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Beta-blockers for heart failure: Why you should use them more

Many physicians are afraid to prescribe beta-blockers for patients with heart failure. Yet in most cases, *not* prescribing them is a mistake.

PRACTICE RECOMMENDATIONS

› *Initiate beta-blocker therapy in low doses for patients with heart failure, and increase the dose gradually until the target dosage is achieved.* (A)

› *The benefit of beta-blocker therapy for patients with heart failure is proportional to the degree of heart rate reduction.* (A)

› *Consider beta-blocker therapy for patients with coexisting chronic obstructive pulmonary disease or decompensated heart failure, although treatment may have to be reduced or temporarily withheld.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

The evidence is clear: Beta-blockers reduce mortality and hospitalization in patients with systolic heart failure.[1-3] Yet this class of drugs is underutilized by physicians who fear that beta-blocker's negative inotropic effect will lead to worsening heart failure.[4]

Our aim in presenting this review is to counter such concerns by detailing the latest evidence. We draw on current research findings to answer questions about beta-blocker selection and dosage and address common misconceptions.

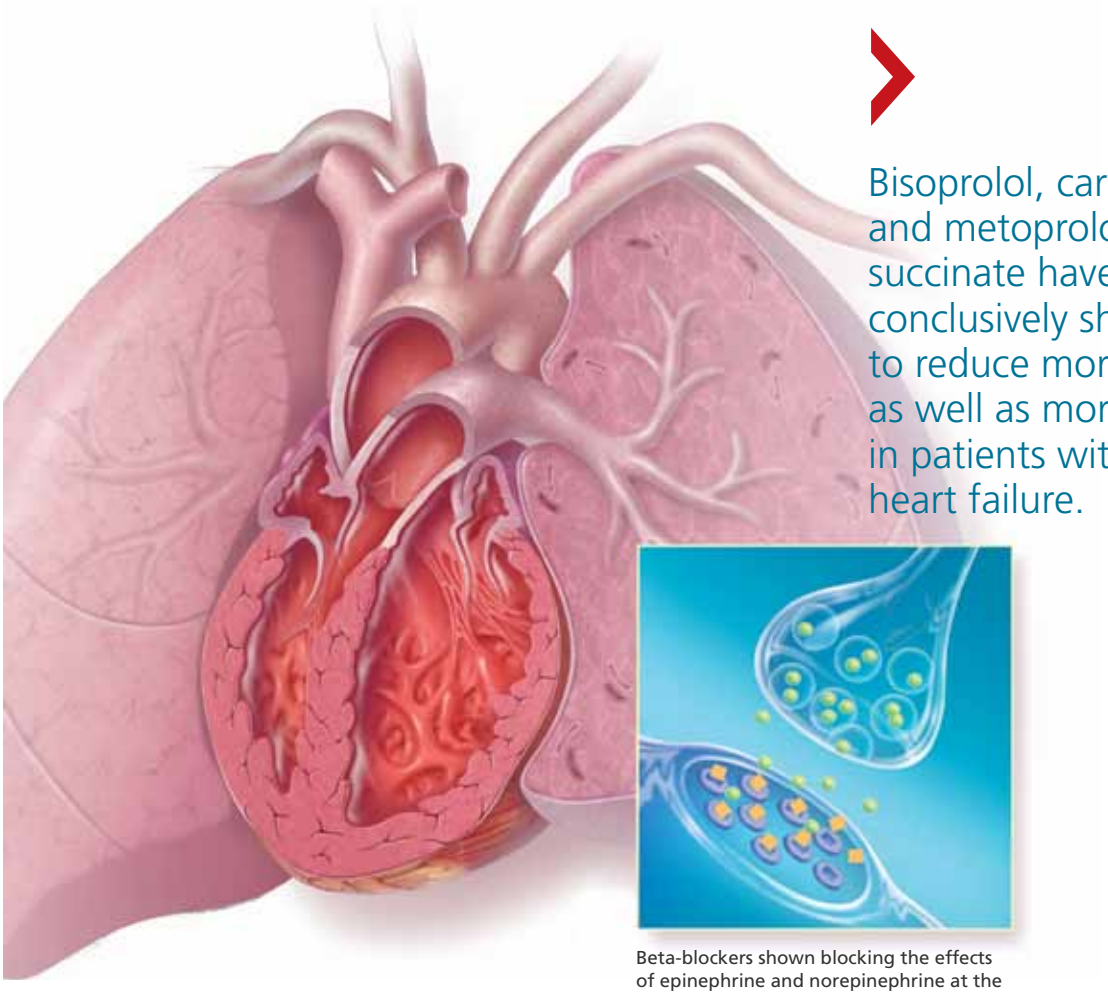
Do beta-blockers lower mortality rates for patients with heart failure?

Yes. Three beta-blockers—bisoprolol, carvedilol, and metoprolol succinate—have been conclusively shown to reduce morbidity as well as mortality in patients with systolic heart failure (**TABLE 1**).[1-3,5,6] Here's a look at the studies:

Bisoprolol. The Cardiac Insufficiency Bisoprolol Study (CIBIS II), a randomized controlled trial (RCT) involving 2647 patients with New York Heart Association (NYHA) Class III or IV heart failure and an ejection fraction (EF) ≤35%, found that bisoprolol reduced the primary end point of all-cause mortality (hazard ratio [HR]=0.66; 95% confidence interval [CI], 0.54-0.81; *P*<.0001) compared with placebo. Cardiovascular mortality rates (HR=0.71; 95% CI, 0.56-0.90; *P*=.0049) and hospitalization rates (HR=0.80; 95% CI, 0.71-0.91; *P*=.0006) were significantly reduced, as well.[1]

Carvedilol. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, an RCT featuring 2289 patients with EF <25%, carvedilol significantly reduced the total death rate (HR=0.65; 95% CI, 0.52-0.81; *P*=.0014) compared with placebo.[2]

Metoprolol succinate. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), a study of nearly 4000 patients with Class II to IV



Bisoprolol, carvedilol, and metoprolol succinate have been conclusively shown to reduce morbidity as well as mortality in patients with systolic heart failure.

Beta-blockers shown blocking the effects of epinephrine and norepinephrine at the receptor sites.

IMAGE © KO STUDIOS

heart failure and EF ≤40%, found that metoprolol succinate lowered total mortality or all-cause hospitalization (HR=0.81; 95% CI, 0.73-0.90; *P*<.001) compared with placebo.[3]

Carvedilol and metoprolol go head-to-head

Although carvedilol and metoprolol have been shown to have similar hemodynamic and heart rate effects, the Carvedilol or Metoprolol European Trial (COMET) found that carvedilol is superior in extending survival. More than 3000 patients with Class II to IV heart failure and an EF <35% were randomized to carvedilol (target dose 25 mg bid) or metoprolol tartrate (target dose 50 mg bid). After 58 months, total mortality was significantly lower in the carvedilol arm (HR=0.83; 95% CI, 0.74-0.93; *P*=.0017).[7]

Which metoprolol formulation? While RCTs have found that metoprolol tartrate has a favorable effect on EF and hemodynamic data, it is not approved by the US Food and Drug Administration (FDA) as a treatment for heart failure—and its ability to reduce morbidity and mortality in patients with heart failure has not been established.[8,9] Thus, metoprolol *succinate*, but not metoprolol *tartrate*, is recommended for heart failure treatment by the American College of Cardiology, American Heart Association, and European Society of Intensive Care Medicine.[10,11]

These agents lack evidence of efficacy

Not all beta-blockers have therapeutic value for patients with heart failure—or evidence to support them.

Bucindolol. The Beta-blocker Evaluation of Survival Trial (BEST), a trial of 2708 patients with Class III or IV heart failure and an EF ≤35%, found no difference in total mortality between bucindolol and placebo.[5] As a result, the drug did not receive FDA approval.[12] The FDA has since designated the investigation of bucindolol (trade name Gencaro) for the reduction of cardiovascular hospitalizations and mortality of heart failure

TABLE 1

Beta-blockers for heart failure patients: What the studies show

Trial	Study group (N)	Mean follow-up	Agent tested	Primary end point	RR; 95% CI; *P* value
BEST[5]	Class III-IV HF, EF ≤35% (2708)	2 y	Bucindolol	All-cause death	0.90; 0.78-1.02; .13
CIBIS II[1]	Class III-IV HF, EF ≤35% (2647)	1.3 y	Bisoprolol	All-cause death	0.66; 0.54-0.81; <.0001
COPERNICUS[2]	HF symptoms, EF ≤25% (2289)	10.4 mo	Carvedilol	All-cause death	0.65; 0.52-0.81; .0014
MERIT-HF[3]	Class II-IV HF, EF ≤40% (3991)	1 y	Metoprolol succinate	Composite*	0.81; 0.73-0.90; <.001
SENIORS[6]	Age >70 y and hospitalization for HF *or* EF ≤35% (2128)	21 mo	Nebivolol	All-cause death and CVD hospitalization	0.86; 0.74-0.99; .039

*All-cause mortality and all-cause hospitalization.

BEST, Beta-blocker Evaluation of Survival Trial; CI, confidence interval; CIBIS II, Cardiac Insufficiency Bisoprolol Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; CVD, cardiovascular disease; EF, ejection fraction; HF, heart failure; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; RR, relative risk; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure.

patients with a particular genotype as a Fast Track development program.[13]

Nebivolol. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) randomized 2128 patients older than 70 years with prior hospitalization for heart failure or an EF ≤35% to nebivolol (1.25-10 mg/d) or placebo. Nebivolol (which is not approved for the treatment of heart failure in the United States) reduced the composite end point of all-cause mortality *and* cardiovascular hospitalization (HR=0.86; 95% CI, 0.74-0.99; *P*=.039), but did not reduce the total mortality rate.[6]

Atenolol. Some retrospective analyses have suggested that heart failure patients do as well on atenolol as patients taking metoprolol or carvedilol.[14,15] Because no RCTs have established the efficacy of atenolol, however, it is not recommended for the treatment of heart failure.

Is the dose sufficient to reduce heart rate?

The benefit of beta-blocker therapy for patients with heart failure is proportional to the degree of heart rate reduction, so it is important to find the highest tolerable dose.[16,17] The COMET study detailed earlier sparked considerable controversy, with some observers contending that the dose of metoprolol used was too small to adequately lower the heart rate.[18,19]

A subsequent study, the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (SHIFT), highlights the importance of rate reduction in heart failure outcomes. In this placebo-controlled trial of 6558 patients with EF ≤35%, treatment with the heart rate-reducing agent ivabradine reduced cardiovascular death and hospitalization from heart failure (HR=0.82; 95% CI, 0.75-0.90; *P*<.0001) compared with placebo.[20] A subsequent analysis showed that the primary outcome increased by 16% for every 5 beats-per-minute (BPM) increase.[21]

Start low, go slow

When initiating and titrating beta-blockers, the major RCTs clearly illustrate the importance of the dictum, "Start low, go slow" (**TABLE 2**).[1-3]

In CIBIS II, patients were started on bisoprolol at a dose of 1.25 mg/d. After a week, the dosage was increased by 1.25 mg. Titration

TABLE 2
Titrating beta-blocker therapy

Trial	Agent	Initial dose	Interval on starting dose	Mean dose achieved	Target dose achieved
CIBIS II[1]	Bisoprolol	1.25 mg/d	1 week	8.5 mg/d	10 mg/d (43%)
COPERNICUS[2]	Carvedilol	3.125 mg bid	2 weeks	18.5 mg bid	25 mg bid (66%)
MERIT-HF[3]	Metoprolol succinate	12.5 mg/d	2 weeks	159 mg/d	200 mg/d (64%)

CIBIS-II, Cardiac Insufficiency Bisoprolol Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure.

continued over a 4-week period until the maximum tolerable dose was reached. Although 43% of patients reached the 10 mg/d target, a third of those studied remained on <5 mg/d.[1]

In COPERNICUS, carvedilol was started at 3.125 mg twice a day and continued at that dosage for 2 weeks. The dose was then titrated up at 2-week intervals, to 6.25 mg bid, then 12.5 mg bid, before attempting to reach the target dose of 25 mg bid. Ultimately, 66% received the target dose.[2]

In MERIT-HF, metoprolol succinate was initiated at 12.5 mg daily and doubled every 2 weeks until the target (200 mg/d) was achieved. Nearly two-thirds (64%) of those in the treatment group reached the target dose.[3]

In COMET, the researchers used the same drug regimen for carvedilol that was used in COPERNICUS (starting at 3.125 mg bid and slowly titrating to reach a 25-mg bid target). Patients on metoprolol tartrate initially received 5 mg bid; the dose was

Are beta-blockers contraindicated for these heart failure patients?

Because of the bradyarrhythmic and hypotensive effects of beta-blockers, the major heart failure trials excluded patients with a heart rate of <50 to 68 beats per minute (BPM) or systolic blood pressure <80 to 100 mm Hg (the ranges cited reflect the variation in cut points from one study to another).[1-3,6] And in clinical practice, physicians often withhold beta-blocker therapy from heart failure patients who also have chronic obstructive pulmonary disease (COPD) or asthma, hypotension, or metabolic risk factors for diabetes.[4] Some avoid prescribing beta-blockers because they believe that the drugs adversely affect patients' quality of life, despite evidence to the contrary.[3,23-25] In all these cases, there is little justification for doing so.

COPD and asthma. Although beta-blockers can worsen and precipitate bronchospasm, recent evidence suggests that patients with COPD and asthma can tolerate them.[26-28] In fact, there is reason to believe that bronchospasm is aggravated by excessive stimulation and sensitization of the beta-2 receptors, and that blocking them may even be of therapeutic value.[29] Nonetheless, the danger of worsening bronchospasm with a nonselective beta-blocker such as carvedilol remains—particularly for patients with asthma, who tend to have a higher degree of bronchial sensitivity and reactivity. So, while beta-blockers are not contraindicated for patients with COPD, their use in this patient population requires caution.[30,31]

Metabolic risk factors. Caution is also needed for patients with metabolic risk factors. Although beta-blockers have been found to increase the risk of diabetes, raise triglycerides, and lower high-density lipoprotein cholesterol,[32-34] the benefits for patients with heart failure outweigh the risk. Physicians must remember that the mortality rate of heart failure, as well as the rate of progression, is higher than that of metabolic abnormalities, asymptomatic bradycardia, hypotension, or bronchospasm, which are relatively benign. In view of evidence that beta-blockers reduce both mortality and hospitalization rates associated with heart failure, the best approach is to continue beta-blocker therapy and seek control of risk factors and adverse effects.

increased every 2 weeks until the target—50 mg bid—was reached. Seventy-five percent of patients reached the targeted carvedilol dose, and 78% reached the metoprolol target.[7]

Help beta-blocker therapy succeed

A significant number of patients with heart failure will be unable to tolerate an adequate dose of beta-blockers, at least on the first attempt.[22] In such cases, a second attempt on another occasion—eg, after symptomatic bronchospasm or acute heart failure has been controlled—should be made.

In CIBIS II, 15% of the patients randomized to bisoprolol stopped taking it;[1] in COPERNICUS, the withdrawal rate from carvedilol was also 15%;[2] and in MERIT-HF, 10% of patients taking metoprolol experienced an adverse event that led to drug withdrawal.[3] Although withdrawal rates were similar among patients on placebo in all 3 trials, they nonetheless suggest that even with the precautions and scrutiny characteristic of clinical trials, 10% to 15% of patients with heart failure will experience difficulty with beta-blocker treatment. (In a study of patients in one heart failure clinic, the withdrawal rate approached 40%.[22])

Considering the benefits of beta-blockers for patients with all levels of heart failure, it is incumbent on physicians to prescribe them for as many of these patients as possible (See "Are beta-blockers contraindicated for these heart failure patients?" on page 475) and to attempt to reduce withdrawal rates.

Educate the patient. One way to do this is to provide adequate patient education, stressing the importance of taking the medication exactly as prescribed and, when necessary, showing patients how to divide pills until the target dose is reached.

Respond to adverse effects. Closely monitoring for adverse effects is crucial, as well. The development of symptomatic bradycardia, second or third degree atrioventricular block, or a heart rate <50 BPM suggests that the dosage be reduced or the medication withheld, with this caveat: There is increasing recognition that heart rate and BP readings change throughout the day, and a decision to adjust or to halt beta-blocker therapy should not be based on a single measure.

That said, physicians should watch for clinical evidence of hypoperfusion, such as postural dizziness or decreasing urine output, when systolic BP approaches 80 to 90 mm Hg in patients with heart failure. In such cases, adjusting the dose, increasing the interval between doses, or even discontinuing beta-blocker therapy may be necessary. JFP

Although beta-blockers can worsen and precipitate bronchospasm, recent evidence suggests that patients with COPD and asthma can tolerate them.

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