Recommendations for the Use of Beta-Adrenergic Blockers in VA Patients with Chronic Heart Failure with Left Ventricular Systolic Dysfunction

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician, however, must make the ultimate judgment regarding the propriety of any course of treatment in light of individual patient situations.

Recommendation

National Clinical Practice Guidelines[1-3] for the management of patients with chronic heart failure (HF) due to systolic dysfunction [i.e., left ventricular ejection fraction (LVEF) < 40%], recommend the following:

- Stable patients with current or prior symptoms of HF (Stage C*) due to systolic dysfunction should receive therapy with a beta-adrenergic blocker that has proven to reduce mortality (i.e., bisoprolol, carvedilol, sustained release metoprolol succinate) unless contraindicated (e.g., reactive airway disease, symptomatic bradycardia, advanced heart block without a pacemaker)
  Strength of Recommendation: A (Strong recommendation that the intervention is always indicated and acceptable)
  Overall Quality of Evidence: I (Good)

*Treatment of chronic HF is based upon classification into four stages by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines: Stage A includes patients who are at high risk for developing HF, but do not have structural heart disease; Stage B are patients who do have structural damage to the heart, but have not developed symptoms; Stage C refers to patients with past or current HF symptoms and evidence of structural heart damage; and Stage D includes patients with end-stage disease, requiring special interventions. It is the intent of the ACC/AHA recommendations to be used in conjunction with the New York Heart Association (NYHA) functional classification that estimates the severity of disease based on patient symptoms. Patients with HF are considered stable if they have a stable blood pressure without symptoms of hypotension, minimal or no signs of fluid overload or volume depletion and are not in an intensive care unit. Beta-adrenergic blockers should not be used in patients with bronchospastic disease, symptomatic bradycardia, or advanced heart block without a pacemaker. Caution should be used in patients with asymptomatic bradycardia with a heart rate of less than 60 beats per minute. It should be noted that patients with diabetes mellitus or chronic obstructive pulmonary disease were not excluded from the clinical trials.

Executive Summary for Use of Beta-Adrenergic Blockers in Patients with Chronic HF

Beta-adrenergic blockers with improved mortality data in patients with HF

- Treatment with bisoprolol, carvedilol, and sustained release metoprolol succinate has been associated with a reduction in morbidity and mortality in patients with chronic HF (refer to Appendix A for clinical trial data). Every effort should be made to achieve target doses of the beta-adrenergic blockers as used in the clinical trials and as tolerated by the patient. Considerations in the selection of one of these agents may be based on patient population studied, medication properties, patient tolerability, adherence, availability, and cost. Without comparative trials to evaluate long-term outcomes, there is no consensus in the literature to support one agent being globally superior to another in the treatment of patients with HF; therefore, once the provider determines there are no patient specific issues, it is recommended to begin initial therapy with an effective, less expensive agent. At the present time, this would lead to the preference of bisoprolol or sustained release metoprolol succinate for beta-blocker naïve patients with NYHA class II or III HF.

Use in patients with NYHA class IV (or more severe) HF

- Carvedilol has been shown to decrease morbidity and mortality in patients with NYHA class II-IV HF. Sustained-release metoprolol succinate has primarily been studied in patients with NYHA class II-III HF with a reduction in morbidity and mortality; according to a subgroup analysis, sustained-release metoprolol succinate may have positive outcomes in patients with more severe HF, as demonstrated with carvedilol. Bisoprolol has also been studied in patients with NYHA class II-IV HF and has also been shown to reduce morbidity and mortality in patients with more severe HF.

Use of beta-adrenergic blockers without clear reduction in mortality

- Other beta-adrenergic blockers including atenolol and immediate-release metoprolol tartrate have been used in the treatment of patients with chronic HF; however, their efficacy and optimal dose in reducing morbidity and mortality have not been established.

Properties of the beta-adrenergic blockers

- One trial attempted to answer the question of whether to use a selective beta-adrenergic blocker (immediate-release metoprolol tartrate was used) versus a non-selective agent with alpha-adrenergic blocking and antioxidant effects (i.e., carvedilol). The results of this trial showed that treatment with carvedilol had a greater reduction in mortality when compared to treatment with immediate-release metoprolol tartrate. It is unknown if the properties of carvedilol or if the dose of immediate-release metoprolol tartrate may have influenced the difference in results.

Evidence Summary

Beta-adrenergic blockers with improved mortality data in patients with HF

Meta-analyses of the beta-adrenergic blocker trials show a reduction in mortality of approximately 30 to 35%.[4-7] The beta-adrenergic blockers that have been studied for chronic HF and have demonstrated a reduction in mortality include bisoprolol, carvedilol, and sustained release metoprolol succinate (refer to Appendix A for details of clinical trial data). It is unknown if other beta-adrenergic blockers have a similar benefit, as not all beta-adrenergic blockers studied have shown a clear reduction in mortality. Every effort should be made to achieve target doses of the beta-adrenergic blockers as used in the clinical trials (refer to Table 2 and Appendix A) and as tolerated by the patient. Implementation of treatment guideline recommendations (refer to PBM-MAP Clinical Practice Guideline for the Pharmacologic Management of Chronic Heart Failure in Primary Care Practice at www.oqp.med.va.gov) should be emphasized in order to provide patients with the opportunity for optimal drug therapy benefit.[8]

Bisoprolol

Bisoprolol, titrated to 10 mg once daily, was compared to placebo in 2647 patients with primarily NYHA class III HF receiving standard therapy in the second Cardiac Insufficiency Bisoprolol Study (CIBIS II). The primary endpoint of all-cause mortality was reduced with bisoprolol, occurring in 11.8% of patients, compared to 17.3% of patients on placebo.[9] Prior to the publication of CIBIS II, bisoprolol was studied in 641 patients (mean age 60 years) with NYHA class III (95%) or IV (5%) HF (mean LVEF 25.8%), of ischemic or nonischemic etiology, for a mean of almost 2 years (CIBIS). Patients received a mean dose of bisoprolol 3.8 $\pm$ 0.2 mg per day, with 51% on 5 mg per day. Bisoprolol decreased total mortality (primary endpoint) by 20%, however this did not achieve statistical significance (p=0.22). Improvement of at least one NYHA functional class was significant and seen in 21% of bisoprolol patients and 15% of placebo patients. Significantly fewer patients required hospitalization for worsening HF.[10] The lower dose and smaller patient population studied in CIBIS should be noted. Another trial compared initiation of bisoprolol 10mg once daily vs. enalapril 10mg administered twice daily in treatment naïve patients. Initiation with either therapy resulted in a similar reduction in the combined endpoint of all-cause mortality or hospitalizations.[11]

Carvedilol

Carvedilol was studied in patients with NYHA class II and III HF (U.S. Carvedilol Heart Failure Study),[12] as well as in patients with more severe HF as in the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS).[13] After a median of 6.5 months, the primary endpoint of death was reported in 3.2% of patients in the U.S. Carvedilol Study receiving carvedilol (target dose 25 mg twice daily; mean 45 mg per day) compared to 7.8% of patients on placebo.[12] In COPERNICUS, the primary endpoint of all-cause mortality occurred in 11.3% of patients randomized to carvedilol (mean 37 mg per day) compared to 16.8% of patients receiving placebo.[13] These results were statistically significant. In the Carvedilol Or Metoprolol European Trial (COMET), carvedilol at a target dose of 25 mg twice daily was compared to the immediate-release formulation of metoprolol tartrate, at target doses of 50 mg twice daily. All-cause mortality was reported to be lower in patients on carvedilol (33.9%) compared to patients receiving immediate-release metoprolol tartrate (39.5%) in this study (additional discussion below).[14]

Metoprolol succinate

Sustained release metoprolol succinate was studied in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). All-cause mortality (primary endpoint) was significantly reduced with the extended-release formulation of metoprolol succinate (target dose 200 mg once daily) compared to placebo; mortality was reported in 7.3% of patients randomized to metoprolol succinate compared to 10.9% of patients receiving placebo.[15]

Use in patients with NYHA class IV (or more severe) HF

In a subgroup analysis of MERIT-HF, 795 patients with NYHA class III or IV HF with a LVEF < 25% who received placebo or sustained release metoprolol succinate were compared.[16] Similar to COPERNICUS with carvedilol,[13] the mean baseline LVEF was 19.1% and the annual mortality for patients in the placebo group was 19%. Patients randomized to sustained release metoprolol succinate experienced a significant decrease in risk of total mortality (39%), death due to worsening HF (55%), hospitalization due to worsening HF (45%), and combined all-cause mortality or all-cause hospitalization (29%) compared to placebo.[16] Patients enrolled in CIBIS II were classified as having NYHA III (83%) or IV (17%) HF, with a mean LVEF of 27.5%. All-cause mortality was reduced by 34% with bisoprolol compared to placebo.[9] In COPERNICUS, treatment with carvedilol reduced all-cause mortality by 35%.[13]

Use of beta-adrenergic blockers without clear reduction in mortality (also refer to Appendix B as indicated)

Prior to publication of MERIT-HF, a trial with immediate-release metoprolol tartrate (Metoprolol in Dilated Cardiomyopathy, or MDC) was conducted.[17] This trial did not demonstrate a statistically significant improvement in the primary endpoint with treatment compared to placebo. After 12 months, the MDC trial reported that the combined primary endpoint of death or need for heart transplant was reduced 34% in patients on immediate-release metoprolol tartrate at a mean dose of 108mg/d (p=0.058). The need for heart transplant was significantly lower in patients on metoprolol (p=0.001). The MDC trial included 343 patients (mean age 49 years) with nonischemic dilated cardiomyopathy, 94% who were in NYHA class II or III HF with a mean LVEF of 22%. Patients on immediate-release metoprolol tartrate experienced a significant improvement in LVEF, exercise capacity, and quality of life.[17] Lower doses were used in these trials compared to MERIT-HF and the study population was not as large. Atenolol has been studied for its effect on combined worsening HF and mortality in 100 patients with NYHA class II to III HF. In this trial, atenolol (mean dose 89 mg per day) significantly reduced the combined primary endpoint compared to placebo (26% vs. 55%, respectively; p<0.01); however, the reduction in death alone was not significant between treatment groups, although the trial was not large enough to adequately assess a difference in mortality.[18] Another trial using bucindolol (not available in the U.S.) was terminated after a mean follow-up of 2 years as there was not a significant difference in the primary endpoint of mortality between treatment and placebo in 2708 patients with NYHA class III or IV HF.[19] An extended release formulation of carvedilol (carvedilol phosphate CR) has been recently approved for the treatment of mild to severe chronic HF. Mortality trials are not available with the extended release formulation, although the recommendations for use are based on trials conducted with immediate release carvedilol (as previously discussed), and the determination that the two formulations are bioequivalent at the following doses: carvedilol 3.125 mg twice daily/carvedilol CR 10 mg once daily; carvedilol 6.25 mg twice daily/carvedilol CR 20 mg once daily; carvedilol 12.5 mg twice daily/carvedilol CR 40 mg once daily; carvedilol 25 mg twice daily/carvedilol CR 80 mg once daily.[20-22]

Properties of the beta-adrenergic blockers

The question of whether to use a selective beta-adrenergic blocker (e.g., bisoprolol or metoprolol) versus a non-selective agent with alpha-adrenergic blocking and antioxidant effects (e.g., carvedilol) remains controversial.[14,23-27] Although COMET demonstrated a statistically significant improvement in survival with carvedilol compared to immediate release metoprolol tartrate, it is unknown whether this is a difference between carvedilol and immediate-release metoprolol tartrate (or sustained release metoprolol succinate) when prescribed at the recommended target doses. Since sustained release metoprolol succinate was not available at the time of enrollment in COMET, immediate-release metoprolol tartrate was selected as the comparator to carvedilol, at doses that were expected to result in comparable beta-blockade. Much of the discussion about the results of COMET include the difference in target dose and effect on resting heart rate. The dose of carvedilol used in COMET achieved a similar reduction in heart rate as seen in U.S. Carvedilol (i.e., 13 beats per minute). The mean dose of immediate-release metoprolol tartrate used in COMET was less than the mean dose in MDC (i.e., 85 vs. 108 mg per day), and resulted in less of a decrease in heart rate (i.e., 11.7 vs. 15 beats per minute). The mean dose in MERIT-HF was 159mg per day and achieved a reduction in heart rate of 14 beats per minute.[12,14,15,17,27] Whether these factors had an influence on the results is unknown. In addition, whether immediate-release metoprolol tartrate provides equivalent benefits as seen with sustained release metoprolol succinate is still to be determined.[28-30] Very few trials with beta-adrenergic blockers that are available in the U.S. other than bisoprolol, carvedilol, or metoprolol have been published.[18,31] It is therefore unknown if treatment with other beta-adrenergic blockers would provide the same benefits as seen with the agents that have demonstrated a reduction in mortality in patients with HF.

Use in patients with HF following acute myocardial infarction (MI)

Clinical practice guidelines also recommend use of a beta-adrenergic blocker in patients with a recent or remote history of MI, regardless of LVEF (Strength of Recommendation: A; Overall Quality: I), and in patients with asymptomatic LV dysfunction without a history of MI [Strength of Recommendation: B (recommendation that the intervention may be useful/effective); Overall Quality: II (Fair)].[1-3]

Beta-adrenergic blockers have been studied in patients shortly following an MI (e.g., propranolol, timolol)[32,33] and in patients during MI followed by continued therapy (e.g., atenolol, immediate release metoprolol tartrate)[34-36] with a reduction in mortality; although these trials often excluded patients with HF. Retrospective analyses of patients with asymptomatic LV dysfunction post-MI found that treatment with beta-adrenergic blockers was beneficial in reducing cardiovascular mortality, an effect that was independent of treatment with an angiotensin-converting enzyme inhibitor.[37] The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial randomized 1959 patients with a LVEF $\leq$ 40% post-MI (3 to 21 days) to carvedilol or placebo. The difference in the primary endpoint of all-cause mortality or cardiovascular hospitalizations was lower (35% vs. 37%) although not statistically significant, with carvedilol compared to placebo. The original primary endpoint of all-cause mortality (changed to co-primary endpoint due to inadequate sample size and power) was also lower with carvedilol (12% vs. 15%), but not statistically significant compared to placebo. The endpoint of all-cause mortality or non-fatal MI was significantly reduced (14% vs. 20%) with carvedilol.[38] Taking into account these results and those of other trials

with the beta-adrenergic blockers, a beta-adrenergic blocker is recommended in patients post-MI, regardless of LVEF. Although the benefit of beta-adrenergic blockers in patients with asymptomatic HF (not in the post-MI setting) has not been critically evaluated, current recommendations include use of a beta-adrenergic blocker in this patient population as well.[37-39]

Table 1. Beta-Adrenergic Blocker Comparison

Beta-blocker	Atenolol	Bisoprolol	Carvedilol	Carvedilol CR[a]	Metoprolol XL[a]	Metoprolol IR[a]
VA National Formulary	X	X	X[b]		X[b]	X
FDA Indication						
Heart Failure			X	X	X	
Angina	X				X	X
AMI	X					X
Post-AMI w/LVEF ≤ 40%			X	X		
Hypertension	X	X	X	X	X	X
Outcome data in HF		X	X		X	
$Beta_1$ cardioselective	X	X			X	X
Alpha-blocker			X	X		
Antioxidant			X	X		
QD regimen	X[c]	X		X	X	

[a] Carvedilol CR=extended release carvedilol phosphate; Metoprolol XL=sustained release metoprolol succinate; Metoprolol IR=immediate release metoprolol tartrate
[b] Restricted to patients with chronic HF
[c] Twice daily regimen used in clinical trial

Table 2. Recommendations for Titration and Target Dose in Patients with HF

Beta-blocker	Strength	Titration	Target Dose[a]
Bisoprolol	5 mg (scored), 10 mg film-coated tablets	• Initial dose 1.25mg once daily • Increase by 1.25mg weekly until 5mg once daily, then 2.5mg every 4 weeks to target dose *CIBIS II excluded patients with SBP < 100 mmHg and HR < 60 bpm*	10 mg once daily
Carvedilol	3.125 mg (not scored), 6.25 mg, 12.5 mg, 25 mg scored tablets	• Initial dose 3.125 mg twice daily (administer with food to reduce orthostatic hypotension; if dizziness occurs, consider separating ACEI, adjusting dose of diuretic, or temporary ACEI dose reduction) • Dose should be doubled at a minimum of every 2 weeks to the target dose *COPERNICUS and US Carvedilol excluded patients with SBP < 85 mmHg and HR < 68 bpm; manufacturer recommends ↓ dose if HR < 55 bpm*	25 mg twice daily (titrate as tolerated to 50 mg twice daily if ≥ 85 kg)
Metoprolol XL	25 mg, 50 mg, 100 mg, 200 mg scored, film-coated tablets	• Initial dose 12.5mg once daily ≥ NYHA class III HF; 25mg once daily < NYHA class III HF • Double dose every 2 weeks until target dose *MERIT-HF excluded patients with SBP < 100 mmHg*	200 mg once daily

[a] Or highest dose tolerated; effects are generally seen in 3-12 months. Beta-adrenergic blockers should not be abruptly discontinued
[b] Carvedilol CR FDA approval for patients with chronic HF based on clinical trials with carvedilol immediate release dosed twice daily; dose equivalency based on pharmacokinetic and pharmacodynamic data

Table 3. Price Comparisons of Select Beta-Adrenergic Blockers for Chronic Heart Failure

Beta-blocker	Regimen	Price per Dose[a]	Price per Patient per Month[a]
Bisoprolol (available as 5 mg [scored], 10 mg film-coated tablets)	1.25 mg once daily[b]	$0.076725 (5 mg split twice)	$2.30
	2.5 mg once daily[b]	$0.15345 (5 mg split)	$4.60
	5 mg once daily	$0.3069	$9.21
	10 mg once daily	$0.3069	$9.21
Carvedilol (available as 3.125 mg [not scored], 6.25 mg, 12.5 mg, 25 mg scored tablets)	3.125 mg twice daily	$1.1222	$67.33
	6.25 mg twice daily	$1.1275	$67.65
	12.5 mg twice daily	$1.1285	$67.71
	25 mg twice daily	$1.1283	$67.70 ($135.40 50mg twice daily if ≥ 85kg)
Metoprolol XL (available as 25 mg, 50 mg, 100 mg, 200 mg scored, film-coated tablets)	12.5 mg once daily[b]	$0.2268 (25 mg split)	$6.80
	25 mg once daily	$0.4536	$13.61
	50 mg once daily	$0.4518	$13.55
	100 mg once daily	$0.6946	$20.84
	200 mg once daily	$1.2528	$37.58

[a] Based on current Federal Supply Schedule or VA Contract Price (prices do not reflect tablet splitting unless indicated)
[b] Tablet splitting would be required

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Appendix A

Clinical Trial Data (Mortality Data with Beta-Adrenergic Blockers in Patients with Chronic HF)

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions
CIBIS III[10] 2005 MC, PROBE (BB 1st vs. ACEI 1st) Europe, Australia, Tunisia Supported by Merck KGaA	NYHA II (49%), III (51%) Mean EF 28.8%	1010	(Initial monotherapy X 6 months) Bisoprolol 10 mg once daily (target dose) vs. (Initial monotherapy X 6 months) Enalapril 10 mg twice daily (target dose) Followed by combination therapy X 6 to 24 months HF therapy Cardiac glycoside: 32% Diuretics: 84% Aldosterone antagonist: 13%	Mean 1.22 yrs	**Primary Endpoints:** Combined all-cause mortality or all-cause hosp (per protocol analysis bisoprolol 1st vs. enalapril 1st HR 0.97 95% CI 0.78-1.21; ITT 178 (35.2%) vs. 186 (36.8%) HR 0.94 95% CI 0.77-1.16; p=0.019[a]) **Endpoint** / **Bisoprolol 1st (N=505[b])** / **Enalapril 1st (N=505[b])** / **p value** Primary: 163 (32.4%) / 165 (33.1%) / 0.046[a] CV death[c]: 55 (NR) / 56 (NR) / 0.86 HF hosp[d]: 63 (NR) / 51 (NR) / 0.23 [a]test for noninferiority; [b]N for ITT; [c] IHR 0.97; [d]HR 1.25 **Target dose on monotherapy:** Bisoprolol (65%) vs. enalapril (84%)	Bisoprolol 1st noninferior to enalapril 1st in ITT analysis, but not by per-protocol analysis; initial therapy with bisoprolol may be as safe and efficacious as starting with enalapril
COMET[13] 2003 MC, R, DB, PG (BB vs. BB) Europe Supported by F Hoffmann La Roche and GlaxoSmithKline	NYHA II (48%), III (48%), IV (4%) Mean EF 26%	3029	Carvedilol 25 mg twice daily (target dose) vs. Metoprolol IR 50 mg twice daily (target dose) HF therapy ACEI: 91% ARB: 7% Digoxin: 59% Diuretics: 99% Aldosterone antagonist: 11%	Mean 58 months	**Primary Endpoints:** 1) All-cause mortality (↓ with carvedilol vs. metoprolol; HR 0.83 95% CI 0.74-0.93; ARR 5.6%, NNT 18); and 2) Composite all-cause mortality or all-cause admission (HR 0.94 95% CI 0.86-1.02) **Endpoint** / **Carvedilol (N=1511)** / **Metoprolol (N=1518)** / **p value** Primary1: 512 (33.9%) / 600 (39.5%) / 0.017 Primary2: 1116 (73.9%) / 1160 (76.4%) / 0.122 **Target dose:** Carvedilol (75%) vs. metoprolol IR (78%) **Mean dose:** Carvedilol (41.8 ± 14.6 mg per day); metoprolol IR (85 ± 28.9 mg per day)	Carvedilol had a greater benefit on survival compared to metoprolol IR in patients with chronic HF on standard therapy (i.e., diuretics plus ACEI)
COPERNICUS[12] 2001 MC, R, DB (vs. placebo) U.S., Canada, Mexico, Europe, S. America, Israel, S. Africa, Australia Supported by SmithKline Beecham and Boehringer-Mannheim	Severe HF (≥ 2 months dyspnea or fatigue at rest or minimal exertion, EF < 25%) Mean EF 19.9%	2289	Carvedilol 25 mg twice daily (target dose) vs. Placebo HF therapy ACEI or ARB: 97% Digoxin: 66% Diuretics: 99% Spironolactone: 20%	Mean 10.4 months (stopped early due to improved survival)	**Primary Endpoint:** All-cause mortality (35% ↓ with carvedilol; 95% CI 0.19-0.48; ARR 5.5%, NNT 18) **Endpoint** / **Carvedilol (N=1156)** / **Placebo (N=1133)** / **p value** Primary: 130 (11.3%) / 190 (16.8%) / 0.0014 Death or hosp: 425 (36.8%) / 507 (44.8%) / <0.001 **Target dose:** Carvedilol (65.1%) vs. placebo (78.2%) at 4 months **Mean dose:** 37 mg per day	Carvedilol reduced the rate of death in patients with severe HF on conventional therapy (i.e., diuretics plus ACEI or ARB)

Clinical Trial Data (continued)

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions
MERIT-HF[14] **1999** MC, R, DB (vs. placebo) U.S., Europe Supported by Astra Hässle AB	NYHA II (41%), III (56%), IV (3.4%) HF Mean EF 28%	3991	Metoprolol XL 200 mg once daily (target dose) vs. Placebo HF therapy ACEI: 90% ARB: 7% Digoxin: 64% Diuretics: 90%	Mean 1 yr (terminated early due to survival benefit)	**Primary Endpoints:** 1) All-cause mortality (↓ with metoprolol XL; RR 0.66 95% CI 0.53-0.81; ARR 3.6%, NNT 28); and 2) Combined all-cause mortality and all-cause hosp admissions (NR) **Endpoint** / **Metoprolol XL (N=1990)** / **Placebo (N=2001)** / **p value** Primary1: 145 (7.3%) / 217 (10.9%) / 0.00009 CV death: 128 (6.4%) / 203 (10.2%) / 0.00003 **Target dose:** Metoprolol XL (64%) vs. placebo (82%) **Mean dose:** 159 mg	Metoprolol XL significantly improved survival in patients with symptomatic HF on standard therapy for HF (i.e., diuretics plus ACEI)
CIBIS II[8] **1999** MC, R, DB (vs. placebo) Europe Supported by E Merck	NYHA III (83%), IV (17%) Mean EF 27.5%	2647	Bisoprolol 10 mg once daily (target dose) vs. Placebo HF therapy ACEI: 96% Digoxin: 52% Diuretics: 99%	Mean 1.3 yrs (stopped early due to improved survival)	**Primary Endpoint:** All-cause mortality (↓ with bisoprolol; HR 0.66 95% CI 0.54-0.81; ARR 5.5%, NNT 18) **Endpoint** / **Bisoprolol (N=1327)** / **Placebo (N=1320)** / **p value** Primary: 156 (11.8%) / 228 (17.3%) / <0.0001 CV death: 119 (9%) / 161 (12.2%) / 0.0049 **Target dose:** Bisoprolol 10 mg (564 patients); 7.5 mg (152 patients); 5 mg (176 patients) **Most common dose:** 10 mg	Bisoprolol significantly improved survival in patients with stable symptomatic HF (NYHA class III to IV) on standard therapy (i.e., diuretics plus ACEI)
US Carvedilol[11] **1996** MC, R, DB (vs. placebo) U.S. Supported by Roche and GlaxoSmithKline	NYHA II (53%), III (44%), IV (3%) Mean EF 23%	1094	Carvedilol 25 to 50 mg twice daily (target dose) or 6.25, 12.5, or 25 mg twice daily (dose-ranging protocol) vs. Placebo HF therapy ACEI: 95% Digoxin: 91% Diuretics: 95%	Median 6.5 months (stopped early due to improved survival)	**Primary Endpoint:** Death (65% ↓ with carvedilol; 95% CI 0.39-0.80; ARR 4.6%, NNT 22) **Endpoint** / **Carvedilol (N=696)** / **Placebo (N=398)** / **p value** Primary: 22 (3.2%) / 31 (7.8%) / <0.001 CV hosp: 98 (14.1%) / 78 (19.6%) / 0.036 **Target dose:** Achieved in 80% of patients **Mean dose:** 45 ± 27 mg per day	Carvedilol reduced the risk of death in patients with symptomatic HF on standard therapy (i.e., diuretics plus ACEI); individual protocols designed to assess nonfatal endpoints, with mortality prespecified to evaluate safety and benefit in overall trial

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ARR=absolute risk reduction; CI=confidence interval; CV=cardiovascular; DB=double-blind; EF=ejection fraction; HF=heart failure; hosp=hospitalizations; HR=hazard ratio; IR=immediate-release; ITT=intention-to-treat analysis; N=number of patients; NNT=number needed to treat; NR=not reported; NYHA=New York Heart Association; PROBE=prospective, randomized, open-label, blinded endpoint evaluation; R=randomized; RR=relative risk; XL=extended-release; yrs=years

Appendix B

Approximate Dose Equivalents of the Beta-Adrenergic Blockers Used in Patients with Chronic HF (may be used if conversion deemed appropriate)

- The beta-adrenergic blockers atenolol and immediate-release metoprolol tartrate (IR) have been studied in patients with HF; however, data as to their long-term clinical outcome benefit and their optimal dose have not been determined. The following dose equivalents have been developed to assist practitioners who elect to convert their patients to a beta-adrenergic blocker with established mortality benefit in patients with chronic HF. Note: recommendations are not based on head-to-head comparison trials; dosage conversions are derived from the initial, mean, and target doses reported in long-term, randomized, placebo-controlled outcome trials[9-15] and from national clinical practice guideline recommendations.[1-3] The following may be modified based on clinical judgment.

- For patients with HF who are currently considered unstable, it is recommended that the patient remain on their current beta-adrenergic blocker until stabilized. The provider should weigh the risk vs. benefit of switching patients to the recommended beta-adrenergic blockers based on the patient's current health status.

Atenolol	Metoprolol IR	Bisoprolol	Carvedilol	Metoprolol XL
25mg once or divided twice daily	6.25 to 12.5mg twice daily	1.25mg once daily	3.125mg twice daily	25mg once daily (12.5mg once daily if > NYHA class II)
50mg once or divided twice daily	12.5 to 25mg twice daily	2.5mg once daily	6.25mg twice daily	50mg (or 25mg) once daily
75mg once or divided twice daily	25 to 50mg twice daily	5mg once daily	12.5mg twice daily	100mg (or 50mg) once daily
100mg once or divided twice daily	50 to 100mg twice daily	10mg once daily	25mg twice daily (may titrate to 50mg twice daily if ≥ 85 kg)	200mg (or 100mg titrated to 200mg) once daily