

Beta-Blockers Use in Heart Failure

What is the evidence for use and how are we doing?

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Congestive Heart Failure, P3

Part 1. Review of β -blockers and Rationale for Their Use

Within one year, 20% of patients suffering from mild symptoms of heart failure (HF) experience clinical deterioration and an additional 10% will die. β -blocker use could reduce heart failure mortality by 65 - 35% based on some clinical trial data. The Heart Failure Society of America guidelines for the treatment of heart failure published in 1999 state " β -blocker therapy should be routinely administered to clinically stable patients with left ventricular systolic dysfunction and mild-to-moderate heart failure symptoms who are on standard therapy, which typically includes ACE inhibitors, diuretics as needed, and digoxin." Eligibility for β -blocker therapy should be based on the selection criteria of patients in clinical trials, but only 8-10% of Louisiana Medicaid patients and ~ 20% of patients nationwide with HF are receiving β -blockers. In an effort to increase the usage of these agents in the Medicaid population, information regarding the use of



The Department of Health and Hospitals, Bureau of Health Services Financing, and the University of Louisiana at Monroe, College of Pharmacy, continue to develop Disease Management programs to address the educational component of the Louisiana Medicaid Pharmacy Benefits Management system.

Selected Medicaid recipients and their health care practitioners receive these educational brochures. We appreciate your taking time to review these and incorporating this information into your practice as you deem appropriate.

Thank you for your continued participation in the Medicaid program. Should you need additional information concerning the Disease Management program, please contact M.J. Terrebonne at (225)342-9768.

Introduction

β -blockers is being sent to Medicaid providers (physicians, pharmacist, nurses) and patients. Later, some providers will also be sent information with regards to their specific β -blocker usage along with a survey to identify barriers to usage.

This article will focus on the pathophysiology and the evidence for the use of β -blocker therapy. The following provider mailing will focus on the practical aspects of using β -blockers in HF.

Rationale for use

Activation of the sympathetic nervous system initially increases cardiac output in the failing heart; however, increases in catecholamines over time adversely affect cardiac myocytes. Acting directly on the heart and indirectly through the peripheral vascular system, catecholamines induce cardiac remodeling and cell death. Acutely, β -blockade will decrease the chronotropic and inotropic actions of this system, and can lead to exacerbations of HF. However, long-term use of β -blockers prevents deterioration and remodeling, improves myocardial systolic dysfunction, reverses remodeling, and improves signal transduction. Thus, although β -blockers were once thought to be contraindicated in HF, the rationale for their use is now clear.

Evidence for use

The Metoprolol in Dilated Cardiomyopathy (MDC) trial enrolled 383 patients referred for consideration of cardiac transplantation. In this trial, the primary endpoint, total mortality and/or need for transplantation, did not reach statistical significance ($p=0.058$). However, when researchers examined the need for transplantation alone, a statistically significant reduction was observed ($p=0.001$).

The Metoprolol CR/XL Randomized Intervention Trials in Congestive Heart Failure (MERIT-HF) enrolled approximately 4000 patients with mild-to-moderate heart failure. The study was stopped prematurely, due to a 34% reduction in all-cause mortality ($p=0.0062$) and a 23% reduction in hospitalizations.

The Cardiac Insufficiency Bisoprolol Study (CIBIS I) enrolled 641 patients with mild to moderate heart failure. The trend was towards improved outcomes in the bisoprolol group, but this failed to reach statistical significance; however, CIBIS I was underpowered and the target dose reached was

Evidence for use (continued)

only 3.8 mg daily. Therefore, CIBIS II included 2,647 patients with a target dose of 10 mg daily. The result was early termination of the trial due to a 34% reduction in all cause mortality in the bisoprolol group ($p=0.0006$).

The US Carvedilol Heart Failure Trials Program enrolled patients with mild, moderate, and severe heart failure after an open label run-in period. Patients able to tolerate therapy were then randomized to carvedilol or placebo. The study was stopped prematurely due to a 65% reduction in mortality and a 27% reduction in cardiovascular hospitalizations. The results of this trial gained further support from two recently completed trials. In the Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS) over 2000 patients with ejection fractions of less than 25% and symptoms at rest or after minimal exertion were enrolled. A 35% decrease in mortality and a 24% decrease in death and hospitalization were seen in the carvedilol group compared to placebo. The Carvedilol Post-infarct Survival Controlled Evaluation (CAPRICORN) showed a 29% reduction in all cause mortality and nonfatal myocardial infarction (MI). CAPRICORN included close to 2000 patients who had recent (<21 days) myocardial infarction and ejection fractions < 40%.

The Beta Blocker Evaluation of Survival Trial (BEST) enrolled over 2500 patients with mild to severe heart failure. Bucindolol, a nonselective β -blocker was used, and unlike previous trials, a statistical difference in all cause mortality was not demonstrated. BEST did differ from other trials in that more Class III and IV and more African American patients were enrolled. The trial was stopped early, not due to adverse events, but due to the totality of data from other trials and BEST that indicated β -blockers were associated with improved outcomes.

A recent meta-analysis of twenty-two β -blocker trials including over 10,000 patients was published in *The Annals of Internal Medicine*. A 12.8% vs. 0.08% death rate and a 1.2% vs. 0.1% hospitalization rate was shown for placebo vs. β -blocker therapy. This translates into 4 deaths and 4 hospitalizations prevented per 100 patients treated with a β -blocker in the first year of therapy. This

Tolerability

The short-term hemodynamic effects of β -blockers include a decrease in cardiac contractility and renal blood flow. These effects can cause dizziness, worsening dyspnea, fatigue, or bradycardia during the first weeks after initiation and after subsequent dose titrations. Despite these effects, approximately 85% of patients in clinical trials were started and continued on long-term therapy with β -blockers. Some of these effects are short-lived and can be minimized by small changes in therapy, which will be discussed in the next publication. Overall, trials have shown decreases in mortality, increases in ejection fraction and improvements in clinical status as early as 4 months after initiation.

FDA approved β -blockers for the treatment of HF

Currently, metoprolol in the extended release formula Toprol CR/XL[®] and carvedilol (Coreg[®]) are FDA approved for the treatment of mild-to-moderate heart failure. The starting dose of metoprolol CR/XL is 25 - 50 mg daily with a target dose of 150 - 200 mg daily. Carvedilol should be started at 3.125 mg bid with food with a target dose of 25 - 50 mg bid. Titration to the target dose can be achieved by doubling the dose of the agent after several weeks of therapy, provided the patient is stable on the existing dose.

Conclusion

Current data demonstrate that the use of β -blockers in heart failure decreases both morbidity and mortality. This evidence has led The Heart Failure Society of America to give the same importance to the recommendation for beta-blockers as it does for ACE-inhibitors. While the use of ACE inhibitors now reaches 60 %, the use of β -blockers remains low. A reason for this gap in therapy is that the evidence for β -blocker use became apparent over the last several years, while the evidence for ACE inhibitors was apparent several years prior. However, other barriers exist, such as the long standing "contraindication" to β -blockers in HF, and the close attention needed to start a patient on a β -blocker therapy. The focus of the next publication will be to give practical guidelines for the use of β -blockers in heart failure. This will include who and when to treat; as well as what to expect and how to deal with complications.

Part 2: Analysis of Beta-Blocker Utilization in Louisiana Medicaid Heart Failure (HF) Patients

Data Source

Unisys Corporation, fiscal intermediary for the Louisiana Medicaid program, provides claims data for Louisiana Medicaid recipients diagnosed with HF to The University of Louisiana at Monroe College of Pharmacy. A recipient was identified as belonging to the HF study population if he/she had at least one claim in 1999 or 2000 with one of the CHF diagnoses listed in Table 1. For the current analysis, only claims for services provided in calendar year 2000 were included. Additionally, a recipient within the HF study population was considered to have been continuously eligible if he/she had at least one claim per quarter.

Table 1. CHF Diagnoses Codes

ICD-9-CM Code	Description
402.01	Malignant Hypertensive Heart Disease with Congestive Heart Failure
402.11	Benign Hypertensive Heart Disease with Congestive Heart Failure
402.91	Unspecified Hypertensive Heart Disease with Congestive Heart Failure
404.01	Malignant Hypertensive Heart and Renal Disease with Congestive Heart Failure
404.03	Malignant Hypertensive Heart and Renal Disease with Congestive Heart Failure and Renal Failure
404.11	Benign Hypertensive Heart and Renal Disease with Congestive Heart Failure
404.13	Benign Hypertensive Heart and Renal Disease with Congestive Heart Failure and Renal Failure
404.91	Unspecified Hypertensive Heart and Renal Disease with Congestive Heart Failure
404.93	Unspecified Hypertensive Heart and Renal Disease with Congestive Heart Failure and Renal Failure
428.0	Congestive Heart Failure
428.1	Left Heart Failure
429.1	Myocardial Degeneration

Inclusion Criteria

There were 27,667 Medicaid recipients identified as belonging to the HF population who received one or more services during calendar year 2000. Demographic information was obtained from the first claim in calendar year 2000 for each recipient in the study population. There were 12 recipients whose demographic information was incomplete and they were not included in this analysis, leaving 27,655 recipients. Seventy-six percent were determined to have been continuously eligible as defined above.

Demographics

Demographics are reported by state, region within the state and rural/urban classification. Table 2 lists parishes considered urban by the US Office of Management and Budget. A map of the DHH Administrative Regions of the state can be found by accessing the following web page:
http://www.dhh.state.la.us/REG_MAP.JPG.

Table 2. Urban Parishes

Acadia	Plaquemines
Ascension	Rapides
Bossier	St. Bernard
Caddo	St. Charles
Calcasieu	St. James
East Baton Rouge	St. John the Baptist
Jefferson	St. Landry
Lafayette	St. Martin
Lafouche	St. Tammany
Livingston	Terrebonne
Orleans	Webster
Ouachita	West Baton Rouge

Demographics (continued)

Demographics for the HF population are reported in Table 3 and show that 88.35% of the study population was over the age of 44 and 61.34% of the population was over the age of 64. The majority (54.04%) were receiving Medicaid because they were qualified to receive Old Age Assistance. Seventy-five percent of this population was female with over 61% residing in urban parishes. Fifty percent were black and 37% were white.

Table 3. Demographics

	Not CE*		CE		Total	
Age group						
Under 1	29	0.43%	61	0.29%	90	0.33%
1-5	74	1.11%	100	0.48%	174	0.63%
6-14	113	1.69%	105	0.50%	218	0.79%
15-20	167	2.50%	83	0.40%	250	0.90%
21-44	916	13.70%	1,575	7.51%	2,491	9.01%
45-64	1,651	24.70%	5,819	27.75%	7,470	27.01%
65-74	1,034	15.47%	4,558	21.73%	5,592	20.22%
75-84	1,284	19.21%	4,835	23.06%	6,119	22.13%
85+	1,416	21.18%	3,835	18.29%	5,251	18.99%
Aid Category						
Old Age Assistance	3,043	45.53%	11,902	56.75%	14,945	54.04%
Disability Assistance	2,197	32.87%	6,910	32.95%	9,107	32.93%
Qualified Medicare Beneficiary	847	12.67%	1,595	7.61%	2,442	8.83%
Other	597	8.93%	564	2.69%	1,161	4.20%
Race						
White	2,765	41.37%	7,455	35.55%	10,220	36.96%
Black	3,193	47.77%	10,606	50.57%	13,799	49.90%
Other	696	10.41%	2,877	13.72%	3,573	12.92%
Unknown	30	0.45%	33	0.16%	63	0.23%
Sex						
Male	2,140	32.02%	5,134	24.48%	7,274	26.30%
Female	4,544	67.98%	15,836	75.51%	20,380	73.69%
Unknown	0	0.00%	1	0.00%	1	0.00%
Region						
1-New Orleans Area	1,175	17.58%	3,628	17.30%	4,803	17.37%
2-Baton Rouge Area	639	9.56%	1,981	9.45%	2,620	9.47%
3-Terrebonne Area	530	7.93%	1,143	5.45%	1,673	6.05%
4-Lafayette Area	1,017	15.22%	3,211	15.31%	4,228	15.29%
5-Southwest LA	452	6.76%	1,316	6.28%	1,768	6.39%
6-Central LA	658	9.84%	2,055	9.80%	2,713	9.81%
7-Northwest LA	814	12.18%	2,918	13.91%	3,732	13.49%
8-Northeast LA	718	10.74%	3,120	14.88%	3,838	13.88%
9-St. Tammany Area	681	10.19%	1,599	7.62%	2,280	8.24%

*CE = Continuously Eligible

Beta Blocker Utilization

A recipient was considered to be a β -blocker user if he/she had at least one claim for a β -blocker in the calendar year 2000. Drugs classified as β -blockers for this analysis are listed in Table 4. Approximately 8% of recipients received at least one prescription for a β -blocker. Among those continuously eligible, 9.0% of 20,971 recipients received a β -blocker.

Table 4 . Beta-blockers

Atenolol
Bisoprolol fumarate
Metoprolol Succinate
Metoprolol Tartrate
Carvedilol
Labetalol HCL
Propranolol

The percent of recipients receiving β -blockers was greater for those continuously eligible compared to those not continuously eligible (Chart 1). However, the percent of patients receiving β -blockers was approximately equal in rural versus urban regions of the state. Region 3, comprised of St. John the Baptist, St. Charles, St. James, St. Mary, Assumption, Terrebonne and Lafouche parishes, had the highest proportion of β -blocker users at 10.7%. Among the continuously eligible Region 3 patients, 13.4% had a β -blocker prescription. Region 1, Orleans Parish and surrounding parishes, had the second highest usage. The area of the state with the lowest β -blocker utilization was Region 7, the northwest parishes of the state.

β -blocker utilization by age group was also examined. There was no β -blocker utilization in those recipients under the age of 21. The highest utilization was in recipients aged 46-64 (11.85%) followed by those 65-74 (10.30%).

Chart 1. Residence by Eligibility

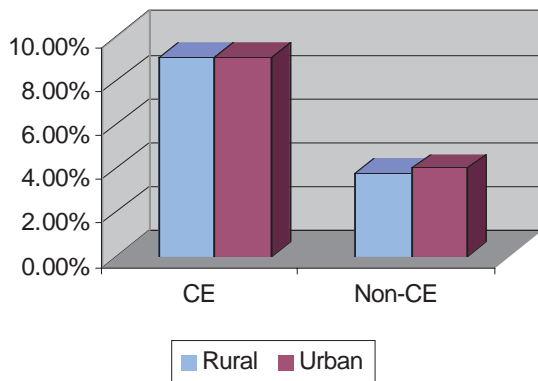
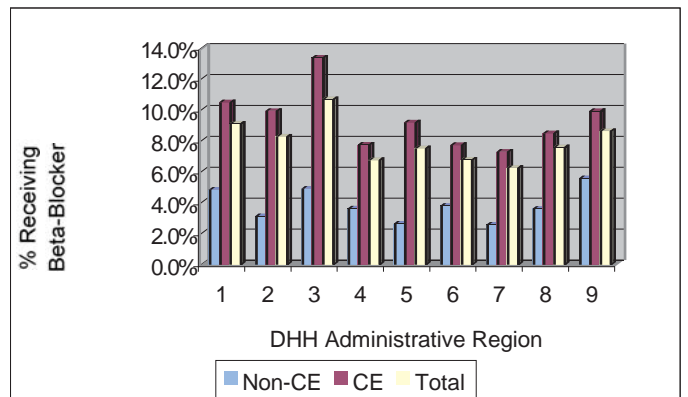


Chart 2. Beta Blocker Utilization by Region



References

1. Bristow MR. Mechanism of Action of Beta-Blocking Agents in Heart Failure. Am J Cardiol 1997;80(11A):26L-40L.
2. Brophy j, Joseph L, Rouleau J. Beta-blockers in Congestive Heart Failure. Annals of Internal Medicine. 2001;134(7):550-560
3. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001 May 5;357(9266):1385-90.
4. Eichorn E, Young J. Optimizing the Use of Beta-blockers in the Effective Treatment and Management of Heart Failure: A Case Study Approach. The American Journal of Medicine.2001; 110(5A):11S-20S.
5. Gheorghiade M, Eichorn E. Practical Aspects of Using Beta-Adrenergic Blockade in Systolic Heart Failure. The American Journal of Medicine. 2001; 110(7A):68S-73S.
6. Heart Failure Society of America Guidelines for the Management of Patients with Heart Failure Caused by Left Ventricular Systolic Dysfunction - Pharmacological Approaches. J of Card Failure 1999;5:357-382.
7. Kennedy, Harold L. Current Utilization Trends for Beta-blockers in Cardiovascular Disease. The American Journal of Medicine. 2001;110(5A):2S-6S
8. Packer M, Coats A, Fowler M, et al. Effect of Carvedilol on Survival in Severe Chronic Heart Failure. New England Journal of Medicine. 2001; 344(22):1651-1658.
9. Packer, Milton. Current Role of Beta-Adrenergic Blockers in the Management of Chronic Heart Failure. The American Journal of Medicine. 2001; 110(7A);81S-94S.
10. Yancy, Clyde W. Clinical Trials of Beta-blockers in Heart Failure: A Class Review. The American Journal of Medicine. 2001; 110(5A):7S-10S.

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Complete Wellness: A Guide to Managing Your Health

** The following is an abbreviated version of the education material sent to selected Medicaid recipients.*

Beta-Blockers for Heart Failure

By: Greg Guillory, Pharm.D., Assistant Professor of Clinical Pharmacy, ULM College of Pharmacy

Many times, you and other people with heart failure (a weak heart) have to take several medications. Sometimes you may wonder, "Why do I need all these medications?" This is a very reasonable question to ask when your doctor would like to add even another medication.

Several medications are needed because:

1. You need medications that treat the symptoms of heart failure like shortness of breath and fluid retention.
2. Other medicines slow down the weakening of the heart and help you live longer.
3. Some medications can do both.

This pamphlet will focus on one of the medications that do both.

Beta-blockers

What are beta-blockers?

Beta-blockers are a type of medication that work directly on the heart so that the heart does not have to work as hard.

Why do people with weak hearts take beta-blockers?

Beta-blockers have been proven to help your heart work better, slow down your heart getting weaker, keep you out of the hospital, and help you live longer.

How do I know if I should be taking a beta-blocker?

The Heart Failure Society of America has said that beta-blockers should be used in all patients with mild to moderate heart failure unless the patient has another condition that prevents their use.

If you are not taking a beta-blocker now, be sure to talk to your doctor about beta-blockers at your next visit.

What should I expect when taking a beta-blocker?

It is important to know that it will take time for your heart to adjust to your beta-blocker medicine. During this time you may feel worse instead of better. You may be more tired and have more shortness of breath. But, over time, you should notice this less and less. Your doctor may adjust the doses of your other medications to help decrease these effects. Don't quit taking your beta-blocker. You may have to feel a little worse at first to feel better later on.



What are some beta-blockers used for heart failure?

Toprol XL----- taken once a day

Coreg-----taken two times a day

How should I take my beta-blocker?

Because your heart needs time to get used to beta-blockers, you will be started on a low dose. Over a period of weeks, your doctor will slowly increase your dose. You should not stop taking the medication without speaking with your doctor.

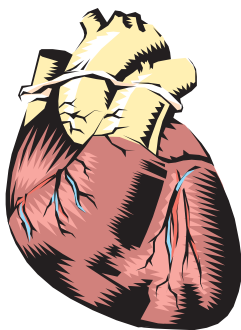
What do I do if I miss a dose of my beta-blocker?

You should try not to miss a dose of your beta-blocker. If you do miss a dose, take your medicine as soon as you do remember. BUT--if it is getting close to the time for the next dose skip that dose and start over. Do not double the dose.

What side effects should I watch for?

- You may be dizzy.
- You may feel lightheaded.
- You may be more tired.
- You may feel short of breath.
- Your feet and legs may swell.
- Your heartbeat may slow down.

(Ask your doctor or pharmacist how to count your heartbeats.)



How can I help reduce the side effects?

1. Some things that feel like side effects may not be from the beta-blocker but may really be symptoms of heart failure.
2. These side effects may become less and less over time.
3. Make sure you take the medication exactly as your doctor or pharmacist told you to.
4. Take your medication with food.
5. Do not take all your heart failure medications at the same time of day. You may want to ask your doctor or pharmacist how to take your medicines during the day.
6. Your doctor may also adjust your other medicines to reduce these side effects.

Contact your doctor if these side effects or symptoms get worse. Do not stop the beta-blocker until your doctor tells you to.

Learn more about heart failure. Call
The Heart Failure Society of America
1-877-510-HFSA

Don't forget the Daily Checklist

- Weigh daily and write it down. Call your doctor if you gain 2 pounds or more in one day, or 5 pounds or more in one week.
- Watch that salt!
- Exercise regularly. Try to fit in some exercise 3-5 times each week. Walking is great exercise for your heart!

Ask your doctor, nurse, and/or pharmacist about the information contained in this brochure

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