

## In-Hospital Initiation of Beta Blocker Therapy for Heart Failure

### Background

Neurohumoral antagonism is the cornerstone of heart failure management. Because of their beneficial effects on disease progression, functional status, hospitalizations, and mortality risk, ACE inhibitors and beta blockers should be prescribed for all patients with left ventricular systolic dysfunction unless specific well defined contraindications exist. Beta blockers have unequivocally been demonstrated to improve survival (35% mortality reduction) in patients with Class IV heart failure due to systolic dysfunction. Additional benefits include reduced hospitalization, myocardial infarction, and sudden death. Beta blockers are also beneficial in patients with asymptomatic left ventricular dysfunction (LVEF < 0.45), myocardial infarction, hypertension, coronary artery disease, cerebral vascular disease, peripheral vascular disease, and diabetes. Patients with diastolic dysfunction heart failure also likely benefit from beta blocker therapy, but this has not been tested in prospective randomized clinical trials.

It has been standard practice to initiate and dose adjust ACE inhibitor therapy during hospitalization for decompensated heart failure. In contrast, initiation of beta blocker therapy was conventionally delayed till the heart failure patient was discharged and demonstrated to be stable as an outpatient for 2-4 weeks. Concern existed that early initiation of even low dose beta blocker therapy in patients during hospitalization could destabilize the patient. It was also felt that it took a few months before the benefits of beta blocker therapy were realized.

The COPERNICUS trial demonstrates survival benefits with the beta blocker carvedilol in patients with severe heart failure and that therapy can be safely initiated during hospitalization. The benefits accrued early with a significant reduction in death and hospitalization being evident in the first 8 weeks of therapy. In-hospital initiation of cardioprotective therapies has been demonstrated in the CHAMP Study to markedly improve treatment utilization, long term patient compliance, and clinical outcomes in cardiovascular disease patients. As substantial numbers of heart failure patients remain untreated with beta blockers, the hospitalization for decompensated heart failure represents an important opportunity to ensure initiation of this evidence based therapy. This document provides guidance regarding in-hospital initiation of beta blocker therapy for heart failure.

### Indications

Beta blockers should be initiated in all patients with mild, moderate, and severe heart failure due to systolic dysfunction in the absence of contraindications or clearly documented intolerance. Beta blocker therapy should not be delayed until patients become resistant to other therapies. Beta blocker therapy should be initiated in patients **after** adequate diuresis and generally **following** initiation of ACE inhibitor treatment. Patients requiring intravenous vasodilators or inotropic agents should have beta blocker therapy deferred for a few days until the patient has stabilized and their heart failure is compensated. Contraindications: cardiogenic shock, symptomatic bradycardia without pacemaker, 2<sup>nd</sup> or 3<sup>rd</sup> degree heart block without pacemaker, severe asthma, and severe COPD. Note that diabetes, peripheral vascular disease, asymptomatic bradycardia, and mild to moderate asthma and COPD are not contraindications. Patients with heart failure and symptomatic bradycardia or 2<sup>nd</sup> or 3<sup>rd</sup> degree heart block without pacemaker, should strongly considered for pacemaker placement given the significant increased mortality risk without beta blocker treatment.

### Patient Selection Criteria

Congestive heart failure (mild, moderate, severe) due to systolic dysfunction or asymptomatic left ventricular dysfunction. Consider in all heart failure patients (i.e. diastolic dysfunction)  
Systolic blood pressure  $\geq$  90 mmHg (patients with SBP 80 to 90 mmHg may be appropriate candidates for in-hospital initiation of beta blocker therapy, but it is recommend this be done in consultation with cardiology/heart failure service)  
Patient not requiring intravenous therapy with inotropic agents or vasodilators  
Patient no longer significantly volume overloaded (No orthopnea, JVP < 8 cm,  $\leq$  1 plus peripheral edema)

## Patient Exclusions

Patients in cardiogenic or other forms of shock

Patients with signs of systemic hypoperfusion (altered mental status, narrow pulse pressure, cold or clammy skin, rising BUN/Cr)

Patients with systolic blood pressure < 80 mmHg

Patients with significant volume overload (delay initiation till adequately diuresed)

Patients with absolute contraindications (symptomatic bradycardia or 2<sup>nd</sup> or 3<sup>rd</sup> degree heart block without pacemaker, severe asthma or COPD)

## Dosage/Administration

### *Initiation*

Because of the favorable initial hemodynamic effects (vasodilation due to alpha blocking preventing fall in cardiac index), no early hospitalization hazard, and demonstrated benefit with in-hospital initiation, carvedilol is the preferred beta blocker for heart failure in this setting. The alternative beta blockers used for heart failure (metoprolol, metoprolol XL, and bisoprolol) have not been evaluated in the inpatient setting and the agents/doses are shown for reference purposes only.

The recommended initiation dose for carvedilol for heart failure is 3.125 mg PO bid. (Hold for SBP < 80 mmHg and/or HR < 45 bpm).

### *Titration*

The dose of beta blocker therapy is generally increased at 2-8 week intervals until the target dose is achieved. Thus hospitalized patients will generally be started on the initial starting dose while in the hospital and discharged home on this dose, with the first dose titration taking place on the first or second outpatient visit. In patients with mild heart failure who are hypertensive, the titration steps may occur more rapidly. In patients who cannot achieve target doses of the beta blocker, the highest dose tolerated should be maintained.

Agent	Initiation Dose	Titration Steps	Target Dose
Carvedilol	3.125 mg bid	6.25 mg bid, 12.5 mg bid	25 mg bid *
Metoprolol	6.25 mg bid	12.5 mg bid, 25 bid, 50 bid	100 mg bid
Metoprolol XL	12.5 mg qd	25 qd, 50qd, 100qd, 150qd	200 mg qd
Bisoprolol	1.25 mg qd	2.5 mg qd, 5 mg qd	10 mg qd

\* Carvedilol in the 6.25 mg bid and 12.5 mg bid dose also shown to reduce mortality

For patients that do not tolerate in-hospital initiation of beta blocker therapy, initiation should be re-attempted on an outpatient basis after 4-8 weeks of clinical stability.

## Monitoring

### Blood Pressure

Blood pressure and heart rate should be monitored per standard routine

Notify physician if patients develops symptomatic hypotension or SBP < 80 mmHg

The beta blocker dose should be held for SBP < 80 mmHg (recheck in one hour, notify physician)

The beta blocker dose should be held for HR < 45 (recheck in one hour, notify physician)

### Weight

Daily weights should be obtained and recorded while patients are hospitalized. Patients should be instructed to measure and record their weight daily at home.

### Symptoms

At the low initiation doses most patients heart failure patients will notice no change in symptoms with beta blockers. The occasional patient may note increased fatigue or slight dizziness. Within the first 2

months of therapy, more patients reported their overall condition improving and less reported worsening with carvedilol compared to placebo in the COPERNICUS trial.

### BNP levels

In patients where it is not clear whether the patients remains significantly congested, consider obtaining a BNP level. If the BNP level is > 400 pg/ml (in patients without renal failure), diurese the patient further before initiating the beta blocker. It is recommended that BNP levels be obtained prior to hospital discharge to help guide assessment of suitability for discharge and risk stratify patients.

### **Concomitant Drug Therapy**

ACE inhibitors are generally initiated prior to beta blocker therapy. ACE inhibitors do not need to be at target doses prior to the initiation of a beta blocker. Both agents may be titrated up to target doses over time. Aldosterone antagonists can be initiated, continued, or dose adjusted before or during beta blocker treatment. Beta blocker therapy should not be initiated while the patient is receiving intravenous nitroprusside, nitroglycerine, nesiritide, dopamine, dobutamine, or milrinone infusions. Initiation should be delayed until the patient is no longer receiving intravenous vasodilators or inotropic agents.

Patients hospitalized with decompensated heart failure who were already treated with beta blocker therapy prior to hospitalization, should continue on beta blocker therapy so long as they are not in cardiogenic shock and do not show signs of systemic hypoperfusion (altered mental status, narrow pulse pressure, cold or clammy skin, rising BUN/Cr). Patients requiring inotropic support for cardiogenic shock or systemic hypoperfusion should have the beta blocker withheld. Patients receiving intravenous vasodilators or diuretics may have the beta blocker continued. If such patients fail to respond the therapy, this should be reassessed.

### **Patient Referral**

Cardiology/heart failure service consultation is recommended for any patient where their candidacy for in-hospital initiation of beta blocker therapy is in question. As ACE inhibitor and beta blocker therapy is associated with significant mortality reduction in patients with mild, moderate, or severe heart failure, failure to be able to initiate or maintain either of these therapies should prompt consideration of referral to a cardiologist and/or the Ahmanson-UCLA Cardiomyopathy Center.

### **Cost Effectiveness**

The number of patients with mild to moderate heart failure needed to treat with a beta blocker for one year to prevent one death is 25. For severe heart failure the NNT to prevent one death is only 14. In comparison, the NNT for ACE inhibitors in mild to moderate heart failure is 59. In the US Carvedilol study, carvedilol was associated with a 28% reduction in cardiovascular hospitalizations, a 37% reduction in mean length of stay, and an 83% reduction in mean number of ICU/CCU days. Total medical costs (medications/monitoring costs minus hospitalizations cost) were reduced by \$2000 per patient over seven months. Beta blocker therapy for heart failure is thus cost dominant (i.e. reduction in mortality occurs with a therapy that reduces total medical cost). As the benefits accrue early and a substantial number of re-hospitalizations occur in the first 2 months of heart failure discharge, in-hospital initiation of beta blocker therapy is expected to result in even more significant reductions in total medical costs as well as lives saved.

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