What’s the Real Story?
• Because of their negative inotropic effects beta-adrenergic receptor blockers were once thought to be absolutely contraindicated in heart failure.
• Over the past 20 years, multiple clinical trials have demonstrated that beta-blockers added to regimens containing an ACE-inhibitor have led to improved LV function and reductions in mortality and hospitalizations for heart failure. New York Heart Association (NYHA) functional class improvements have also been noted in some trials.
• Despite this clinical data demonstrating the benefits of beta-blocker use in heart failure, a significant number of heart failure patients do not receive this therapy.

What do the Clinical Guidelines Say?
• “Currently, both the Heart Failure Society of America Practice Guidelines and the Consensus Recommendations for the Management of Chronic Heart Failure mandate that all patients with NYHA Class II-IV HF should be treated with a beta-blocker unless there is a contraindication, or if the patient has been shown to be unable to tolerate treatment with the drug.”
• “Clinical trial data now confirm that, for the treatment of chronic heart failure, the addition of beta-blocking agents to the standard medical regimen that includes an ACE-inhibitor will reduce mortality by approximately 35%.”

Which Beta-blocker should I use? (Warning - there is no simple answer)
• Beta-blockers are not a homogeneous class of drugs and there are significant differences between members of the class.
• Beta-blockers that have been shown to be effective in the treatment of HF include bisoprolol and metoprolol succinate (beta-1 selective) and carvedilol (blocks alpha-1, beta-1 and beta-2 receptors).
• Cardioselectivity may not be as important at the doses that have been shown to reduce mortality –i.e. metoprolol succinate 200 mg qd, bisoprolol 10 mg qd and carvedilol 25 mg bid.
• Beta-blockers with intrinsic sympathomimetic activity (such as pindolol and acebutolol) should be avoided.
  ▪ Randomized, controlled trials have shown that treatment with carvedilol, metoprolol succinate (controlled release) or bisoprolol decreases mortality by at least 34% in patients with heart failure.
  ▪ Currently there are only 2 beta-blockers that have regulatory approval in the U.S. for treatment of patients with heart failure: carvedilol (Coreg®) and the long acting form of metoprolol succinate (Toprol XL®).
  ▪ Recent small studies have alluded to the additional effects of carvedilol including improved glucose metabolism, reduction in the risk of new-onset diabetes, and a 7-unit improvement in Left Ventricular Ejection Fraction (LVEF). Large, randomized, placebo controlled trials still need to be conducted to determine clinical significance.
  ▪ For mild to moderate heart failure metoprolol succinate (Toprol® XL) or bisoprolol could be considered first line due to significant reduction in mortality and cost-effectiveness.
  ▪ For severe heart failure, carvedilol (Coreg®) could be considered first line due to evidence from the COPERNICUS trial and it’s significant reduction in mortality.
What about generic metoprolol if my patient can’t afford Toprol XL®?

- Generic metoprolol has never been shown to be of survival benefit in heart failure. Earlier studies (i.e. MDC) showed no effect at the usual prescribed dose and frequency. Its use is not recommended, but if expense is an issue, the patient's physician should discuss this with their patient -- extrapolation of its use in lieu of the succinate form of metoprolol has not been shown to be of benefit and is not FDA approved for this indication.
- Patient Assistance Program for Toprol XL (AstraZeneca) 1-800-424-3727 or http://www.astrazeneca-us.com/pap/
- Patient Assistance Program for Coreg® (GlaxoSmithKline) 1-866-728-4368 or http://bridgestoaccess.gsk.com

What does the Carvedilol or Metoprolol European Trial (COMET) tell us?

- Patients with chronic heart failure and reduced LVEF were treated with carvedilol (25mg BID) or metoprolol tartrate (50mg BID). After 58 months all cause mortality was lower in the carvedilol group (34% vs. 40%). There was no difference in re-hospitalization between groups.
- Controversies over results because the formulation of metoprolol was different from the one used in the MERIT-HF trial (tartrate vs. slow release succinate) and the target dose was lower (50mg/12 h vs. 100mg/12 h). Other limitations include: open labeled run-in phase; the limited number of deaths; the limited time of follow up; and the fact that mortality was predefined as a safety, not as an efficacy, end point.
- Illustrates that the selection of the beta-blocker and the dosage used may have significant impact on patient outcomes.
- Studies comparing the effects of metoprolol succinate with carvedilol on relevant clinical endpoints are not available, and at present, the question of comparable efficacy of metoprolol succinate as compared with carvedilol remains unanswered.

Beta-blocker Dosing Strategies in Heart Failure

- Beta-blocker action may be biphasic with long-term improvement, possibly preceded by initial symptom worsening. Transient worsening failure, hypotension, or bradycardia may occur during the titration period or thereafter.
- Start with a low dose and increase slowly. The initial dosage should be doubled every two to four weeks until the patient is unable to tolerate higher levels or the target dose is reached.
  - If worsening of symptoms, first increase the dose of diuretics or ACE-inhibitor; temporarily reduce the dose of beta-blocker if necessary.
  - If patient hypotensive, first reduce the dose of vasodilators; reduce the dose of the beta-blocker if necessary.
  - Reduce or discontinue drugs that may lower heart rate in presence of bradycardia; reduce dose of beta-blockers if necessary, but discontinue only if clearly necessary.
  - Always consider the reintroduction and/or uptitration of the beta-blocker when the patient becomes stable.
- Aim for target dose or, if not tolerated, the highest tolerated dose.
- In addition, beta-blockers can initiate or exacerbate asthma and induce peripheral vasoconstriction.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Target Dose</th>
<th>Target Dose Cost per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toprol-XL® (Metoprolol Succinate)</td>
<td>12.5mg-25mg daily</td>
<td>200mg daily</td>
<td>$58.99</td>
</tr>
<tr>
<td>Coreg® (Carvedilol)</td>
<td>3.125mg twice daily</td>
<td>25mg twice daily (50mg twice daily for patients with body weight &gt; 85 kg)</td>
<td>$94.99 to $189.98</td>
</tr>
<tr>
<td>Bisoprolol (generic Zebeta®)</td>
<td>1.25mg daily</td>
<td>10mg daily</td>
<td>$35.13 (generic)</td>
</tr>
</tbody>
</table>

Dosages and Cost of Primary Drugs used to treat CHF

Retrieved from Drugstore.com, April 26, 2005
When to Initiate Beta-Blocker Therapy in Heart Failure

- No evidence of fluid overload (use diuretics accordingly)
- ACE- inhibitor should be initiated first, if not contraindicated
- In stable patients, in the hospital or outpatient setting
- NYHA class IV/severe CHF patients – specialist consult may be indicated

Contraindications to Beta-Blockers

- Moderate to severe asthma
- Advanced heart block
- Severe bradycardia
- Symptomatic hypotension
  - Diabetes should not be considered an absolute contraindication.

So, what do I do about my diabetic patients with heart failure?

- Diabetic patients with heart failure are generally treated in the same fashion as nondiabetics including the use of ACE-inhibitors and beta blockers.
- Patients with heart failure and diabetes have a greater risk of hospitalization than patients without diabetes.
- A meta-analysis of beta blocker trials in heart failure included 1883 diabetics and 7042 nondiabetics. The survival benefit with beta blocker therapy was significant for both those with diabetes and for those without. The difference in risk reduction between diabetics and nondiabetics was not significant.
- Beta-blockers should be used very cautiously in diabetic patients with repeated hypoglycemia or in whom the sensation of hypoglycemia is impaired.

What about my patients with asthma and COPD?

- Beta-blockers are often avoided in patients with COPD because of the fear of bronchoconstriction.
- The prevalence of COPD in patients with known CHF ranges from 23% to 33%.
- Bottom line: we should not avoid life saving use of beta-blockers for questionable risk of worsening airway disease; risk vs. benefit should be considered.
- The literature supports the safety and mortality benefits of using beta-blockers in patients with mild to moderate COPD. Patients with severe or irreversible airway disease have not been studied.
- Patients with mild to moderate COPD and stable disease without active wheezing should receive cardioselective beta-blocker without intrinsic sympathomimetic activity (Toprol® XL) or the non-selective beta-/alpha-blocker (Coreg®) are preferred when a strong indication exists.
- Minimal data on use of beta-blockers in asthmatic patients with heart failure exists.
  - Most likely unsafe to use beta-blockers in patients with active wheezing.
  - Patients with a history of asthma but with clear lungs and no recent exacerbation – risk vs. benefit assessment; use cardioselective without intrinsic sympathomimetic beta-blocker (Toprol® XL) and monitor closely.

References for Beta-blockers and Diabetes:


References for Beta-blockers and Asthma/COPD:


General References:
ACC/AHA Guidelines for the Evaluation and Management of Heart Failure.
http://www.acc.org/clinical/guidelines/failure/hf_index.htm


