

# The use of metoprolol CR/XL in the treatment of patients with diabetes and chronic heart failure

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**Abstract:** About 5 million Americans suffer from heart failure. Given the correlation of heart failure with age and the rising life expectancy, the prevalence of heart failure continues to increase in the general population. Sympathetic stimulation intensifies with progressive heart failure. The rationale to use  $\beta$ -blockers in individuals with impaired myocardial function is based on experimental evidence supporting the notion that prolonged  $\alpha$ - and  $\beta$ -adrenergic stimulation leads to worsening heart failure. Until recently, safety concerns have precluded the use of  $\beta$ -blockers in patients with diabetes and heart failure. However, several large, randomized, placebo-controlled clinical trials such as Metoprolol Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) have shown that  $\beta$ -blockers can be safely used in patients with diabetes and heart failure. Moreover,  $\beta$ -blockers significantly improved morbidity and mortality in this population. Based on this evidence, it is now recommended to add  $\beta$ -blockers such as metoprolol CR/XL with an escalating dosage regimen to the treatment of patients with symptomatic heart failure who already are receiving a stable medical regimen including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretics, vasodilators, or digitalis.

**Keywords:** metoprolol, heart failure, diabetes mellitus,  $\beta$ -adrenergic blocking agents, MERIT-HF

## Introduction

The first  $\beta$ -adrenergic receptor antagonist for medical purposes was introduced by Powell and Slater (1958) (dichloroisoproterenol), but its use was limited by a partial agonist activity (Hoffman and Lefkowitz 1996). The synthesis of pronethalol (Black and Stephenson 1962) was soon followed by the chemically similar propranolol, and the latter remains the prototype to which other  $\beta$ -adrenergic receptor antagonists are compared. Propranolol has equal affinity for  $\beta_1$  and  $\beta_2$  receptors; this caused bronchospasm and peripheral arterial vasoconstriction in susceptible individuals. The molecule was subsequently modified to achieve  $\beta_1$  selectivity. This led to the discovery of many new compounds (Cruikshank 1980; Benfield et al 1986; Reynolds et al 1986). Among them was metoprolol tartrate (Waagstein et al 1975), with a half-life of 3 to 4 hours. In the early 1990s, metoprolol succinate was developed, which is less water-soluble than the tartrate salt and provides a longer half-life (Polsker and Clissold 1992).

The metoprolol controlled/extended release (CR/XL) formulation utilizes the succinate salt of the drug. Each metoprolol CR/XL tablet comprises individual spherical pellets of the active drug coated with a non-proteolytic polymeric membrane, mainly ethylcellulose. A 100 mg CR/XL tablet contains 95 mg of metoprolol succinate and is considered to have equivalent activity to 100 mg metoprolol tartrate. After

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ingestion, the tablet disintegrates into individual pellets and each pellet acts as a diffusion cell releasing the drug at a relatively constant rate over a period of approximately 20 hours (Amitabh and Markham 2000). In this article, we will review and analyze the available studies on the use of metoprolol CR/XL in the treatment of patients with diabetes mellitus and chronic heart failure (CHF).

## Diabetes and heart failure

National hospital surveys estimate that about 5 million Americans have heart failure (AHA 2004). The prevalence of heart failure and left ventricular dysfunction increases steeply with age. As an example, the Framingham Heart Study found a prevalence in men of 8 per 1000 at age 50 to 59 years, increasing to 66 per 1000 at ages 80 to 89 years; similar values (8 and 79 per 1000) were noted in women (Ho et al 1993). The prevalence in African-Americans is reported to be 25% higher than in Caucasians. Diabetes was found to be an independent predictor of heart failure in this cohort. The risk of heart failure was increased 2–4-fold in men and 5-fold in women with diabetes when compared with those without diabetes, after adjusting for the presence of hypertension and coronary artery disease (Kannel et al 1974; Marwick 2006). Population-based studies showed that, depending on the sensitivity of the screening method, 30% to 60% of subjects with well-controlled type 2 diabetes had diastolic dysfunction (Bell 2003).

The pathogenesis of heart failure in patients with diabetes is multifaceted. There is a direct relationship between pathologic changes seen in the myocardium of patients with diabetes, such as myocardial fibrosis, matrix expansion, and thickening of the capillary basement membranes, as well as functional changes in the heart (Fischer et al 1979; van Hoven and Factor 1990). These abnormalities, termed diabetic cardiomyopathy, lead to both systolic and diastolic dysfunction (Arvan et al 1988; Stone et al 1989). In addition, the prevalence of coronary artery disease is particularly high among patients with diabetes, and 75% of type 2 diabetic subjects have hypertension, 71% left ventricular hypertrophy, and 52% have diastolic dysfunction. All are known risk factors for the development of CHF (Kannel and McGee 1979; Almdal et al 2004). Other pathologic aspects associated with heart failure and diabetes mellitus include autonomic neuropathy, impaired metabolic demands due to abnormal epicardial vessel tone, and microvascular dysfunction (due in part to down regulation of the expression of vascular endothelial growth factor), and the decrease in

insulin availability or responsiveness that can impair energy-independent transport of glucose (Zarich and Nesto 1989; Sun et al 1994; Rossen 1996; Yoon et al 2005). For a detailed discussion of the pathogenetic mechanisms underlying diabetic cardiomyopathy we refer the reader to a recently published review (Fang et al 2004). The importance of glycemic control is illustrated by the finding that every 1% increase in glycosylated hemoglobin (A1c) is associated with an 8% increased risk of heart failure (Iribarren et al 2001).

## Treatment of chronic heart failure

The American Heart Association (AHA) recently published their updated 2005 guideline for the diagnosis and management of CHF in the adult (Hunt 2005). These guidelines recommend the use of both angiotensin-converting enzyme (ACE) inhibitors and  $\beta$ -blockers to prevent the progression of CHF. Three  $\beta$ -blockers have been shown to reduce the risk of death in patients with CHF: bisoprolol (Dargie and Lechat 1999), metoprolol (Hjalmarson et al 2000), and carvedilol (Dargie 2001; Packer et al 2001). The rationale to use  $\beta$ -blockers is based on the markedly increased sympathetic activity in patients with CHF. The positive inotropic effect of this sympathetic activation is far outweighed by its adverse effects, which include myocardial ischemia, arrhythmogenicity, sodium retention, hypokalemia, and myocardial cell death and apoptosis (Gebhardt and Wisenberg 1985; Sundberg and Gordin 1986; Molina-Viamonte et al 1991; Kaumann and Sanders 1993; Knowlton et al 1993; Communal et al 1998). In the following, we will briefly review the most relevant and most recent studies that support the use of metoprolol for the treatment of heart failure.

## Metoprolol Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)

After the conclusion of the MERIT-HF pilot study (Goldstein et al 1999), which established safety and efficacy using intermediate endpoints, MERIT-HF was launched. MERIT-HF is a randomized double-blind placebo-controlled trial with a single blind, 2-week placebo run-in period (Hjalmarson et al 2000). A total of 3991 patients with symptomatic CHF and decreased left ventricular ejection fraction who were stabilized with standard treatment, were randomized to receive placebo (2001 patients) or metoprolol CR/XL (1990 patients). The first 3 predefined outcomes in

MERIT-HF were all-cause mortality, the combined end point of all-cause mortality plus all-cause hospitalization (time to event analysis), and all-cause mortality or hospitalizations due to worsening heart failure (time to event analysis). Additional predefined endpoints were the total number of hospitalizations due to cardiovascular causes and to worsening heart failure, withdrawal of study drug for any cause and worsening heart failure. The major inclusion criteria were symptomatic heart failure for at least 3 months, corresponding to New York Heart Association (NYHA) class II to IV, and a left ventricular ejection fraction of 40% or less in men and women aged 40 to 80 years. Patients had to be receiving optimal treatment (defined as any combination of diuretics and an ACE inhibitor) for at least 2 weeks prior to randomization. Digitals preparations were allowed but not required. If an ACE inhibitor was not tolerated, hydralazine, long-acting nitrates, or an angiotensin receptor blocker (ARB) could be used. The starting dosage of metoprolol CR/XL was 25 mg daily in NYHA class II and 12.5 mg for patients with NYHA functional class III or IV. The goal was to double the dose after each 2-week period to reach the target of 200 mg per day of metoprolol CR/XL or placebo.

The trial was stopped early because the second interim analysis showed a significant 34% reduction in total mortality in the metoprolol CR/XL group compared with the placebo group. The second primary endpoint, a composite of all-caused mortality or all-caused hospitalizations, was reduced by 19% (95% confidence interval [CI], 10%–27%). Analysis of secondary endpoints showed that total mortality or hospitalization for worsening heart failure was reduced by 31% (95% CI, 20%–40%), death or heart transplantation by 32% (95% CI, 16%–45%), and cardiac death or nonfatal acute myocardial infarction by 39% (95% CI, 25%–51%). Total mortality or hospitalization or emergency department visit due to worsening heart failure was lowered by 32% (95% CI, 21%–41%). Compared with placebo, metoprolol CR/XL reduced the number of patients with any hospitalization ( $p=0.04$ ), the total number of hospitalizations ( $p=0.05$ ), and the total numbers of days in the hospital ( $p=0.04$ ), due to all causes. Improvement in NYHA functional class was recorded in 28.6% versus 25.8% in the metoprolol CR/XL and placebo groups, respectively. Adverse events necessitating withdrawal of study drug were similar in both groups.

A subgroup analysis evaluated outcomes in the 985 patients with diabetes that were included in this study (Deedwania et al 2005). Those in the placebo arm

experienced an 8% increase in mortality and markedly increased hospitalization rates when compared with patients without diabetes (48% risk increase for hospitalizations due to cardiovascular causes; 76% risk increase for hospitalizations due to heart failure). Hospitalization rates were significantly lower in patients with diabetes who received metoprolol (risk reduction [RR] for all-cause hospitalization: 37%,  $p=0.0026$ ). This risk reduction was greater in those with severe heart failure (RR 53%,  $p=0.0087$ ). Given the small sample size, a mortality benefit could not be shown (RR 18%,  $p>0.2$ ).

## Carvedilol or Metoprolol European Trial (COMET)

The COMET trial is a multicenter, randomized, double-blind, parallel-group trial to compare the effect on mortality and morbidity of carvedilol and metoprolol in patients with CHF (Poole-Wilson et al 2003). 3029 patients were randomized to receive either 3.125 mg carvedilol twice daily or 5 mg metoprolol tartrate twice daily. Eligible patients were men or women with symptomatic CHF (NYHA II–IV) who had at least one cardiovascular admission during the previous 2 years and who received stable heart failure treatment with ACE inhibitors and diuretics for at least 4 weeks. Digitals, angiotensin II inhibitors, or vasodilators could be used alternatively. Left ventricular ejection fraction had to be 35% or lower at study entry. The dosage of medication was titrated every 2 weeks up to the target doses (carvedilol 25 mg twice daily or metoprolol 50 mg twice daily). The primary endpoints were all-cause mortality, cardiovascular deaths, non-cardiovascular deaths, and all-cause mortality or all-cause hospital admission. Overall, this study favored carvedilol over metoprolol in terms of all-cause and cardiovascular mortality, as well as serious and non-serious adverse events. However, the mortality difference between the metoprolol or carvedilol group in the subgroup of patients with diabetes, which comprised 24% of the patients in either arm, did not reach statistical significance (hazard ratio [HR] 0.85, 95% CI, 0.69–1.06).

## Comments and conclusions

Many physicians are still hesitant to prescribe  $\beta$ -blockers to patients with diabetes and CHF. This may be in part due to concerns about tolerability and safety as well as to the paucity of data in regard to efficacy on mortality and hospitalizations. Based on recent clinical data,  $\beta$ -blockers clearly confer a benefit in patients with diabetes and heart

failure, prompting the AHA to endorse this therapy in its recent practice guidelines (Hunt 2005). In fact, a recent meta-analysis of the survival benefit of  $\beta$ -blockers in the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), MERIT-HF, and the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) showed a 25% survival benefit for patients with diabetes and CHF who received a  $\beta$ -blocker (Deedwania et al 2005). This is in line with prior analyses that studied sub-populations of patients with heart failure (race, gender, and diabetes) using ACE inhibitors and  $\beta$ -blockers (Shekelle et al 2003). In a meta-analysis including CIBIS-II, Beta-Blocker Evaluation in Survival Trial (BEST), Australia–New Zealand–Carvedilol, Carvedilol US Trials (COPERNICUS), and MERIT-HF, the benefit derived from  $\beta$ -blocker therapy appeared to be smaller in those with diabetes when compared with subjects without diabetes who had CHF (Haas et al 2003). A more recent meta-analysis of seven randomized-controlled trials with carvedilol did not find a significant difference in the relative RR for mortality in subjects with or without diabetes (28% vs 37%) or the number needed to treat, which was 23 for nondiabetic patients, and 25 for the diabetic group (Bell et al 2006). However, given the higher absolute risk for death in patients with diabetes (Deedwania et al 2005), a similar relative RR will still result in more deaths in the diabetic than in the nondiabetic group.

The discussion whether the choice of  $\beta$ -blocker will result in significantly different outcomes is still ongoing. Two major criticisms have been brought forward in regard to COMET. The achieved dose of metoprolol was only 78 mg daily, versus 155 mg in MERIT-HF. In addition, patients randomized to carvedilol achieved a 1.8 mm Hg greater reduction in systolic blood pressure at 4 months. These differences make it more difficult to put the COMET results into perspective. It should be noted, however, that the achieved reduction in heart rate in COMET participants was equivalent in both the metoprolol and carvedilol group, suggesting a comparable degree of  $\beta$  blockade. In addition, a post-hoc analysis of the MERIT-HF study according to achieved dose ( $\leq 100$  mg vs  $> 100$  mg) did not show a significant mortality difference (Wikstrand et al 2002). In the post study phase of the COMET trial, which allowed crossover, mortality was lower in those patients who switched therapy from metoprolol to carvedilol than in those who switched from carvedilol to metoprolol or those who stayed on metoprolol (Di Lenarda et al 2005). In addition, a randomized controlled trial in patients with diabetes and hypertension treated with either carvedilol or metoprolol

showed that metabolic control was significantly better in those receiving carvedilol (Bakris et al 2004).

There is a special concern regarding  $\beta$  blockade in patients with diabetes mellitus. Theoretically, the activation of  $\beta$ -adrenergic receptors increases glucose production by stimulating both glucogenolysis and gluconeogenesis, protecting against the development of hypoglycemia. It has been shown that nonselective  $\beta$ -blockers could retard recovery from insulin-induced hypoglycemia (Antonis et al 1967; Reveno and Rosenbaum 1968), and the reactions could be severe, presumably due to diminished or absent early warning signs (Hirsch et al 1991). However, others found that the effects on glucose metabolism are less prominent with  $\beta_1$ -selective preparations, making it difficult to demonstrate an increased risk of serious hypoglycemia among diabetic populations (Deacon and Barnett 1976; Shorr et al 1997).

Additional prospective data are needed to decide whether selective  $\beta_1$  blockade is equivalent to combined  $\beta_1$ ,  $\beta_2$ , and  $\alpha_1$  blockade. However, based on the evidence from large randomized controlled clinical trials showing a significant survival benefit, the use of  $\beta$  blockers in patients with diabetes and CHF should be encouraged.  $\beta$ -blockers should be introduced at a low starting dose, which is 12.5 mg daily for metoprolol CR/XL, in symptomatic patients who already are receiving a stable medical regimen including ACE inhibitors or ARBs and diuretics, or an alternative regimen with vasodilators if neither ACE inhibitors nor ARBs are tolerated. The  $\beta$ -blocker dose should be maximized as tolerated, and a reasonable target dose for metoprolol appears to be 150–200 mg daily based on the MERIT-HF data. Used in this fashion, extended-release preparations of metoprolol can be safely used in patients with diabetes and heart failure to reduce morbidity and mortality.

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