of diagnosis.) For this reason, new strategies are constantly being designed and tested.

- 3) Use of BB's to interfere with the actions of the sympathetic nervous system seems to be a logical choice since we know that:
 - Neurohormonal activation can adversely affect survival.³
 - Neurohormonal antagonism (at least with an ACE inhibitor) should be used to prolong life in patients with CHF.⁶

- BB's can decrease the risk of death in postinfarction patients, particularly those with CHF.⁷

Carvedilol, (Coreg): The First BB Approved For Treating CHF

Carvedilol has several properties that make it more appropriate for treating this condition than other BB's:

- It has alpha-blocking activity which reduces systemic vascular resistance, thereby reducing afterload. This might compensate for the initial negative inotropic effects of beta blockade.
- It is nonselective and has no sympathomimetic activity, thus it maximizes the benefits of adrenergic blockage by more completely antagonizing the sympathetic nervous system.
- It has direct antioxidant effects that may decrease the loss of myocardial cells in the progression of CHF.

How To Use Carvedilol In CHF^{8 9 10}

Patient Selection

- Mild to moderate heart failure (NY heart Class II & III)
- Already receiving angiotensin-converting enzyme inhibitors, a diuretic and digoxin
- Not recommended in patients hospitalized for decompensated heart failure or who have significant hypotension or pulmonary congestion.

Dosage

- Start with 3.125 mg twice a day for 2 weeks, regardless of disease severity, weight or age.
- Observe the patient for side effects 1 to 2 hours after initial dose and each dose increase, or have the patient take these doses at bedtime and inform them of side effects.
- If first dose is tolerated well, increase to 6.25 mg twice a day after 2 weeks.

- Double the dose every 2 weeks until target is reached: 25 mg twice a day in patients weighing 85 kg or less or 50 mg twice a day in patients weighing more than 85 kg.
- Tell the patient to take carvedilol with meals.

Side Effects During Upward Titration

- Vasodilator effects (dizziness or lightheadedness)
 - Give the drug with food.
 - Give drug 2 hours before other agents.
 - Consider reducing diuretic or vasodilator doses temporarily.
 - Reduce carvedilol dose.
 - May require no attention, as symptoms are often self-limiting.
- Worsening CHF (edema, weight gain, dyspnea)
 - Intensify salt restriction.
 - Increase diuretic dose.
 - Reduce carvedilol dose.
- Significant bradycardia (consistently, 60-65/minute with symptoms)
 - Reduce carvedilol dose.
 - Monitor digoxin levels.
 - Reduce digoxin dose.

Conclusion: Clinical trials have found that carvedilol reduces mortality and morbidity when added to first line treatment (ACE inhibitors, diuretics and digoxin) for CHF. It may also slow the progression of CHF. It should be considered as a valuable adjunctive treatment for mild to moderate compensated CHF.

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¹ N ENGL J MED 1996; 334: 1349-55

² CIRCULATION 1996; 94: 2800-06

³ J AM COLL CARDIOL 1992; 20: 248-54

⁴ AM J CARDIOL 1993; 71: 12C-22C

⁵ N ENGL J MED 1996; 335: 496-98

³ J AM COLL CARDIOL 1992; 20: 248-54

⁶ J AM COLL CARDIOL 1995; 26: 1376-98

⁷ CIRCULATION 1986; 73: 503-10

⁸ CLEV CL J MED 1997; 64: 415-22

⁹ EVIDENCE-BASED CV MED 1997; 1: 27-28

¹⁰ AM J CARDIOL 1997; 79: 794-98