A Review of Evidence-Based β-Blockers in Special Populations With Heart Failure

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Guidelines recommend 1 of 3 β-blockers (bisoprolol, carvedilol, metoprolol succinate) for the treatment of systolic heart failure (HF). β-Blockers have been established to be effective in reducing mortality in more than 20 randomized, placebo-controlled clinical trials involving more than 20,000 patients with HF. However, they are not utilized in a substantial portion of eligible HF patients, possibly because physicians are unsure of the safety and benefit of β-blockers in special populations (women, the elderly, African Americans, patients with diabetes, and patients with atrial fibrillation). The current standard of care is to treat all heart failure (HF) patients according to the recommendations for the overall population. A review of the clinical trial data reveals that there is no evidence that one evidence-based β-blocker is preferential over the others in women or in the elderly with HF. In contrast, carvedilol may confer greater benefit in HF patients with diabetes and atrial fibrillation as well as in African American patients. Further data are needed to provide evidence-based recommendations.
[Rev Cardiovasc Med. *2008;9(2):84-95*]

Key words: Heart failure • African Americans • Atrial fibrillation • β-Blockers • Diabetes mellitus

Heart failure (HF) affects 5.2 million Americans, and 550,000 additional patients are diagnosed with this condition every year.[1] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines currently recommend 1 of 3 β-blockers (bisoprolol, carvedilol, and metoprolol succinate) for the treatment of chronic systolic HF due to their proven efficacy in reducing mortality.[2] Solid clinical trial data support mortality reductions with use of bisoprolol,[3] carvedilol,[4-6] and metoprolol succinate[7] in the

general systolic HF population. However, not only are specific patient subgroups underrepresented in these clinical trials, but also the strength of evidence in these special subpopulations is underwhelming when compared with the general population. Despite the fact that certain patient characteristics (older age, African American, or female) or concomitant conditions (diabetes or atrial fibrillation) may increase a patient's risk for morbidity and/or mortality, these patients are often excluded from or underrepresented in clinical trials. This article will review the clinical trial evidence supporting the use of bisoprolol, carvedilol, and metoprolol succinate in the general HF population and examine the evidence in special high-risk HF subgroups (the elderly, women, African Americans, concomitant diabetes, and concomitant atrial fibrillation).

Evidence-Based, Guideline-Recommended β-Blockers for HF

β-Blockers have been established to be effective in reducing mortality in more than 20 randomized, placebo-controlled clinical trials involving more than 20,000 patients with HF.[2] Three β-blockers have been shown to be effective in reducing the risk of death in patients with chronic HF: bisoprolol and sustained-release metoprolol (succinate), which selectively block β_1-receptors, and carvedilol, which blocks α_1-, β_1-, and β_2-receptors.[2]

Bisoprolol

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) was a placebo-controlled trial studying the effects of the β_1-selective blocker bisoprolol (1.25-10 mg/d) in 2647 patients with symptomatic HF (New York Heart Association [NYHA] class III or IV) and left ventricular ejection fraction (LVEF) at or less than 35% due to ischemia, dilated cardiomyopathy, or undefined reasons (Table 1).[3] Other medications included diuretics and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker. The trial was terminated early (mean follow-up of 1.3 years) due to a statistically significant 32% lower mortality rate with bisoprolol for the primary endpoint of all-cause mortality (11.8% vs 17.3%; $P < .0001$). The estimated annual mortality rate was 8.8% in the bisoprolol group and 13.2% in the placebo group (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.54-0.81), and patients in the bisoprolol group also experienced 25% fewer cardiovascular deaths (9% vs 12%; $P = .0049$) and 33% fewer sudden deaths (4% vs 6%; $P = .0011$) than those in the placebo group. There were no statistically significant mortality differences by HF etiology or severity.[3]

Carvedilol

The US Carvedilol HF Study Group compared carvedilol (6.25-50.0 mg bid) with placebo in 1094 patients with NYHA class II to IV HF and LVEF at or less than 35% (Table 1).[5] The mean carvedilol dose was 22.5 mg twice daily, and almost all patients were treated with an ACE inhibitor, digitalis, and diuretics. The trial was terminated early after a mean follow-up of 6.5 months because of a statistically significant survival benefit with carvedilol treatment. Treated patients experienced a 65% lowered risk of all-cause mortality (95% CI, 0.20-0.61; $P < .001$) as well as comparable mortality benefits for cardiovascular mortality, sudden death, and death due to worsening HF.[5]

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial compared carvedilol (3.125-25 mg bid) with placebo in 2289 patients with severe symptomatic chronic HF (LVEF $< 25\%$) due to ischemic or nonischemic cardiomyopathy (Table 1).[4] At 4 months, 65.1% of carvedilol-treated patients were receiving the target dose of 25 mg twice daily, and the mean dose was 18.5 mg of carvedilol twice daily. Almost all patients received concomitant treatment with diuretics and an ACE inhibitor. The trial was terminated early (mean follow-up of 10.4 months) due to a statistically significant 35% lower mortality rate with carvedilol for the primary endpoint of all-cause mortality (11.4% vs 18.5%; 95% CI, 0.52-0.81; $P = .0014$). The 1-year mortality rate was 11.4% in the carvedilol group and 18.5% in the placebo group. There were no statistically significant mortality differences by baseline characteristics.[4]

The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial compared carvedilol (6.25-25 mg bid) with placebo in 1959 patients (Table 1).[6] These patients had a recent myocardial infarction (MI) (within 21 days) and an LVEF at or less than 40% (mean 32.8%), and were receiving contemporary MI treatment, including ACE inhibition and aspirin. Half of the patients enrolled in CAPRICORN had symptomatic HF.[8] In this trial, 74% of patients reached the target dose (25 mg bid).[6] After an average follow-up period of 1.3 years, carvedilol-treated patients had a 23% lower mortality risk than placebo-treated patients ($P = .031$). The positive survival effect of carvedilol in addition to an ACE inhibitor and aspirin was also evident for the endpoint of reinfarction. The risk of fatal or nonfatal reinfarction was reduced by 40% in patients on carvedilol therapy (95% CI, 11%-60%; $P = .01$).[6,8]

Table 1
Clinical Trial Data on Guideline-Recommended β-Blockers for HF

Trial, Year Published (β-Blocker)	Patients	Mean Follow-Up (months)	Baseline Characteristics	Concomitant Medications	Mortality Reduction			
					All-Cause	Cardiovascular	Sudden	Worsening HF
CIBIS-II, 1999[3] (Bisoprolol)	N = 2647 Bisoprolol = 1327 Placebo = 1320	15.6	NYHA class III: 83% NYHA class IV: 17% LVEF: 28% Ischemic: 50% DCM: 12% Other: 38%	Diuretics: 98% ACE inhibitor: 96% Nitrates: 58% Digoxin: 52%	34% (95% CI, 29-46) $P < .0001$	29% (95% CI, 10-44) $P = .0049$	44% (95% CI, 20-61) $P = .0011$	26% (95% CI, −14-52) $P = .17$
US Carvedilol HF Study Group, 1996[4,5] (Carvedilol)*	N = 1094 Carvedilol = 696 Placebo = 398	6.5	NYHA class II: 53% NYHA class III: 44% NYHA class IV: 3% LVEF: 23% Ischemic: 48% Nonischemic: 52%	Diuretics: 95% ACE inhibitor: 95% Digitalis: 90%	65% (95% CI, 39-80) $P < .001$	27% (95% CI, 3-45) $P = .036$†	55% (NA) *P* value NA	79% (NA) *P* value NA
COPERNICUS, 2001[50-51] (Carvedilol)	N = 2289 Carvedilol = 1156 Placebo = 1133	10.4	LVEF: 19.9% Ischemic: 67% Nonischemic: 33%	Diuretics: 99% ACE inhibitor: 97% Digitalis: 66%	35% (95% CI, 19-48) $P = .0014$	23% (NA) $P = .0003$†	36% (NA) $P = .016$	28% (NA) $P = .0001$‡
CAPRICORN, 2001[6,52] (Carvedilol)	N = 1959 Carvedilol = 975 Placebo = 984	15	LVEF: 32.8% Symptoms of HF: 47%	ACE inhibitor: 98% Aspirin: 86%	23% (95% CI, 2-40) $P = .031$	25% (95% CI, 4-42) $P = .024$	26% (95% CI, −6-49) $P = .098$	40% (95% CI, −7-67) $P = .083$
MERIT-HF, 1999[7] (Metoprolol succinate)	N = 3991 Metoprolol = 1990 Placebo = 2001	12	NYHA class II: 41% NYHA class III: 56% NYHA class IV: 3% LVEF: 28% Ischemic: 65% Nonischemic: 35%	Diuretics: 91% ACE inhibitor: 89% Digitalis: 63%	34% (95% CI, 19-47) $P = .0062$	38% (95% CI, 22-50) $P = .00003$	41% (95% CI, 22-55) $P = .0002$	49% (95% CI, 21-67) $P = .0023$

HF, heart failure; CIBIS-II, Cardiac Insufficiency Bisoprolol Study II; NYHA, New York Heart Association; LVEF, left ventricular systolic dysfunction; DCM, diabetic cardiomyopathy; ACE, angiotensin-converting enzyme; CI, confidence interval; NA, not available; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Heart Failure.
*The US Carvedilol Trials did not include mortality as a prespecified endpoint.
†Data only available for cardiovascular hospitalization, not cardiovascular mortality.
‡Data only available for hospitalization for worsening HF, not mortality due to worsening HF.

A once-daily formulation of carvedilol, carvedilol CR, was approved by the US Food and Drug Administration for the same indications as carvedilol, including mild-to-severe HF and post-MI left ventricular dysfunction, based on bioequivalence to carvedilol from pharmacokinetic and pharmacodynamic studies.[9] Therefore, the same benefit seen with carvedilol in the trials noted above can be expected with carvedilol CR, with the potential of better adherence with once-daily dosing. Metoprolol succinate (discussed below) and bisoprolol are dosed once daily as well.

Metoprolol Succinate

The Metoprolol CR/XL Randomised Intervention Trial in Heart Failure (MERIT-HF) compared the extended-release formulation of the β_1-selective blocker metoprolol succinate (12.5-200 mg/d) with placebo in 3991 patients with symptomatic HF (NYHA class II to IV) and LVEF at or less than 40% (Table 1).[7] At the trial's conclusion, 64% of metoprolol succinate–treated patients were receiving the target dose of 200 mg/d, and the mean dose was 159 mg/d; almost all patients received concomitant treatment with diuretics and an ACE inhibitor or other vasodilator. The trial was terminated early (mean follow-up 1 year) due to a statistically significant 34% lower mortality rate with metoprolol succinate for the primary endpoint of all-cause mortality (7.2% vs 11%; 95% CI, 0.53-0.81; $P = .0062$). Patients in the metoprolol succinate group also experienced 38% fewer cardiovascular deaths (6.4% vs 10.1%; 95% CI, 0.50-0.78; $P = .00003$), 41% fewer sudden deaths (4.0% vs 6.6%; 95% CI, 0.45-0.78; $P = .0002$), and 49% fewer deaths due to worsening HF (1.5% vs 2.9%; 95% CI, 0.33-0.79; $P = .0023$) than those in the placebo group.[7]

Based on these studies and the evidence available to date, the ACC/AHA guidelines give a Class 1, Level of Evidence A, recommendation for the use of the β-blockers bisoprolol, carvedilol, or sustained-release metoprolol succinate for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated.[2] The guidelines note that, within drug classes, agents may differ pharmacologically, and these differences may translate into differences in clinical outcomes.

β-Blockers in Special Populations

Special populations have generally been underrepresented in clinical trials. Until further studies are done in special populations, however, the current standard of care is to treat all HF patients according to the recommendations for the overall population. The ACC/AHA HF guidelines recommend that "groups of patients including (a) high-risk ethnic minority groups (eg, blacks), (b) groups underrepresented in clinical trials, and (c) any groups believed to be underserved should, in the absence of specific evidence to direct otherwise, have clinical screening and therapy in a manner identical to that applied to the broader population."[2] Many patients with HF are members of subpopulations who are likely to exhibit unique responses that may alter the development or progression of HF. Populations other than predominantly white, middle-aged men are less often studied in clinical trials, stressing the importance of subgroup analysis. A review of some of the special populations with HF and the therapeutic benefits of specific β-blockers follows.

Elderly

The prevalence of HF increases exponentially with age.[1] Not only is the mean age of patients with HF greater than 70 years old,[10] but HF is also the most common reason for hospitalization in elderly patients.[2] Given that the mean age of patients in HF trials is 65 years, little is known about the older HF patient who is at increased risk of morbidity and mortality.

All 3 guideline-recommended β-blockers appear to be effective in elderly patients, although tolerability may vary and therapy should be individualized. CIBIS-II examined mortality in patients younger than 71 years and 71 years or older.[11] Bisoprolol was equally effective in both age groups, as evidenced by a similar risk of mortality, and there was no interaction effect (Table 2). Bisoprolol-treated patients 71 years or older had a 32% reduced risk of all-cause mortality when compared with placebo-treated patients (95% CI, 0.48-0.97), whereas bisoprolol-treated patients younger than 71 years had a 31% reduced risk of all-cause mortality when compared with placebo-treated patients (95% CI, 0.55-0.86). Bisoprolol treatment reduced the risk of death due to HF in elderly patients by more than 50%, but it did not have an effect on sudden death.[11]

Patients 65 years or older in COPERNICUS experienced reductions in all-cause mortality with carvedilol use that were similar in direction and magnitude to the total population.[4] Data from the US Carvedilol Trials showed that the 51% of patients who were 59 years or older (59 years was also the mean age) experienced similar mortality reductions (HR, 0.38; 95% CI, 0.19-0.77) as patients younger than 59 years (HR, 0.30; 95% CI, 0.11-0.80).[5] The effect of carvedilol on outcomes (morbidity and mortality) in patients 65 years or older (n = 631) was investigated in a meta-analysis of 7 large-scale, placebo-controlled trials of carvedilol. The combined risk of

Table 2
Subgroup Analyses From β-Blocker Trials

Subgroup/Trial or Meta-Analysis	Active Treatment	% of Total Population/ No. of Patients	All-Cause Mortality Reduction With Active Treatment
Diabetes			
COPERNICUS[17]	Carvedilol (vs placebo)	26% (n = 586)	32% (95% CI, 0-53) *P* value NA
Meta-analysis (including US Carvedilol Trials, ANZ Heart Failure Study, CAPRICORN, and COPERNICUS)[6,33]	Carvedilol (vs placebo)	25% (n = 1411)	28% (95% CI, 3-46) *P* = .029
CIBIS-II[11]	Bisoprolol (vs placebo)	12% (n = 312) Bisoprolol = 157 Placebo = 155	19% (95% CI, –28-49) *P* value NA
MERIT-HF[36]	Metoprolol (vs placebo)	25% (n = 985) Metoprolol = 495 Placebo = 490	18% (95% CI, –19-44) *P* > .2
Atrial Fibrillation			
US Carvedilol Trials[41,53]*	Carvedilol (vs placebo)	12% (n = 134) Carvedilol = 82 Placebo = 52	65% (95% CI, –33-9) *P* = .12
COMET[43]	Carvedilol (vs metoprolol tartrate)	20% (n = 600)	16% (95% CI, 6-26) decrease with carvedilol *P* = .0042
COPERNICUS†	Carvedilol (vs placebo)	5% (n = 110) Carvedilol = 47 Placebo = 63	18% (95% CI, –19-44) *P* = .2958
CIBIS-II[3,39]	Bisoprolol (vs placebo)	20.5% (n = 521) Bisoprolol = 257 Placebo = 264	16% (95% CI NA) increase in risk *P* value NA
MERIT-HF[7,40]	Metoprolol (vs placebo)	14% (n = 556) Metoprolol = 274 Placebo = 282	6% (95% CI, –77-36) *P* > .2
African American			
COPERNICUS[17,20]	Carvedilol (vs placebo)	5% (n = 121)	40% (95% CI, –105-82) *P* value NA
US Carvedilol Trials[17,21]*	Carvedilol (vs placebo)	20% (n = 217) Carvedilol = 127 Placebo = 90	56% (95% CI, –28-85) *P* = .13
CIBIS-II[22]	Bisoprolol (vs placebo)	0.3%	NA
MERIT-HF[17,23]	Metoprolol (vs placebo)	5% (n = 207) Metoprolol = 106 Placebo = 101	15% (95% CI, –98-63) *P* > .05
Elderly			
US Carvedilol Trials[5]*	Carvedilol (vs placebo)	51% ≥ 59 years (n = 554) Carvedilol = 346 Placebo = 208	62% (95% CI, 23-81) *P* value NA
CIBIS-II[11]	Bisoprolol (vs placebo)	20% ≥ 71 years (n = 539) Bisoprolol = 264 Placebo = 275	32% (95% CI, 3-52) *P* value NA

Table 2
Subgroup Analyses From β-Blocker Trials (Continued)

Subgroup/Trial or Meta-Analysis	Active Treatment	% of Total Population/ No. of Patients	All-Cause Mortality Reduction With Active Treatment
Elderly			
MERIT-HF[13]	Metoprolol (vs placebo)	49% ≥ 65 years (n = 1982) Metoprolol = 990 Placebo = 992 12% ≥ 75 years (n = 490) Metoprolol = 243 Placebo = 247	37% (NA) *P* = .0008 29% (95% CI, –19-58) *P* value NA
Women			
COPERNICUS[4,17]	Carvedilol (vs placebo)	20% (n = 465)	37% (95% CI, –4-61) *P* value NA
US Carvedilol Trials[17]*	Carvedilol (vs placebo)	23% (n = 256) Carvedilol = 162 Placebo = 94	68% (95% CI, 7-89) *P* = .028
CIBIS-II[3,54]	Bisoprolol (vs placebo)	19% (n = 515) Bisoprolol = 257 Placebo = 258	48% (95% CI, 11-70) *P* value NA
MERIT-HF[18]	Metoprolol (vs placebo)	22.5% (n = 898) Metoprolol = 451 Placebo = 447	7% (95% CI, –49-42) *P* = NS

*The US Carvedilol Trials did not include mortality as a prespecified endpoint.
†Data on File. GlaxoSmithKline, Philadelphia, PA.
COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; CI, confidence interval; NA, not available; ANZ, Australia/New Zealand; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CIBIS-II, Cardiac Insufficiency Bisoprolol Study II; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Heart Failure; COMET, Carvedilol or Metoprolol European Trial; NS, not significant.

all-cause mortality and hospitalization was significantly reduced with carvedilol (RR, 0.71; 95% CI, 0.55-0.91; *P* = .007). Risk for cardiovascular hospitalization was also decreased (RR, 0.67; 95% CI, 0.51-0.87; *P* = .003). Testing for interaction showed no difference in patients younger and older than 65 years.[12]

Retrospective subgroup analysis by age in MERIT-HF revealed that, compared with placebo, treatment with metoprolol succinate significantly reduced the risk of all-cause mortality by 37% (*P* = .0008), sudden death by 43% (*P* = .0032), and death from worsening HF by 61% (*P* = .0005) in patients 65 years or older (n = 1982) (Table 2).[13] Patients 75 years or older (n = 490) treated with metoprolol succinate experienced similar risk reductions for all-cause mortality (HR, 0.71; 95% CI, 0.42-1.19), sudden death (HR, 0.47; 95% CI, 0.20-1.10), and death from worsening HF (HR, 0.75; 95% CI, 0.32-1.77).

Some elderly patients cannot tolerate higher doses of β-blockade, and therefore it is important to note the mean dose achieved with different β-blockers. Results from the Carvedilol Open Label Assessment (COLA II) in 1030 elderly patients (> 70 years) with NYHA class II to IV HF and an LVEF less than 40% show that carvedilol is well tolerated in this population.[14] After 6 months of follow-up, 80% of all patients were able to tolerate carvedilol treatment (mean dose 31.2 mg/d), and patients of all ages experienced significantly improved LVEF and HF symptoms. Previous studies demonstrated that lower doses (6.25 and 12.5 mg bid) of carvedilol produced significant mortality benefit.[15]

There was a statistically significant difference by age for mean daily dose achieved of metoprolol succinate: subjects 65 years or older achieved 146 mg (81% ≥ 100 mg) and subjects younger than 65 years achieved 168 mg (90% ≥ 100 mg) (*P* < .0001). The mean daily dose of metoprolol succinate was lower in patients 75 years or older: 140 mg (76% ≥ 100 mg, 50% on 200 mg). There was also a difference for those patients with severe HF: subjects 65 years or older achieved 140 mg (78% ≥ 100 mg) whereas subjects younger than 65 years achieved 157 mg (84% ≥ 100 mg) (*P* < .0001).[13] There is no current evidence to suggest that one of the 3 evidence-based β-blockers is preferential in elderly patients with HF.

Women

Although women have a slightly lower prevalence of HF than men (2.2% vs 2.8%), they have an alarmingly high mortality rate (61% vs 39%).[1] Women also face increased risk of HF as they age. Prevalence increases from 1.5% for ages 55 to 64 years, to 5.2% for ages 60 to 79 years, and to 12.4% for ages 80 years and older.[1] Not surprisingly, not only do women constitute the majority of elderly HF patients, but the prevalence of HF in women surpasses that in men from age 80 on (12.4% vs 11.6%).[16] All of the guideline-recommended β-blockers have similar retrospective or post-hoc data that show benefit in this important patient population. For example, women were 20% of the total treatment population in COPERNICUS and experienced reductions in all-cause mortality that were similar in direction and magnitude to the total population (HR, 0.63; 95% CI, 0.39-1.04).[4,17] In the US Carvedilol Trials, women were 23% of the total population and experienced a 68% risk reduction in all-cause mortality with carvedilol treatment (HR, 0.32; 95% CI, 0.11-0.93).[17] Of the female patients in CIBIS-II, 13.6% (35 out of 258) in the placebo group died compared with 7.0% (18 out of 257) in the bisoprolol-treated group, resulting in a 48% reduction in all-cause mortality.[18]

There were no significant differences between placebo-treated and metoprolol succinate–treated women (n = 898, 23% of the total population) in a post-hoc analysis of MERIT-HF for any type of mortality: all-cause, sudden, cardiovascular, or worsening HF.[18] However, women treated with metoprolol succinate experienced fewer hospitalizations. A 21% reduction in the primary combined endpoint of all-cause mortality/all-cause hospitalizations (P = .044) was observed. The number of cardiovascular hospitalizations was reduced by 29% (P = .013), and hospitalization for worsening HF was reduced by 42% (P = .021).[18]

African Americans

African Americans have a higher prevalence of HF (3%) than that experienced by the general US population (2.5%).[1] African American women have the highest prevalence (3.3%), followed by white men (2.8%), African American men (2.7%), and white women (2.1%). In addition, their relative risk of mortality is also greater. The overall death rate for HF is 19.1%, but it is correspondingly higher for both African American men (22.9%) and women (19.0%) than for white men (20.3%) and women (18.3%).[1] It appears that physicians cannot assume a class effect when using β-blockers in African Americans. For example, results from the Beta-Blocker Evaluation of Survival Trial (BEST),[19] in which bucindolol did not confer a survival benefit in African Americans, illustrate the fact that not all β-blockers are alike.

The risk reductions in mortality seen with carvedilol in the African American patients from HF trials are consistent with the overall risk reduction for all patients in the trials (Table 2). African Americans were 5% of the total trial population in COPERNICUS, and a post-hoc analysis revealed that carvedilol reduced the risk of all-cause mortality in 121 African American patients by 40% (95% CI, 0.18-2.05) and the risk of death due to HF by 38% (95% CI, 0.19-2.01).[17,20] Nonblack patients experienced a 35% all-cause mortality reduction (95% CI, 0.52-0.81).[17,20] In the US Carvedilol Trials, African Americans were 20% of the total trial population and, after a mean follow-up of 6.5 months, carvedilol-treated patients (n = 127) had a 56% lower risk of all-cause mortality (95% CI, 0.15-1.28; P = .13) compared with placebo-treated patients (n = 90).[17,21] The risk of death due to HF was reduced by 47% (95% CI, 0.19-1.48). The magnitude of all-cause mortality risk reduction was similar to that experienced by nonblack participants (HR, 0.32; 95% CI, 0.17-0.62), and there was no interaction effect. Notably, only the US Carvedilol Trials studied a meaningful number of African Americans.

There was no subgroup analysis by race in CIBIS-II because African Americans were only 0.3% of the total trial population (Table 2).[22] A subgroup analysis of African Americans from MERIT-HF (5% of the total trial population) revealed nonsignificant trends toward reductions in all-cause mortality (HR, 0.85; 95% CI, 0.37-1.98), cardiovascular mortality (HR, 0.68; 95% CI, 0.28-1.67), and death due to HF (HR, 0.79; 95% CI, 0.36-1.76) (Table 2).[17,23] These risk reductions did not appear to be as great as in the overall population; however, the directional trends observed in MERIT-HF in the African American population were consistent with the overall population.

Diabetes Mellitus

Diabetes mellitus is a common comorbid condition of HF,[24] and the prevalence of HF among diabetic patients is 2 to 3 times that of age-matched controls.[25] Further cause for concern comes from the results of a meta-analysis of β-blocker trials in HF patients showing that diabetic patients have a lower mortality risk reduction compared with nondiabetic patients (16% vs 28%) as well as a higher absolute risk of mortality (P = .023).[26] The incidence of diabetes has been rising steadily both in the United States and globally,[1,27] necessitating greater attention to

ameliorating morbidity and mortality in this high-risk population. Concomitant diabetes in patients with HF is a very important consideration when deciding among the 3 indicated β-blockers, as there are pharmacological differences between carvedilol (which blocks α_1-receptors, resulting in vasodilation that in turn can improve metabolic parameters, including glucose and lipoprotein/triglyceride metabolism) and β_1-selective blockers that can result in worsened metabolic parameters.[28-30]

Bisoprolol-treated HF patients with diabetes mellitus in CIBIS-II had a 19% reduced risk of all-cause mortality (95% CI, 0.51-1.28) compared with placebo-treated patients, whereas nondiabetic patients experienced a 34% reduction (95% CI, 0.54-0.81).[11] Although the number of patients was too small for a definitive conclusion, diabetic patients treated with bisoprolol had reduced risk of death due to worsening HF, but not sudden death, when compared with nondiabetic patients.[11]

Diabetic patients in COPERNICUS were 26% of the total population.[17] Carvedilol-treated patients with diabetes had a 35% reduced risk of all-cause mortality (95% CI, 0.43-0.99) and a 32% reduced risk of death due to HF (95% CI, 0.47-1.00).[17,31] A subgroup analysis of diabetic patients in the US Carvedilol Trials (Multicenter Oral Carvedilol Heart Failure Assessment [MOCHA]) showed that carvedilol treatment significantly reduced mortality to a comparable degree in both diabetic and nondiabetic patients with HF.[32] Mortality rates also decreased with increasing carvedilol doses ($P < .05$ for both).[32] Additional data show that carvedilol treatment may be particularly advantageous in HF patients with diabetes. In contrast to a previous meta-analysis[26] that found that HF patients with diabetes did not benefit from β-blockers to as great a degree as those without diabetes, a more recent meta-analysis of placebo-controlled carvedilol trials shows that diabetic patients with HF experienced mortality reductions similar to those of their nondiabetic counterparts (HR, 0.72; 95% CI, 0.54-0.97; $P = .03$ vs HR, 0.63; 95% CI, 0.52-0.77; $P < .0001$, respectively).[33] The number needed to treat with carvedilol for 1 year to save 1 life was also similar among all patients: 23 for all patients, 25 for diabetic patients, and 23 for nondiabetic patients.[33] Results from the Carvedilol Or Metoprolol European Trial (COMET)—the β-blocker study between carvedilol and metoprolol tartrate in 3029 patients with NYHA class II to IV HF and LVEF at or less than 35%—showed that carvedilol was superior to metoprolol tartrate in reducing mortality.[34] In this large-scale, head-to-head trial, mortality was reduced with carvedilol versus metoprolol tartrate both in patients with diabetes at baseline (RR, 0.85; 95% CI, 0.69-1.06) and those without (RR, 0.82; 95% CI, 0.71-0.94).[35]

Diabetic patients in MERIT-HF, who comprised 25% of the total population, did not experience a significant reduction in mortality regardless of HF severity.[36] The overall diabetic subgroup treated with metoprolol succinate experienced an 18% relative risk reduction for all-cause mortality (95% CI, 0.44-1.19; $P > .2$), and those with severe HF experienced a 29% risk reduction (95% CI, 0.65-1.41; $P > .2$).[36]

Atrial Fibrillation

Atrial fibrillation is a frequent comorbid condition in HF patients (about 10% to 50%) and is also the most common cardiac arrhythmia.[37] Atrial fibrillation places HF patients at increased risk of stroke and mortality, especially due to sudden death, and these patients should be treated with β-blockers.[2,37,38] There appears to be a possible difference in the effects of different β-blockers for patients with both HF and atrial fibrillation. Results from trials with β_1-selective blockers (MERIT-HF, CIBIS-II) diverge from those trials with the nonselective β/α_1-blocker carvedilol.

Patients in CIBIS-II with atrial fibrillation fared worse than patients in sinus rhythm.[39] Patients with normal heart rhythm experienced significantly improved mortality reduction with bisoprolol treatment; however, the 20% of CIBIS-II patients with atrial fibrillation experienced increased all-cause and cardiovascular mortality. HF patients with atrial fibrillation had a 16% increased risk of all-cause mortality when treated with bisoprolol (P = NS).[39]

As shown by a recent analysis, there were 61 deaths among the 362 (17%) patients with atrial fibrillation in MERIT-HF: 31 deaths occurred in the placebo group and 30 occurred in the metoprolol group.[40] Metoprolol succinate did not reduce the risk of death of all causes (RR, 1.0; 95% CI, 0.61-1.65) or cardiovascular mortality compared with placebo, and it appeared to increase the risk of sudden death in patients with atrial fibrillation at baseline (18 sudden deaths noted in the placebo arm and 20 noted in the metoprolol arm).[40]

In contrast, a subgroup analysis of HF patients with atrial fibrillation in the US Carvedilol Trials showed that carvedilol treatment resulted in a trend toward mortality reduction as compared with placebo (HR, 0.35; 95% CI, 0.09-1.33; $P = .12$).[41] In addition, an analysis from the CAPRICORN adverse events database showed that carvedilol treatment reduced the occurrence of atrial fibrillation/flutter by 59% compared with

placebo (95% CI, 0.25-0.68; P = .0003).[42]

An analysis of severe HF patients enrolled in the COPERNICUS trial showed that there was no significant heterogeneity between the effect of carvedilol on all-cause mortality in patients with or without atrial fibrillation at baseline (P = .175). Among patients with atrial fibrillation, the incidence of all-cause mortality was 15.2% in the carvedilol-treated group and 19.0% in the placebo-treated group (data on file, GlaxoSmithKline, Philadelphia, PA). Furthermore, results from COMET demonstrated that carvedilol reduced the risk of death both in patients in sinus rhythm and in the 19.8% of patients with AF (HR, 0.836; 95% CI, 0.74-0.94; P = .0042).[43]

Data From Registries

Although the focus of this article is to summarize data from randomized clinical trials, special patient populations with HF have not been well represented in these trials. It is noteworthy that a number of registries have provided more information about the real-world HF population and are able to provide evidence on the effectiveness of therapy in these populations, more so than we have been able to glean from retrospective or post-hoc analyses of clinical trials.

The Carvedilol Heart Failure Registry (COHERE) examined use of carvedilol therapy in 4280 patients with HF in a community setting.[44] In an analysis of characteristics, outcomes, and carvedilol dosing among black patients (n = 523) and white patients (n = 3433), black patients had more severe HF symptoms than white patients despite similar systolic function. At similar carvedilol maintenance doses, symptoms improved in 33% of black patients and 28% of white patients, while worsening in 10% and 11%, respectively (both nonsignificant). Rates of HF hospitalizations were reduced comparably in both groups (−58% vs −56%, respectively; both $P < .001$). Also similar were the incidence and HRs of death in black and white patients (6.9% vs 7.5%; HR, 1.2 vs 1.0; P = .276). In this community setting, carvedilol was shown to be similarly effective in black and white patients with HF, a finding consistent with results from clinical trials.[44]

Additional analyses from COHERE evaluated the effects of carvedilol in women (n = 1485) and in the elderly (≥ 75 years; n = 1188, 28%).[45] Women tended to have worse HF functional class, but significantly higher LVEF and blood pressure. Women also had more HF hospitalizations, had less use of ACE inhibitors, and received lower doses of carvedilol. Among the elderly, LVEF, blood pressure, and HF functional class were all higher. During the year of follow-up, both women and men experienced greater than 40% reductions in HF hospitalizations ($P < .001$), and HF hospitalizations were reduced by 40% in all age groups after starting carvedilol ($P < .001$). Mortality was 7.3% in women compared with 9.1% in men (P = .085). Although characteristics of women and the elderly with HF in the community suggest they are at increased risk, both populations respond well to carvedilol therapy.[45] Similar registry data in these subpopulations are not available for other evidence-based β-blockers.

The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) quality of care initiative and registry enrolled 48,612 patients hospitalized for HF at 259 US hospitals.[46] A prespecified total of 5791 patients at 91 hospitals participated in the 60- to 90-day follow-up. The early effects of carvedilol use at discharge on mortality and rehospitalization was compared with outcomes in patients who were eligible for, but did not receive, β-blockers before discharge.[47] A total of 2720 patients had left ventricular systolic dysfunction, among whom 2373 (87.2%) were eligible to receive a β-blocker at discharge; carvedilol was prescribed in 1162 (49.0%). Carvedilol use at discharge was associated with a significant reduction in mortality risk after 60 to 90 days (HR, 0.46; 95% CI, 0.30-0.73; P = .0006) and in mortality or rehospitalization (OR 0.71; 95% CI, 0.53-0.94; P = .0175) compared with no predischarge β-blocker. The importance of using an evidence-based β-blocker in HF is emphasized by further results from this analysis. Of the 2373 patients eligible for β-blocker prescription at discharge, 434 (53%) received either sustained-release metoprolol succinate or bisoprolol, and 386 (47%) received atenolol or metoprolol tartrate or another non–evidence-based β-blocker for HF. The effect of β-blocker strategy on risk- and propensity-adjusted all-cause mortality and mortality and/or rehospitalization at 60 to 90 days postdischarge was compared in the groups. Similar findings as those for carvedilol were observed for other evidence-based β-blockers. The use of sustained-release metoprolol succinate or bisoprolol at hospital discharge resulted in the detection of a statistically significant reduction in all-cause mortality (HR, 0.49; 95% CI, 0.28-0.86; P = .013). In contrast, use of non–evidence-based β-blockers (atenolol, metoprolol tartrate, and others) did not confer a significant reduction in mortality. Data from this registry do not show a difference in efficacy between carvedilol, metoprolol succinate, and bisoprolol in patients with HF; however, this analysis was not powered

to further separate patients by ethnicity or other subgroups. The effect of carvedilol was consistent in all clinically relevant subgroups examined, including age, sex, race, diabetes status, chronic obstructive pulmonary disease status, and renal function.[47]

Discussion

The ACC/AHA recommendation for the use of 1 of 3 β-blockers (bisoprolol, carvedilol, metoprolol succinate) as the standard of care in all patients with systolic HF who are without contraindications is based on compelling clinical trial evidence.[2] Despite these guideline recommendations, there is an extensive body of evidence documenting that many HF patients do not receive β-blocker therapy. Registry data show that β-blockers are not utilized in a substantial portion of eligible HF patients.[48] This treatment gap is due to a number of factors,[49] one of which is that some HF patients may be left untreated because physicians are unsure of the safety and benefit of β-blockers in special populations and high-risk patients. The evidence reviewed above indicates that efficacy varies in special populations even among the guideline-recommended β-blockers. Agents within the same drug class may differ pharmacologically, and these differences may translate into discordant results in clinical outcomes. In the case of β-blockers, a class effect cannot be presumed. Therefore, it is incumbent upon the physician to prescribe the specific agents that are evidence-based and guideline-recommended.

There is no evidence to suggest heterogeneity in women and elderly patients with HF; any of the 3 guideline-recommended evidence-based β-blockers should be used in these HF patients. Although elderly HF patients appear to benefit equally from all 3 recommended β-blockers, there may be subtle differences in tolerability. In African American HF patients and HF patients with concomitant diabetes or atrial fibrillation, there is a suggestion that there may be differences in efficacy among β-blockers, with carvedilol preferred. However, further confirmation with larger studies that are prospectively designed and powered to detect efficacy in these subgroups is required. Metoprolol succinate or bisoprolol is more beneficial in HF patients without concomitant diabetes or atrial fibrillation than in HF patients with these conditions. Carvedilol appears to have an equal or greater effect on risk reduction in HF patients with diabetes or atrial fibrillation compared with HF patients without those conditions. Additionally, data from recent HF registries help augment the available clinical trial data, supporting the evidence from large-scale clinical trials and showing that the 3 recommended β-blockers are efficacious in a "real-world" setting as well as in clinical trials. The data from registries such as COHERE and OPTIMIZE-HF have shown that evidence-based β-blockers reduce the risk of rehospitalization and death in all HF patients, including the elderly, women, African Americans, and those with concomitant conditions. Further analyses of these subgroups will be beneficial.

It is important to be cautious when interpreting effects in subgroups. Some of the subgroup analyses reviewed in this article were not prespecified, and the number of patients studied usually was too small to detect statistical significance. Therefore, the purpose of this article is not to definitively conclude that one β-blocker is better than another in a specific population, but to summarize the data available.

Conclusions

HF significantly increases a patient's risk of morbidity and mortality. Significant mortality reductions with the use of the 3 evidence-based β-blockers (bisoprolol, carvedilol, and

Main Points

- Until further studies are done in special populations—such as women, the elderly, African Americans, patients with diabetes, and patients with atrial fibrillation—the current standard of care is to treat all heart failure (HF) patients according to the recommendations for the overall population using 1 of the 3 evidence-based β-blockers, bisoprolol, carvedilol, or metoprolol succinate.
- Atrial fibrillation is a frequent comorbid condition in HF patients (about 10% to 50%) and is also the most common cardiac arrhythmia.
- Physicians may want to consider potential differences among β-blocker efficacy and tailor treatment to the particular patient by choosing the agent with the greatest clinical trial evidence supporting its use.
- There is no evidence to suggest heterogeneity among β-blockers in women and elderly patients with HF.
- In African American HF patients, HF patients with concomitant diabetes, and HF patients with atrial fibrillation, there is a suggestion that carvedilol may provide greater benefit than other β-blockers.

metoprolol succinate) have been demonstrated in randomized clinical trials and observed to be effective in registry studies of broad HF patient populations. National guidelines recommend the use of 1 of the 3 evidence-based β-blockers in all eligible HF patients. Similar benefits have been demonstrated with all 3 β-blockers in some but not other specific high-risk patient populations. Physicians who treat HF patients may want to consider these potential differences and use β-blocker(s) with the greatest clinical trial evidence supporting use for that specific special population. Further data are needed to refine evidence-based recommendations for β-blockers in these special patient populations. ■

Acknowledgment: Dr. Fonarow has performed research, consulted, and spoken for GlaxoSmithKline and AstraZeneca. Malini Iyengar, PhD, of GlaxoSmithKline, Philadelphia, PA, provided statistical analysis of data from the COPERNICUS trial. Corbett Accel Healthcare Group provided technical assistance.

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