Position Statement on
β-BLOCKER THERAPY IN CHRONIC HEART FAILURE

Well over 18,000 patients have been studied in randomized clinical trials designed to evaluate the efficacy of β-blocking agents in prolonging life and reducing cardiovascular morbidity in patients with chronic heart failure.[1-15] It is paramount that this evidence be integrated into patient care.

Based on the results of the available β-blocker trials, we advocate the following:

1. All patients with left ventricular systolic dysfunction should receive β-blocker therapy if not otherwise contraindicated.
   - β-blocker therapy should be initiated in patients with stable disease, i.e. those without fluid retention and not requiring inotropic therapy.
   - Although limited data is available regarding β-blocker therapy for asymptomatic patients with left ventricular systolic dysfunction, we strongly advocate the use of these agents to prevent development of clinical heart failure.
   - β-blocker therapy should be initiated very cautiously in patients with tenuous blood pressure or hypoperfusion.
2. Following myocardial infarction, patients with left ventricular systolic dysfunction or clinical heart failure should receive β-blocker therapy if not contraindicated.
   - Although the evidence supporting the use of carvedilol is strongest in this patient population[12], all of the β-blockers validated for use in heart failure should be considered (e.g., carvedilol, bisoprolol, and metoprolol succinate; see below) since post-myocardial infarction left ventricular systolic dysfunction may eventually progress to clinical heart failure.
     (Note: bisoprolol is not on the University Health System Formulary.)
3. The treatment of patients with chronic heart failure with those β-blockers whose use is supported by clinical evidence:

Drug	Brand Name	Target Dose
Carvedilol	Coreg®	25 mg po bid
Bisoprolol	Zebeta®	10 mg po qd
Metoprolol succinate	Toprol XL®	200 mg po qd

   - Although the data supporting the use of metoprolol tartrate (Lopressor®, target dose 75 mg po bid or 50 mg po tid) for treatment of heart failure is less robust, it remains a therapeutic option in patients without economic access to the other agents.
   - In light of the results of COMET[15], carvedilol 25 mg po bid should be considered to be superior to metoprolol tartrate 50 mg po bid in reducing total mortality in these patients. It is unclear whether these data result from differences in β-receptor selectivity, the additional α-blocking or antioxidant properties of carvedilol, or the dosage and formulation of metoprolol used in this study.

Clinical Trials Supporting the Use of Beta-Blockers in Chronic Heart Failure

- Metoprolol in Dilated Cardiomyopathy trial (MDC)
- Cardiac Insufficiency Bisoprolol Study (CIBIS)
- US Carvedilol Heart Failure Trials Program
- Australia/New Zealand Heart Failure Research Collaborative Group
- Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)
- Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)
- Beta-Blocker Evaluation of Survival Trial (BEST)
- Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction study (CAPRICORN)
- Carvedilol Prospective Randomized Cumulative Survival trial (COPERNICUS)
- Carvedilol or Metoprolol European Trial (COMET)

Metoprolol in Dilated Cardiomyopathy trial (MDC)[1]

Objective: MDC was designed to evaluate the effect of metoprolol tartrate on morbidity and mortality in patients with idiopathic dilated cardiomyopathy.

Methods: 383 patients with heart failure from idiopathic dilated cardiomyopathy (ejection fraction < 40%) were randomly assigned to receive metoprolol tartrate (target dose, 100 – 150 mg daily) or a matching placebo following an open-label test period of 2-7 days. Background therapy consisted of furosemide (78% in the metoprolol tartrate group and 73% in the placebo group), ACE inhibitors (78% in the metoprolol tartrate group and 82% in the placebo group), and digitalis (78% in the metoprolol tartrate group and 79% in the placebo group). Patients were excluded if their systolic blood pressure was < 90 mm Hg or heart rate was < 45 bpm. The minimum follow-up was one year.

Results:

- The majority of patients in MDC were NYHA Class II (42% of the metoprolol tartrate group and 47% of the placebo group) and III (51% of the metoprolol tartrate group and 47% of the placebo group. 4% of both groups were NYHA Class IV. 3% of the metoprolol tartrate group and 2% of the placebo group were NYHA Class I.
- The mean daily dose achieved was 108 mg for patients receiving metoprolol tartrate.
- The composite endpoint of all-cause mortality or need for heart transplantation was not statistically different between the two groups (25% in the metoprolol tartrate group and 38% in the placebo group, $p = 0.058$).
- There was a statistical difference between the two groups' need for heart transplantation: 2% of the metoprolol tartrate group and 19% of the placebo group ($p = 0.0001$).
- Heart rate and pulmonary wedge pressure decreased significantly from baseline in the metoprolol tartrate group compared to the placebo group. Systolic pressure, stroke volume, and stroke work index increased significantly in the metoprolol tartrate group compared to the placebo group.

- Quality of life was significantly improved in the metoprolol tartrate group compared to the placebo group ($p = 0.01$).

Conclusions: In patients with idiopathic dilated cardiomyopathy, the addition of metoprolol tartrate therapy did not show a statistical mortality benefit, though symptoms and cardiac function improved.

Cardiac Insufficiency Bisoprolol Study (CIBIS)[2]

Objective: CIBIS was designed to evaluate the tolerability of bisoprolol in heart failure and its effect on mortality in these patients.

Methods: 641 patients with NYHA Class III or IV heart failure (ejection fraction < 40%) were randomly assigned to receive either bisoprolol (target dose 5 mg po qd) or a matching placebo. Background therapy consisted of diuretics (100%), ACE inhibitors (89% in the bisoprolol group and 91% in the placebo group), dihydropyridine calcium channel antagonists (8% in the bisoprolol group and 7% in the placebo group), and other vasodilators (41% in the bisoprolol group and 40% in the placebo group). Patients with hypertrophic or restrictive cardiomyopathy were excluded. Patients were also excluded if their systolic blood pressure was < 100 or > 160 mm Hg, heart rate was < 65 bpm, or serum creatinine was > 300 μmol/L. The mean follow-up was 1.9 years.

Results:
- The majority of patients in CIBIS were NYHA Class III (95%). The remaining patients (5%) were NYHA Class IV.
- The mean achieved daily dose of bisoprolol was 3.8 mg. 59% of patients receiving bisoprolol reached the target dose of 5 mg po qd.
- All-cause mortality was not significantly different between the two treatment groups: 16.6% in the bisoprolol group and 20.9% in the placebo group ($p = 0.22$).

Conclusions: Although not statistically significant, CIBIS demonstrated a trend toward improved mortality with bisoprolol therapy in chronic heart failure.

US Carvedilol Heart Failure Trials Program[3-6]

Objective: The US Carvedilol Heart Failure Trials Program was designed to evaluate the effect of carvedilol on mortality in patients with varying degrees of heart failure.

Methods: 1094 patients with chronic heart failure for at least two months, LVEF ≤ 35%, and on standard therapy were placed into one of four independent, free-standing trials based on exercise performance during a 6 minute walk test. Those unable to walk 150 meters were placed in the SEVERE trial, patients who walked 150-450 meters were enrolled in either MOCHA (dose ranging study) or PRECISE and subjects who walked 450 to 550 meters were studied in the MILD trial. Subjects were given open label carvedilol 6.25 mg po bid for 2 weeks prior to randomization to active drug or placebo; those who could not tolerate low dose β-blockade were excluded. Background therapy

consisted of diuretics (95%), ACE inhibitors (95%), digitalis (91% in the carvedilol group and 90% in the placebo group). Patients were also excluded for a systolic blood pressure of < 85 mm Hg or > 160 mm Hg or heart rate < 68 bpm. The median follow-up was 6.5 months

Results:

- The US Carvedilol program was stopped prematurely by the data safety and monitoring board because of a highly statistically significant impact of carvedilol on overall mortality, at an average follow-up of 6 months, when all 4 trials were combined and evaluated together.
- The proportions of patients in each NYHA Class for each group were as follows: II, 53.7% in the carvedilol group and 52.3% in the placebo group; III, 43.5% in the carvedilol group and 44.5% in the placebo group; IV, 2.7% in the carvedilol group and 3.3% in the placebo group.
- Compared with placebo, patients in the carvedilol group had a greater frequency of symptomatic improvement and lower risk of clinical deterioration as evaluated by changes in the NYHA functional class or by a global assessment of progress judged either by the patient or the physician. In addition, treatment with carvedilol was associated with a significant increase in ejection fraction, decrease in CHF hospitalizations, and decrease in background diuretic dosages.
- Additionally, the results of the MOCHA trial demonstrate that carvedilol's impact on improvement in left ventricular systolic function was dose-dependent and linear ($p < 0.01$).

Conclusions: Taken together, the US Carvedilol trials demonstrated that treatment with carvedilol significantly reduces heart failure morbidity and mortality.

Australia/New Zealand Heart Failure Research Collaborative Group[7]

Objective: The Australia/New Zealand Heart Failure Research Collaborative Group trial was designed to evaluate the effect of carvedilol on left ventricular ejection fraction, exercise capacity, and the rates of hospital admission and mortality.

Methods: 415 patients with NYHA Class II-III heart failure (ejection fraction < 45%) as a result of ischemic heart disease were randomized to receive either carvedilol (maximum 25 mg po bid) or a matching placebo. Treatment was initiated following a 2-3 week open treatment period. Background therapy consisted of diuretics (75% in the carvedilol group and 76% in the placebo group), ACE inhibitors (86% in the carvedilol group and 85% in the placebo group), and digitalis (38%). Patients with NYHA Class IV heart failure, systolic blood pressure < 90 mm Hg, heart rate < 50 bpm, serum creatinine > 250 μmol/L, or treadmill exercise duration < 2 min or > 18 min were excluded. Patients were also excluded for an inability to tolerate beta-blockade during the initial run-in period. The mean follow-up was 19 months.

Results:

- The majority of patients in the Australia/New Zealand Heart Failure Research Collaborative Group trial were NYHA Class II (59% in the carvedilol group and 49% in the placebo group). 29% of patients in the carvedilol group and 30% of

patients in the placebo group were NYHA Class I, and 11% of patients in the carvedilol group and 21% of patients in the placebo group were NYHA Class III.
- The mean dose achieved was 41 mg in the carvedilol group. 48% of the patients were receiving the target dose at the end of follow-up.
- After 12 months, left-ventricular ejection fraction had increased by 5.3% ($p<0.0001$) above baseline and end-diastolic and end-systolic dimensions had decreased by 1.7 mm ($p=0.06$) and 3.2 mm ($p=0.001$), respectively, in the carvedilol group, compared with the placebo group.
- Similar to that found in the US Carvedilol Trials, carvedilol did not impact on treadmill exercise duration or 6-minute walk distance. Unlike that observed in the US Carvedilol Trials, the NYHA Class or SAS score did not change.
- At the end of follow-up, the frequency of episodes of worsening heart failure was similar in the carvedilol and placebo groups but the rate of death or hospital admission was lower in the carvedilol group than in the placebo group, relative risk 0.74 [0.57 – 0.95].

Conclusions: In patients with mild to moderate heart failure, carvedilol therapy improves left ventricular function and reduces the incidence of death or hospital admission.

Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[8]

Objective: CIBIS-II was designed to further explore the conclusion found in CIBIS, a non-significant trend toward a benefit of bisoprolol on mortality and the rate of hospitalization.

Methods: 2647 patients with NYHA Class III-IV with an ejection fraction ≤ 35% were randomly assigned in a double-blind fashion to receive either bisoprolol (target dose, 10 mg po qd) or placebo. Concurrent therapy consisted of diuretics (98% in the bisoprolol group and 99% in the placebo group), ACE inhibitors (96%), and digitalis (53% in the bisoprolol group and 51% in the placebo group). Patients were excluded if their systolic blood pressure was < 100 mm Hg, heart rate was < 60 bpm, or serum creatinine was > 300 μmol/L. The mean follow-up was 1.3 years.

Results:
- CIBIS-II was terminated at a mean follow-up of 1.3 years due to a significantly lower mortality rate in the bisoprolol group.
- The patients in CIBIS-II were primarily in NYHA Class III (83%), though 17% of patients were Class IV.
- 564 patients reached the target dose of bisoprolol, 10 mg po qd. 152 and 176 patients reached 7.5 mg and 5 mg po qd, respectively.
- The primary endpoint of all-cause mortality was 11.8% in the bisoprolol group and 17.3% in the placebo group ($p < 0.0001$). The annual mortality rate was 8.8% in the bisoprolol group and 13.2% in the placebo group (hazard ratio 0.66, 95% CI, 0.54 – 0.81).
- The cause of mortality was determined to be cardiovascular in nature in 12% of the bisoprolol group and 9% in the placebo group ($p = 0.0049$).

- Significantly fewer patients in the bisoprolol group compared to the placebo group were admitted to the hospital for all causes (p = 0.0006). Additionally, the composite endpoint of cardiovascular death and cardiovascular hospital admission was significantly lower for patients in the bisoprolol group (p = 0.0004).

Conclusions: The addition of bisoprolol to standard therapy improves morbidity and mortality in patients with heart failure.

Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)[9-10]

Objective: MERIT-HF was designed to compare the effects of placebo and metoprolol succinate on morbidity and mortality in patients with moderate to severe chronic heart failure.

Methods: 3991 patients with NYHA II-IV with an ejection fraction ≤ 40% were randomly assigned in a double-blind fashion to receive metoprolol succinate (target dose, 200 mg po qd) or placebo. Background therapy consisted of diuretics (91% in the metoprolol succinate group and 90% in the placebo group), ACE inhibitors (89% in the metoprolol succinate group and 90% in the placebo group), angiotensin II receptor antagonists (7% in the metoprolol succinate group and 6% in the placebo group), and digitalis (63% in the metoprolol group and 64% in the placebo group). Patients were excluded if they had a systolic blood pressure < 100 mmHg. The mean follow-up was one year.

Results:
- The MERIT-HF trial was terminated at an interim analysis based on the number of deaths that occurred.
- The majority of patients were NYHA class II (41%) and III (56% in the metoprolol succinate group and 55% in the placebo group). Only 3.4% and 3.8% of patients in the metoprolol succinate and placebo groups were NYHA class IV, respectively.
- The mean daily dose achieved in the metoprolol succinate group was 159 mg po qd, with 64% of patients achieving the target dose. The mean heart rate reductions were 14 bpm in the metoprolol succinate group and 3 bpm in the placebo group.
- Overall mortality was 29.1% in the metoprolol succinate group and 33.3% in the placebo group (p = 0.004). The yearly mortality rates were 7.2% and 11.0% in the metoprolol succinate and placebo groups, respectively.
- There were 128 cardiovascular deaths in the metoprolol succinate group and 203 in the placebo group (relative risk, 0.62; 95% CI 0.50 – 0.78; p = 0.00003).
- For the composite end point of total mortality or all-cause hospitalization, the relative risk reduction with metoprolol succinate was 19% (95% CI, 10-27%).

Conclusions: In patients with standard background therapy, the addition of once-daily metoprolol succinate is associated with a reduction in mortality and the rate of hospitalization.

Beta-Blocker Evaluation of Survival Trial (BEST)[11]

Objective: BEST was designed to evaluate the effect of bucindolol on all-cause mortality in patients with moderate to severe chronic heart failure.

Methods: 2708 patients with NYHA Class III or IV heart failure with an ejection fraction ≤ 35% were randomly assigned in a double-blind fashion to receive either bucindolol (50 mg po bid or 100 mg po bid for patients ≥ 75 kg) or placebo. Background therapy consisted of diuretics (94%), ACE inhibitors (91%), angiotensin II receptor antagonists (6% in the bucindolol group and 7% in the placebo group), and digitalis (93% in the bucindolol group and 92% in the placebo group). Patients were excluded if they were candidates for heart transplantation or if their heart rate was < 50 bpm or serum creatinine was > 3.0 mg/dL. The mean follow-up was 2.0 years.

Results:

- BEST was terminated early by the data and safety monitoring board due to the "totality of evidence regarding the usefulness of β-blocker treatment derived from BEST and other studies."
- The majority of patients were NYHA Class III (92%). The remaining 8% of patients were NYHA Class IV.
- The mean daily dose achieved was 76 mg po bid for patients receiving bucindolol.
- All-cause mortality was not statistically different between the two groups at the end of the study: 30% in the bucindolol group and 33% in the placebo group ($p = 0.13$). The annual mortality rates were 15% and 17% for the bucindolol and placebo groups, respectively.
- The rate of death due to cardiovascular causes was lower for patients in the bucindolol group than those in the placebo group ($p = 0.04$).

Conclusions: The addition of bucindolol to standard therapy for patient with moderate to severe heart failure did not demonstrate a significant mortality benefit, likely due to its early termination.

Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction study (CAPRICORN)[12]

Objective: CAPRICORN was designed to evaluate the effect of carvedilol on morbidity and mortality in patients with left ventricular systolic dysfunction after myocardial infarction with and without clinical heart failure.

Methods: 1959 patients with left ventricular systolic dysfunction (LVEF ≤ 40%) after myocardial infarction were randomized to receive either carvedilol (target dose, 25 mg po bid) or an identical placebo. The patients' concurrent therapy at the time of randomization consisted of ACE inhibitors (98% in the carvedilol group and 97% in the placebo group) and aspirin (86%). Patients with a systolic blood pressure of < 90 mmHg or heart rate < 60 bpm were excluded. Mean follow-up was 1.3 years.

Results:

- The average LVEF's were 32.9% and 32.7% in the carvedilol and placebo groups, respectively.
- 74% of patients achieved the carvedilol target dose of 25 mg po bid. 11% and 7% of patients were able to tolerate 12.5 mg and 6.25 mg po bid, respectively.
- Overall mortality was 12% in the carvedilol group and 15% in the placebo group ($p = 0.031$).
- For 11% of patients in the carvedilol group and 14% of patients in the placebo group, the cause of death was cardiovascular in nature ($p = 0.024$).
- The composite endpoint of all-cause mortality and cardiovascular-cause hospital admission was not different between the two groups, 35% in the carvedilol group and 37% in the placebo group ($p = 0.296$).

Conclusions: In patients post-myocardial infarction with left ventricular systolic dysfunction, the addition of carvedilol therapy reduces mortality.

Carvedilol Prospective Randomized Cumulative Survival trial (COPERNICUS)[13-14]

Objective: COPERNICUS was designed to evaluate the effect of carvedilol on survival in severe heart failure.

Methods: 2289 patients with symptoms of heart failure at rest or with minimal exertion were randomly assigned in a double-blind fashion to receive either carvedilol (target dose, 25 mg po bid) or placebo. Concurrent therapy consisted of diuretics (99%), ACE inhibitors or angiotensin II receptor antagonists (97%), digitalis (67% in the carvedilol group and 65% in the placebo group), and spironolactone (19% in the carvedilol group and 20% in the placebo group). Patients were excluded for systolic blood pressure < 85 mm Hg, heart rate < 65 bpm, or a serum creatinine > 2.8 mg/dL. Mean follow-up was 10.4 months.

Results:

- COPERNICUS was terminated early due to a significant survival benefit seen with carvedilol.
- The mean left ventricular ejection fractions were 19.9% in the carvedilol group and 19.8% in the placebo group.
- The mean daily dose achieved in the carvedilol group was 37 mg. 65.1% of patients in the carvedilol group reached the target dose of 25 mg po bid.
- 130 patients in the carvedilol group and 190 patients in the placebo group died during the study (relative risk reduction, 35%, 95% CI 19-48%, $p = 0.0014$). The cumulative risk of death at one year was 11.4% in the carvedilol group and 18.5% in the placebo group.
- The relative risk reduction for the composite end point of all-cause death or hospitalization was 24% (95% CI 13-33%, $p < 0.001$).

Conclusions: The addition of carvedilol to standard therapy reduces mortality and hospitalization in patients with severe heart failure.

Carvedilol or Metoprolol European Trial (COMET)[15]

Objective: COMET was designed to directly compare the effects of carvedilol and metoprolol tartrate on morbidity and mortality in patients with mild to severe chronic heart failure.

Methods: 3029 patients with NYHA Class II-IV heart failure with an ejection fraction ≤ 35% were randomly assigned in a double-blind fashion to receive carvedilol (target dose, 25 mg po bid) or metoprolol tartrate (target dose, 50 mg po bid). Background therapy consisted of diuretics (99%), ACE inhibitors (92% in carvedilol group and 91% in metoprolol tartrate group), angiotensin II receptor antagonists (6% in carvedilol group and 7% in metoprolol tartrate group), and digitalis (61% in carvedilol group and 58% in metoprolol tartrate group). Patients were excluded for a systolic blood pressure of < 85 or > 170 mm Hg, a diastolic blood pressure of > 105 mm Hg, or a heart rate of < 60 bpm. The mean follow up was 58 months.

Results:

- The majority of patients were NYHA class II (48% in carvedilol group and 49% in metoprolol tartrate group) and III (48% in carvedilol group and 47% in metoprolol tartrate group). 3% and 4% of patients in the carvedilol and metoprolol tartrate groups were NYHA class IV, respectively.
- The mean daily dose achieved was 41.8 mg for carvedilol and 85 mg for metoprolol tartrate. The mean heart rate decreased from baseline 13.3 bpm in the carvedilol group and 11.7 bpm in the metoprolol tartrate group.
- The yearly mortality rate was 8.3% for carvedilol and 10.0% for metoprolol tartrate, and the overall mortality rate was 35% for carvedilol and 40% for metoprolol tartrate ($p = 0.002$).
- For 29% of patients in the carvedilol group and 35% of patients in the metoprolol group, the cause of death was cardiovascular in nature ($p = 0.0004$).
- The composite endpoint of all deaths and all-cause admission was not different between the two groups (74% for the carvedilol group and 76% for the metoprolol tartrate group, $p = 0.122$).

Conclusions: At the doses defined in COMET, treatment with carvedilol has a significantly greater benefit on mortality compared to metoprolol tartrate.

Evidence table

Clinical trial	Patients	Exclusion	Intervention	Follow-up	NYHA Class	Overall Mortality
MDC (1993)[1]	IDC LVEF < 40% n = 383	SBP < 90 HR < 45	Metoprolol tartrate 100-150 mg daily	Minimum 1 year	I, 2-3% II, 42-47% III, 47-51% IV, 4%	P, 20.1% Metoprolol tartrate, 12.9% NS
CIBIS (1994)[2]	LVEF < 40% n = 641	SBP < 100 or > 160 HR < 65 SCr > 300 μmol/L	Bisoprolol 5 mg po qd	Mean 1.9 years	III, 95% IV, 5%	P, 20.9% Bisoprolol, 16.6% NS
US Carvedilol Trials[3-6]	LVEF ≤ 35% n = 1094	Intolerant of beta-blockade SBP < 85 or > 160 HR < 68	Carvedilol 25-50 mg po bid	Median 6.5 months	II, 52-53% III, 43-44% IV, 3%	P, 7.8% Carvedilol, 3.2% p ≤ 0.01
Australia/New Zealand[7]	LVEF < 45% n = 415	Intolerant of beta-blockade SBP < 90 HR < 50 SCr > 300 μmol/L Treadmill exercise duration < 2 or > 18 min	Carvedilol 25 mg po bid	Mean 19 months	I, 29-30% II, 49-59% III, 11-21%	P, 12.6% Carvedilol, 9.6% NS
CIBIS II (1999)[8]	LVEF ≤ 35% n = 2647	SBP < 100 HR < 60 SCr > 300 μmol/L	Bisoprolol 10 mg po qd	Mean 1.3 years	III, 83% IV, 17%	P, 17.3% Bisoprolol, 11.8% p < 0.001
MERIT-HF (1999)[9-10]	LVEF ≤ 40% n = 3991	SBP < 100	Metoprolol succinate 200 mg po qd	Mean 1 year	II, 41% III, 55-56% IV, 3.4-3.8%	P, 33.3% Metoprolol succinate, 29.1% p = 0.004

Evidence table (continued)

BEST (2001)[11]	LVEF ≤ 35% n = 2708	HR < 50 SCr > 3.0	Bucindolol 50 or 100 mg po bid	Mean 2.0 years	III, 92% IV, 8%	P, 33% Bucincolol, 30% p = 0.13
CAPRICORN (2001)[12]	LVEF ≤ 40% Post-MI n = 1959	SBP < 90 HR < 60	Carvedilol 25 mg po bid	Mean 1.3 years	N/R	P, 15% Carvedilol, 12% p = 0.031
COPERNICUS (2003)[13-14]	Symptoms at rest or with minimal exertion n = 2289	SBP < 85 HR < 68 SCr > 2.8	Carvedilol 25 mg po bid	Mean 10.4 months	N/R	P, 16.8% Carvedilol, 11.2% p = 0.0014
COMET (2003)[15]	LVEF ≤ 35% n = 3029	SBP < 85 or > 170 DBP > 105 HR < 60	Carvedilol 25 mg po bid Metoprolol tartrate 50 mg po bid	58 months	II, 48-49% III, 47-48% IV, 3-4%	Carvedilol, 35% Metoprolol tartrate, 40% P = 0.002

DBP, diastolic blood pressure; HR, heart rate; IDC, idiopathic dilated cardiomyopathy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/R, not reported; NS, not significant; NYHA, New York Heart Association; P, placebo; SBP, systolic blood pressure; SCr, serum creatinine

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