Beta-Blockers Review

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Beta-Blockers Review

Overview

Heart failure (HF) affects over five million patients in the United States with an estimated $33.2 billion dollars in direct and indirect costs in 2007.[1] Despite combination therapy with angiotensin converting enzyme (ACE) inhibitors, diuretics, and digoxin, five-year mortality rates remain high. The ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult who has had symptoms of heart failure recommend that ACE inhibitors, or possibly an angiotensin receptor blocker (ARB) in an ACE inhibitor-intolerant patient, and beta-adrenergic blockers be used in patients with any history of myocardial infarction (MI) regardless of the left ventricular ejection fraction (LVEF).[2,3]

The two beta-blockers with the FDA-approved indication for HF are metoprolol succinate extended-release (Toprol XL®), which is a $beta_1$-selective (cardioselective) adrenergic antagonist, and carvedilol (Coreg® and Coreg CR®), which is a combined alpha- and non-selective beta-blocker.[4,5,6] Bisoprolol (Zebeta®) is a cardioselective beta-blocker that has been studied in HF. The Cardiac Insufficiency Bisoprolol Study (CIBIS-II) which was a randomized trial of HF patients with left ventricular ejection fraction ≤ 35 percent, was stopped early due to 33 percent lower relative risk of death in the bisoprolol group compared with placebo.[7] However, bisoprolol is not currently FDA-approved for this indication. Bisoprolol, metoprolol succinate ER, and carvedilol have been shown to reduce symptoms of HF and improve clinical status and patients' well-being plus reduce the risk of death and the combined risk of death and hospitalization.[8] All three drugs have been shown to reduce mortality in HF.[9,10,11,12,13] There have been many placebo-controlled trials of beta-blockers in patients with systolic dysfunction already treated with the standard therapy of diuretics and ACE inhibitors.

Most beta-blockers are indicated for the treatment of hypertension (HTN). First line therapy for HTN according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) is diuretics.[14] This recommendation is supported by a number of studies.[15,16,17] Previously, beta blockers were contraindicated in heart failure patients due to their negative inotropic activity so prior versions of the JNC guidelines did list beta-blockers as first line therapy along with diuretics; those recommendations have since changed.[18] The current JNC-VII guidelines suggest beta-blockers be used for those patients with compelling indications such as ischemic heart disease or angina pectoris (calcium channel blockers, CCBs, as an alternative), acute coronary syndrome/unstable angina pectoris and acute MI (ACE inhibitors are an alternative), post-MI (ACE inhibitors and aldosterone antagonists are alternatives), and asymptomatic and symptomatic HF (ACE inhibitors, ARBs, and aldosterone antagonists are alternatives).[19] In diabetic patients, beta-blockers have been shown to reduce the risk of cardiovascular disease (alternatives include thiazide diuretics, CCBs, ACE inhibitors, and ARBs).[20] Black patients generally have a suboptimal response to beta-blockers in blood pressure reduction compared to diuretics and CCBs; however, they still benefit from the reduction of risk from clinical outcomes when the same blood pressure reduction is achieved.

Nebivolol (Bystolic™) is a new beta-1 selective adrenergic antagonist indicated in hypertension, alone or in combination with other antihypertensive agents. It is has been studied against placebo in heart failure in the elderly population in the SENIORS study, but it has not been FDA approved for the treatment of heart failure.[21,22]

The majority of generically available beta-blockers are indicated for HTN. Many of these agents also have indications for the treatment of angina and/or arrhythmias. The focus of this review will be the use of these agents in the management of HF.

Pharmacology

Beta-blockers inhibit the adverse effects of the sympathetic nervous system (SNS) in heart failure patients. Although cardiac adrenergic drive initially supports the performance of the failing heart, long-term activation of the SNS exerts deleterious effects. These effects include increased ventricular volumes and pressures, cardiac hypertrophy, provocation of arrhythmias, and apoptosis. Beta-blockers antagonize SNS activation, minimize damage, and ultimately slow disease progression.

Carvedilol is a racemic mixture; the S(-) enantiomer has nonselective beta-adrenergic blocking activity and the R(+) and S(-) enantiomers have alpha-adrenergic blocking activity.[23] Metoprolol has beta-1 selective adrenergic blocking activity at therapeutic concentrations; however, as concentrations increase, metoprolol also blocks the beta-2 adrenergic receptors.[24] Neither agent has intrinsic sympathomimetic activity (ISA).

FDA-approved Indications

Drug	Manufacturer	Indication(s)
acebutolol (Sectral®)	generic	• HTN • Ventricular arrhythmias
atenolol (Tenormin®)	generic	• Angina pectoris • HTN • MI
betaxolol (Kerlone®)	generic	• HTN
bisoprolol (Zebeta)	generic	• HTN
carvedilol (Coreg, Coreg CR)[25,26]	generic GlaxoSmithKline	• Mild to severe HF, to reduce the risk of hospitalization and improve survival • HTN • Reduce risk of death following MI with Left Ventricular Dysfunction (LVD) in patients with or without HF symptoms
labetalol (Normodyne®, Trandate®)	generic	• HTN
metoprolol tartrate (Lopressor®)	generic	• Angina pectoris • HTN • MI
metoprolol succinate ER (Toprol XL)	generic Astra-Zeneca	• Angina pectoris • HF – New York Heart Association (NYHA) Class II or III – to reduce the risk of death and hospitalizations • HTN
nadolol (Corgard®)	generic	• Angina pectoris • HTN
nebivolol (Bystolic)	Forest	• HTN
penbutolol (Levatol®)	Schwarz Pharma	• HTN
pindolol (Visken®)	generic	• HTN
propranolol (Inderal®)	generic	• Angina pectoris • Cardiac arrhythmias • Essential tremor • HTN • Hypertrophic subaortic stenosis • Migraine prophylaxis • MI • Pheochromocytoma
propranolol LA (Inderal® LA)	generic	• Angina pectoris • HTN • Hypertrophic subaortic stenosis • Migraine prophylaxis
propranolol XL (Innopran XL®)	Reliant	• HTN
sotalol (Betapace®)	generic	• Ventricular arrhythmias
sotalol (Betapace AF™)	generic	• Maintenance of normal sinus rhythm in atrial fibrillation/flutter
timolol	generic	• HTN • Migraine prophylaxis • MI

Beta-Blocker Combinations with Diuretics

Drug	Manufacturer	FDA-Approved Indication
atenolol / chlorthalidone (Tenoretic®)	generic	HTN
bisoprolol / hydrochlorothiazide (Ziac®)	generic	HTN
metoprolol / hydrochlorothiazide (Lopressor® HCT)	generic	HTN
nadolol / bendroflumethiazide (Corzide®)	generic	HTN
propranolol / hydrochlorothiazide (Inderide®)	generic	HTN

Pharmacokinetics

Drug	Bioavailability (%)	Half-life (hrs)*	Metabolism	Excretion
carvedilol (Coreg)[27]	25-35 (C_{max} reduced in presence of food)**	7 - 10	Three weakly active metabolites via CYP2D6 and CYP2C9	Primarily Feces
carvedilol controlled-release (Coreg CR)[28]	25 - 35 (C_{max} reduced in presence of food)***	5 - 12	Three weakly active metabolites via CYP2D6 and CYP2C9	Primarily Feces; less than 7 percent in the urine
metoprolol succinate ER (Toprol XL)[29]	50	3 - 7	Inactive metabolites via CYP2C9	Predominantly Renal

* Half-life of beta-blockers does not directly correlate with the duration of activity.
**Because the presence of food in the gut reduces the maximum concentration (C_{max}) of carvedilol, it is recommended that this drug be taken with food to minimize the risk for hypotension.[30]
***The AUC and C_{max} of carvedilol controlled-release (Coreg CR) are decreased when given in a fasting state, therefore carvedilol controlled-release (Coreg CR) should be administered with food to enhance absorption.[31]
Carvedilol controlled-release (Coreg CR) has 85 percent the bioavailability of the carvedilol immediate-release tablets.

Clinical Trials

Search Strategy

Studies were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included carvedilol and metoprolol for the management of HF. Very few comparative clinical trials in HF have been performed with agents in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probably clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer

sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

carvedilol (Coreg)

US Carvedilol Heart Failure Study: A double-blind, placebo-controlled study (n=1,094) evaluated carvedilol use in HF.[32] The primary endpoint was all-cause mortality with a secondary endpoint of cardiovascular morbidity (hospitalization). The population was mostly men with ischemic heart disease, NYHA Class II and III, with a LVEF ≤35 percent. Therapy with ACE inhibitors and diuretics for at least two months was required for inclusion in the study. Carvedilol was initiated at 6.25 mg twice daily (open-label). If tolerated, patients were randomized to carvedilol 12.5 mg twice daily or placebo in a double-blind manner. The target doses of carvedilol were 25 to 50 mg twice daily for six to 12 months. The trial was stopped early due to the carvedilol group having a 65 percent lower relative risk of death than the placebo group ($p<0.001$). Carvedilol patients had a 27 percent relative risk reduction in hospitalization for cardiac reasons ($p=0.036$). Worsening of HF was the most common reason for withdrawal from the study and was seen more frequently in the placebo group.

carvedilol in severe HF (COPERNICUS): In a double-blind study evaluating the use of carvedilol in severe chronic HF, 2,289 patients with LVEF <25 percent were randomized to carvedilol or placebo and evaluated for rates of hospitalizations and death.[33] Patients had symptoms at rest or with minimal exertion despite therapy with diuretics, ACE inhibitors or ARBs. The carvedilol group had a 35 percent decrease in the relative risk of death over the placebo group in the mean 10.4-month study period ($p=0.0014$). The relative combined risk of death and hospitalization was reduced by 24 percent in the carvedilol group compared to the placebo group ($p=0.00002$). More patients withdrew from the study in the placebo group due to adverse effects or other reasons ($p=0.02$). An evaluation of carvedilol dose titration during the first eight weeks of therapy did not demonstrate an increase, but rather a decrease of deaths, hospitalizations, and numbers of patients withdrawing from the study as compared to placebo.[34] Worsening of HF was similar in both groups (carvedilol 5.1 percent, placebo 6.4 percent).

carvedilol (Coreg) after MI with LVD (CAPRICORN): A trial enrolling 1,959 patients evaluated carvedilol in the setting of acute MI complicated by LVD.[35] In this multicenter, double-blind, placebo-controlled trial, patients with MI and LVEF <40 percent were randomized to carvedilol 6.25 mg twice daily or placebo. The primary outcomes were all-cause mortality or hospital admission for cardiac reasons. Eligible patients were receiving ACE inhibitors and diuretics. Therapy was titrated to a maximum of carvedilol 25 mg twice daily over four to six weeks. The mean follow-up was 1.3 years. All-cause mortality was lower in the carvedilol group compared to placebo (12 percent carvedilol, 15 percent placebo, 23 percent relative risk reduction; $p=0.03$). Atrial and ventricular antiarrhythmic effects by carvedilol have been observed in this population.[36]

carvediolol controlled-release (Coreg CR)

Support for the use of carvedilol CR for the treatment of mild to severe HF and for patients with LVD following MI is based on the equivalence of pharmacokinetic and pharmacodynamic parameters between carvedilol immediate- and controlled-release products. A Phase III clinical trial is currently underway to compare the effects of the two dosage forms on LVEF from baseline to six months post randomization as measured by two dimension echocardiography compared to baseline. Secondary outcomes will include the change from baseline in brain natriuretic peptide (BNP) levels, number of hospitalizations for HF, number of hospitalizations

from all causes, all-cause mortality and safety and tolerability.

carvedilol (Coreg) and metoprolol tartrate (Lopressor)

One hundred fifty patients with HF and LVEF <35 percent were randomized to double-blind treatment with either metoprolol or carvedilol.[37] When compared with metoprolol (average dose 124±55 mg/day), patients treated with carvedilol (49±18 mg/day) showed larger increases in LVEF at rest (+10.9 percent versus +7.2 percent, p=0.038) and in LV stroke volume and stroke work during exercise (both p<0.05) after 13 to 15 months of treatment. Carvedilol produced greater decreases in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and during exercise, compared to metoprolol (all p<0.05). In contrast, the metoprolol group showed greater increases in maximal exercise capacity than the carvedilol group (p=0.035). Both drugs improved symptoms, submaximal exercise tolerance, and quality of life to a similar degree. After a mean of 23 months of follow-up, 21 patients in the metoprolol group and 17 patients in the carvedilol group died or underwent transplantation.

COMET trial: COMET was a randomized, double-blind trial comparing carvedilol and metoprolol tartrate in 3,029 patients with HF for effects on all-cause mortality.[38] Most patients were classified as NYHA Class II and III and were on diuretics, ACE inhibitors, or ARBs with optional treatment with digoxin and spironolactone. All patients had a history of a cardiovascular event within two previous years. The average LVEF was 26 percent at baseline. Baseline heart rates were identical between the groups. Patients were randomized to carvedilol 3.125 mg twice daily and titrated to 25 mg twice daily or metoprolol tartrate 5 mg twice daily and titrated to 50 mg twice daily. The target dose was achieved by 75 percent of carvedilol patients and 78 percent of the metoprolol patients. The average daily dose was 42 mg for carvedilol and 85 mg for metoprolol tartrate. Patients were followed for a mean of 58 months. All cause mortality was 34 and 40 percent for carvedilol and metoprolol tartrate, respectively (p=0.0017); COMET demonstrated a 17 percent relative risk reduction in all-cause mortality with carvedilol. The annual mortality rate was 8.3 percent for carvedilol group and 10 percent for metoprolol tartrate. The secondary endpoint of all-cause mortality and all-cause hospitalization was similar between the two groups. Fewer carvedilol patients experienced cardiovascular death (p=0.0004).[39] After four months, carvedilol reduced heart rate by a mean of 13.3 beats per minutes whereas metoprolol reduced heart rate by 11.7 beats per minute. After 16 months, heart rate was similar between the groups. Overall, 32 percent of patients in both groups withdrew from the study. A criticism of the study is the lack of possible dose equivalency with carvedilol having a higher dose and lower heart rate therefore possibly greater benefits than metoprolol tartrate.

An analysis of the COMET trial compared the effects of carvedilol and metoprolol tartrate on vascular events.[40] Vascular endpoints were cardiovascular death, stroke, stroke death, myocardial infarction, and unstable angina. MI was seen in 69 carvedilol and 94 metoprolol patients (hazard ratio 0.71, 95% confidence interval (CI) 0.52 to 0.97, p=0.03). Cardiovascular death and nonfatal MI combined were reduced by 19 percent in carvedilol versus metoprolol (hazard ratio 0.81, 95 percent CI 0.72 to 0.92, p=0.0009). Unstable angina was seen in 56 carvedilol-treated patients versus 77 metoprolol-treated patients (hazard ratio 0.71, 95 percent CI 0.501 to 0.998, p=0.049). Stroke was reported in 65 versus 80 patients receiving carvedilol and metoprolol, respectively (hazard ratio 0.79, 95 percent CI 0.57 to 1.10, p=0.163). Stroke or MI combined occurred in 130 carvedilol-treated and 168 metoprolol-treated patients (hazard ratio 0.75, 95 percent CI 0.60 to 0.95, p=0.015), and fatal MI or fatal stroke occurred in 34 patients on carvedilol versus 72 patients receiving metoprolol (hazard ratio 0.46, 95 percent CI 0.31 to 0.69, p=0.0002). The results show carvedilol improves vascular outcomes compared to metoprolol, however the possible lack of dose equivalency in the COMET trial must be taken

into account.

The objective of GEMINI, a randomized, double-blind, parallel-group trial, was to compare metoprolol tartrate and carvedilol in diabetics.[41] A total of 1,235 diabetics aged 36 to 85 years (mean age 61 years) were enrolled in GEMINI at 205 sites in the United States. All participants in GEMINI had stage 1 or 2 HTN (systolic blood pressure, SBP, 130-179 mm Hg and diastolic blood pressure, DBP, 80-109 mm Hg), currently on an ACE inhibitor or ARB, and controlled type 2 diabetes (baseline glycosylated hemoglobin, HbA_1c, 6.5 to 8.5 percent and C-peptide>0.6 ng/mL). There were no significant differences in baseline characteristics between the two groups. Less than 10 percent of patients had a history of coronary artery disease. Patients were randomized to carvedilol 6.25 mg twice daily (titrated to a maximum of 25 mg twice daily) or metoprolol tartrate 50 mg twice daily (titrated to maximum of 200 mg twice daily) and followed for a maximum of 35 weeks. Open-label hydrochlorothiazide 12.5 mg followed by a dihydropyridine CCB was added, if needed, to achieve blood pressure targets. The primary outcome was the mean change from baseline HbA_1c following five months of maintenance therapy. Based on last observation carried forward, the carvedilol group had a significant change from baseline HbA_1c (-0.12 percent; p=0.006). A greater proportion of subjects on metoprolol than on carvedilol had increases in HbA_1c of greater than 0.5 percent (30 versus 22 percent, respectively) or greater than one percent (14.2 versus seven percent, respectively). Since blood pressure control and mean heart rate, as well as use of antihypertensive and lipid-lowering medications, were similar in the two treatment groups, the GEMINI investigators believe that these could not have accounted for differences in HbA_1c. Subjects in the carvedilol group had improved insulin resistance, as measured by the homeostasis model assessment insulin resistance index (HOMA-IR) (p=0.04), and less microalbuminuria, as measured by urinary albumin/creatinine excretion rate, compared with the metoprolol group (p=0.003). Significantly fewer subjects on carvedilol developed new-onset microalbuminuria compared with those on metoprolol (6.6 versus 11.1 percent; odds ratio, 0.53; 95% CI, 0.30-0.93; p=0.05). The frequency of bradycardia was higher with metoprolol (p=0.007) which may be indicative of a lack of equivalent doses between the two agents. Diabetes worsened in more patients in the metoprolol group (p=0.07) with more patients withdrawing due to worsening glycemic control (p=0.04). Weight gain was higher with metoprolol (1.2 kg versus 0.2 kg, p<0.001).

metoprolol succinate ER (Toprol XL)

MERIT-HF trial: A double-blind, placebo-controlled study enrolled 3,991 patients with chronic HF (NYHA Class II-IV and LVEF <40 percent).[42] Patients were stabilized on optimal concomitant therapy including diuretics, ACE inhibitors, cardiac glycosides, and nitrates. At randomization, 41 percent of patients were NYHA Class II and 55 percent were NYHA Class III. Patients were started on 12.5 mg once daily of metoprolol succinate ER if NYHA Class III-IV or 25 mg once daily if NYHA Class II. Dose titration was occurred over an eight-week period, if tolerated. The mean daily dose of metoprolol succinate ER at the end of the trial was 159 mg. The target dose of metoprolol succinate ER 200 mg daily was achieved in 64 percent of patients. The trial was terminated early (mean duration of one year) because of a 34 percent relative risk reduction in all-cause mortality.

Numerous subgroup analyses have found positive effects with metoprolol succinate ER in HF. In the MERIT-HF study, women (n=898) with NYHA III and IV were found to benefit from metoprolol succinate ER. A 21 percent relative risk reduction was noted in the combined endpoint of all-cause mortality and all-cause hospitalization for women (p=0.044).[43] The relative risk of hospitalization for worsening HF was also reduced by 42 percent in the metoprolol succinate ER group compared to placebo. The relative risk reduction in total mortality was also

observed for hypertensive patients and for patients with severe HF randomized to metoprolol succinate ER.[44,45] In a subanalysis, metoprolol succinate ER provided benefits in black patients with clinically stable HF and LVD.[46]

The REversal of Ventricular Remodeling with Toprol-XL (REVERT) trial: In a randomized, controlled study, 149 patients with left ventricular ejection fraction of less than 40 percent, mild left ventricular dilation, and no symptoms of heart failure (NYHA class I) received metoprolol succinate ER 200 mg, 50 mg, or placebo for twelve months.[47] At one year, the metoprolol succinate ER 200 mg group showed a 14 +/- three mL/m^2 decrease in end systolic volume index and a six +/- percent increase in left ventricular ejection fraction ($p<0.05$ versus baseline and placebo for both). In the metoprolol succinate ER 50 mg group, there were no statistical differences in end-systolic and end-diastolic volume indexes versus placebo, however ejection fraction increased by four +/- one percent ($p<0.05$ versus baseline and placebo).

Special Populations

Pediatrics

Safety and effectiveness of the beta-blockers in children have not been established for most agents in this class.[48,49,50] Many of the agents have been used in children; however, clinical trial data are lacking. While safety and effectiveness have not been established with sotalol, the characteristics of pharmacokinetics, electrophysiological and beta-blocking effects, in children ages three days to 12 years have been completed.[51]

A randomized trial of metoprolol succinate ER in 140 hypertensive children ages six to 16 years of age for four weeks showed lowering of both systolic and diastolic blood pressure with no serious adverse events.[52] A pediatric hypertension study of children ages six to 16 years of age did not meet its primary endpoint (dose response for reduction in SBP), however it demonstrated effectiveness in some other prespecified secondary endpoints.[53] A double-blind trial of 161 children ages two months to 17 years (45 percent less than two years old) with chronic heart failure, were randomized to placebo versus two dose levels of carvedilol. Carvedilol resulted in placebo-corrected heart rate reduction of four to six beats per minute, indicative of beta-blockade activity. An eight month follow-up showed no significant effect of treatment on clinical outcomes. Adverse events which occurred in greater than ten percent in the carvedilol versus placebo-treated patients included, chest pain (17 versus six percent), dizziness (13 versus two percent), and dyspnea (11 versus zero percent).[54]

A double-blind, randomized, placebo-controlled, multicenter US study evaluated the effects of carvedilol in 161 children and adolescents with symptomatic systemic ventricular systolic dysfunction.[55] During the eight month study, patients were randomized to twice daily dosing with placebo, low dose carvedilol (0.2 mg/kg per dose if weight less than 62.5 kg or 12.5 mg per dose if weight greater than 62.5 kg) or high dose carvedilol (0.4 mg/kg per dose if weight less than 62.5 kg or 25 mg per dose if weight greater than 62.5 kg). There was no statistically significant difference in the primary outcome of composite measure of heart failure in the carvedilol groups versus placebo. Of the 54 patients in the placebo group, 30 improved (56 percent), 16 worsened (30 percent), and eight were unchanged (15 percent). Of the 103 patients in the carvedilol groups, 58 improved (56 percent), 25 worsened (24 percent), and 20 were unchanged (19 percent). The odds ratio (OR) for worsened outcome in patients in the combined carvedilol group versus placebo was 0.79 (95 percent CI, 0.36 to 1.59, $p=0.47$). This study did not show a significant improvement in heart failure outcomes in children and adolescents with symptomatic systolic heart failure.

Pregnancy[56,57,58,59]

Carvedilol and metoprolol are Pregnancy Category C.

Other[60,61,62,6364]

Beta-blocker therapy is recommended for chronic HF patients including those who are elderly and/or diabetic.

Drug Interactions[65,66,67]

The CYP2D6 enzyme is one of the enzymes that metabolizes carvedilol and metoprolol. Strong inhibitors of CYP2D6, such as fluoxetine, quinidine, paroxetine, and propafenone, will cause the beta-blocker concentrations to increase. There will be an increased risk of adverse effects and a reduction in the cardioselectivity of metoprolol. Additionally, beta-blockers, when given with catecholamine-depleting drugs such as MAO inhibitors and reserpine, may cause an exaggerated hypotensive response. Monitoring for hypotension, bradycardia, vertigo, syncope, and postural hypotension should be performed. Concurrent administration with clonidine has been reported to potentiate the hypotensive effects and worsening of bradycardia.

Cyclosporine levels have been reported to increase with concurrent carvedilol therapy. Monitoring of cyclosporine levels and possible reduction in the cyclosporine dosage may be necessary. When digoxin and carvedilol are administered concurrently, elevations in serum concentrations of digoxin by 15 percent have been reported. Monitoring of digoxin levels should be performed periodically.

Rifampin, a strong CYP 450 enzyme inducer, has been reported to reduce the bioavailability of carvedilol by 70 percent.

Contraindications/Warnings[68,69,70]

Patients with severe liver disease should not receive carvedilol. Patients with cirrhosis have been reported in single-dose studies to have significantly higher concentrations of carvedilol (four- to seven-fold) compared to healthy patients.

Carvedilol is contraindicated in patients with asthma and related bronchospastic conditions, second or third degree AV block, sick sinus syndrome, or severe bradycardia (unless a permanent pacemaker is in place) or in patients with cardiogenic shock or who have decompensated HF requiring the use of inotropic therapy.[71,72]

Metoprolol succinate ER are contraindicated in severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, and sick sinus syndrome (unless a permanent pacemaker is in place). Metoprolol succinate ER may be used with caution in patients with bronchospastic disease such as asthma who do not respond or can not tolerate other antihypertensives. Since $beta_1$-selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol succinate ER should be used.

Patients with second or third degree AV block, sick sinus syndrome, or severe bradycardia (unless a pacemaker is in place) generally should not receive beta-blockers unless the benefits outweigh the risks.

In patients with bronchospastic conditions, caution should be used with all beta-blockers including $beta_1$-selective agents, especially with high-dose therapy. A Cochrane systematic review found that cardioselective beta-blockers in COPD patients were not related to respiratory adverse effects.[73] It should be noted that several of the included studies were single-dose studies or for short durations.

In general, coronary heart disease patients should not abruptly discontinue therapy with beta-blockers. Severe exacerbations of angina and/or MI have been reported. Tapering of therapy over one to two weeks prior to discontinuation reduces the risk of these adverse effects.

In diabetic patients, beta-blockers can mask the tachycardia associated with hypoglycemia. Other symptoms of hypoglycemia such as dizziness or sweating may not be significantly affected by beta-blocker therapy.

Patients with peripheral arterial disease (PAD) may experience worsening of symptoms on beta-blocker therapy. Conflicting data from a prospective observational cohort study demonstrating beneficial effects of beta-blocker therapy in PAD was recently published.[74] Beta-blockers may also mask tachycardia associated with hyperthyroidism. Abrupt beta-blocker withdrawal may be associated with an exacerbation of symptoms of hyperthyroidism and may precipitate thyroid storm.

Adverse Effects

Adverse effects in HF patients are listed below.

Drug	Hypotension/ Postural Hypotension	Syncope	Dizziness/Vertigo	Bradycardia	Hyperglycemia
carvedilol (Coreg, Coreg CR)[75,76]	9-14 (3-8)	3-8 (3-5)	24-32 (17-19)	9-10 (1-3)	5-12 (3-8)
metoprolol succinate ER (Toprol XL)[77]	> 1	> 1	1.8 (1)	1.5 (0.4)	> 1

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses.

A meta-analysis of 15 trials with beta-blockers evaluated the risks of depression, fatigue, and sexual dysfunction.[78] For depressive symptoms, seven trials with over 10,000 patients found there was no difference in the frequency of depressive symptoms in patients taking beta-blockers compared to those on placebo. In ten trials with over 17,000 patients, fatigue was more frequently reported in patients taking beta-blockers. Older beta-blockers were more commonly associated with complaints of fatigue. In six trials with almost 15,000 patients, beta-blockers had slightly more reports of sexual dysfunction than placebo.

Adverse effects of beta-blockers in HF patients were evaluated in an analysis.[79] Beta-blockers were associated with the increased risk of hypotension (11 per 1000; 95% CI, 0-22), dizziness (57 per 1000; 95% CI, 11-104), and bradycardia (38 per 1000; 95% CI, 21-54). Fatigue was not associated with beta-blockers. Beta-blockers were associated with a reduction in all-cause withdrawal from therapy (14 per 1000; 95% CI, -2 to 29), lower all-cause mortality (34 per 1000; 95% CI, 20-49), HF hospitalizations (40 per 1000; 95% CI, 22-58), and worsening HF (52 per 1000; 95% CI, 10-94).

Dosages

Drug	Hypertension	Angina Pectoris	Heart Failure	Other Indications	Availability
acebutolol	200-400 mg twice daily	-	-	See package insert for other indications	200, 400 mg capsule
atenolol	50-100 mg daily	50-200 mg daily	-	MI: 50 mg twice daily or 100 mg daily	25, 50, 100 mg tablets
betaxolol	10-20 mg daily	-	-	-	10, 20 mg tablets
bisoprolol	2.5-20 mg daily	-	-	-	5, 10 mg tablets
carvedilol	6.25-25 mg twice daily	-	3.125 - 25 mg twice daily	LVD following MI: 3.125 – 25 mg twice daily	3.125, 6.25, 12.5, 25 mg tablets
carvedilol CR (Coreg CR)	20–80 mg once daily	-	10 mg – 80 mg once daily	LVD following MI: 20 mg to 80 mg once daily	10, 20, 40, 80 mg capsules
labetalol	100-400 mg twice daily	-	-	-	100, 200, 300 mg tablets
metoprolol tartrate	100-450 mg daily	50 mg twice daily to 400 mg daily	-	MI: 25-50 mg every six hours, then 100 mg twice daily	25, 50, 100 mg tablets
metoprolol succinate ER	25-400 mg daily	100-400 mg daily	12.5 - 200 mg daily	-	25, 50, 100, 200 mg tablets
nadolol	40-80 mg daily	40-80 mg daily	-	-	20, 40, 80, 120, 160 mg tablets
nebivolol (Bystolic)	5-40 mg daily	-	-	-	2.5, 5, 10 mg tablets
penbutolol (Levatol)	20-40 mg daily	-	-	-	20 mg tablet
pindolol	5 mg twice daily to 60 mg daily	-	-	-	5, 10 mg tablets
propranolol	40 mg twice daily initially, then 120-240 mg/day in divided doses	80-320 mg daily in divided doses	-	See package insert for other indications	10, 20, 40, 60, 80 mg tablets; 20 mg/5 ml, 40 mg/5 ml solution
propranolol ER (Innopran XL)	80 or 120 mg at bedtime	-	-	-	80, 120 mg capsules
propranolol LA	80 mg daily, then 120-160 mg daily	80-320 mg daily	-	See package insert for other indications	60, 80, 120, 160 mg capsules
sotalol	-	-	-	See package insert for other indications	80, 120, 160, 240 mg tablets
timolol	10-30 mg twice daily	-	-	MI: 10 mg twice daily See package insert for other indications	5, 10, 20 mg tablets

Metoprolol succinate ER (Toprol XL) may be used for treatment of hypertension in pediatrics aged ≥ six years old: 1 mg/kg once daily (max 50 mg/day). Dose should be adjusted based on patient response (max 2 mg/kg or 200 mg/day).

Dosages (continued)

Drug	Initial Hypertension Dosage	Maximum Hypertension Dosage	Availability
atenolol / chlorthalidone (Tenoretic)	50/25 mg once daily	100/25 mg once daily	50/25, 100/25 mg tablets
bisoprolol / hydrochlorothiazide (Ziac)	2.5/6.25 mg once daily	20/12.5 mg once daily	2.5/6.25, 5/6.25, 10/6.25 mg tablets
metoprolol tartrate / hydrochlorothiazide (Lopressor HCT)[80]	50/25 mg twice daily	100/25 mg given as 1-2 tablets in a single or divided doses 100/50 mg given a single dose	50/25, 100/25, 100/50 mg tablets
nadolol / bendroflumethiazide (Corzide)	40/5 mg once daily	80/5 mg once daily	40/5, 80/5 mg tablets
propranolol / hydrochlorothiazide (Inderide)	40/25 mg twice daily	80/25 mg once or twice daily	40/25, 80/25 mg tablets

Summary

Bisoprolol (Zebeta), metoprolol succinate ER (Toprol XL), and carvedilol (Coreg, Coreg CR) all have clinical data to support their use in the management of HF; however, only metoprolol succinate ER and carvedilol are FDA-approved for heart failure. The most recent heart failure guidelines published by the American College of Cardiology and American Heart Association do not recommend one beta-blocker for heart failure but three – bisoprolol, carvedilol, or metoprolol succinate ER. The COMET trial (Carvedilol or Metoprolol European Trial) found that carvedilol reduced the relative risk of all cause mortality by 17 percent in patients with HF compared to metoprolol tartrate, however the study design limits the clinical application of this finding. Beta-blocker therapy is recommended for chronic HF patients including those who are elderly and/or diabetic.

Nebivolol (Bystolic) is effective in lowering blood pressure, appears to be well tolerated, and has the unique mechanism on the nitric oxide pathway, however it does not confer additional clinical benefit over existing beta-blockers. Long-term outcomes data for nebivolol (Bystolic) are lacking.

For the treatment of HTN, diuretics are first line agents. If elevated blood pressure persists, combination therapy is warranted. Compelling indications should guide selection of a second agent for the treatment of HTN. For HTN, beta-blockers should be considered for patients with ischemic heart disease, angina, post-MI, or HF. For indications other than HF, a number of beta-blockers are FDA-approved and may be considered.

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