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Scientific Update™

A New Strategy in the Treatment of Heart Failure: New Results from the MERIT-HF Trial

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Patients with heart failure have a grave prognosis. The angiotensin-converting enzyme inhibitors (ACEI) were the first class of agents shown to improve survival in these patients.[1] A ten-year follow-up of the patients enrolled in CONSENSUS, the first trial that demonstrated the survival benefit of ACEI in heart failure, was recently reported.[2] Only one patient was lost to follow-up. Five patients, all in the enalapril group, were long-term survivors. The beneficial treatment effect of enalapril during a mean treatment period of six months was sustained for at least four years, or for another 3.5 years after the conclusion of the double-blind treatment. Overall survival was prolonged by 50%, from 521 to 781 days. Clearly, in spite of our most modern therapy, the prognosis of patients with heart failure remains dismal. Since the introduction of ACEI, there has been little success in finding any other classes of agents which could improve the prognosis of these patients. Many agents, including the inotropes and vasodilators, turned out to be disappointing and possibly even harmful.

The rationale for the use of ß-blockers in heart failure has been the subject of many investigations for over two decades. With the publication this year of two powerful, well-designed studies – the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[3] and the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure study (MERIT-HF),[4] – there is now unmitigated evidence supporting the beneficial effect of ß-blockers in heart failure.

Under-utilization of beta-blockade

The survival benefit of ß-blockade therapy in patients following myocardial infarction (MI) is well established. However, physicians prescribe ß-blockers to less than one-third and cardiologists to less than one-half of their post-MI patients. Advanced age, impaired heart function, and diabetes have often been cited as reasons for not prescribing. Yet data from patients following MI suggest that patients with diabetes and left ventricular dysfunction may derive the most benefit and show the most pronounced risk reduction from ß-blockade therapy.[5,6] The Cooperative Cardiovascular Project was a nationwide program to evaluate all Medicare patients with a diagnosis of MI in the United States. By definition, all patients were over 65 years of age. The project evaluated the relationship between treatment and outcomes with over 400 variables derived from 207,752 post-MI patients. The mortality outcome of patients treated with ß-blockers was compared with those not given the medications due to "presumed" contraindication to their use: older age, low ejection fraction, chronic obstructive lung disease, diabetes mellitus, low blood pressure, and low heart rate.[7]

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The mean duration of comparison was 724±336 days post-MI. Only 34% of patients received ß-blockers. The percentage was lower among the elderly, blacks, and patients with the lowest ejection fractions, heart failure, chronic obstructive lung disease, and diabetes. In patients with MI and no other complications, treated patients had 40% lower mortality. The same mortality reduction was seen in patients with non-Q-wave MI and in those with chronic obstructive lung disease. Older patients, those with chronic lung disease, left ventricular ejection fraction less than 20%, serum creatinine greater than 1.4 mg/dL or diabetes also showed a significant reduction in mortality, although the percentage of reduction was smaller.

This analysis therefore demonstrates that ß-blockade therapy is under-utilized in post-MI patients. Patients in many subgroups are not treated despite a 23-40% decrease in mortality. In fact, almost all patients are likely to benefit from ß-blockade therapy after an MI.

Beta-blockers for heart failure: achieving 24-hour efficacy

Selective $ß_1$-adrenergic receptor blockade may theoretically be more advantageous than non-specific ß-blockade in heart failure. Another property that is sought in a heart failure drug is to provide effective, even, and long-lasting receptor blockade, along with the confirmed cardioprotective effect. To satisfy these properties, a $ß_1$-selective adrenergic blocker formulated into a carefully designed pharmaceutical preparation was required. These criteria formed the basis for the development of metoprolol CR/XL (controlled release/-extended release).

To achieve continuous, even, and selective $ß_1$-receptor blockade, it was first necessary to define the relationship between effective $ß_1$-blockade and plasma drug concentrations of metoprolol. Using the reduction in exercise-induced tachycardia as a measure of $ß_1$-blockade, the therapeutic plasma drug concentration was found to be in the range of 100-250 nmol/L.[8]

The metoprolol CR/XL tablet is a multiple unit formulation containing metoprolol succinate in the form of individual drug delivery units or pellets.[9] These pellets are contained in a tablet which releases the drug into the gastrointestinal tract over a period of 20 hours. A constant 24-hour plasma concentration with once daily dosing has been documented.[10]

At relatively low plasma levels, metoprolol has little impact on $ß_2$-receptors. However, at peak plasma levels (approximately 600 nmol/L) such as those achieved by administering the conventional immediate release preparation of 100 mg metoprolol tartrate, $ß_2$-receptor stimulation is likely to be achieved. However, at the "therapeutic" $ß_1$-blockade plasma levels provided by metoprolol CR/XL, little $ß_2$-mediated response was noted.[11]

Finally, the ß-blockers that have been shown to reduce sudden death post-MI are those with lipophilic properties. Metoprolol is lipophilic, and clinical trials have shown it to reduce sudden death post-MI, as well as in hypertension and heart failure patients; therefore, metoprolol is cardioprotective.[12] Based on these considerations, metoprolol CR/XL was the drug of the choice in the MERIT-HF trial. Metoprolol CR/XL is not yet approved for use in heart failure in Canada.

A historical perspective on beta-blockade in heart failure

The first report on the possible beneficial effect of chronic ß-blockade therapy in patients with dilated cardiomyopathy appeared 24 years ago.[13] At that time, the medical community was not prepared to accept this treatment concept. This could be explained by the fact that the main focus of drug development for the treatment of heart failure at that time was on hemodynamically-active agents. The concept that the failing heart could be an energy-starved organ was ignored.

The key studies of ß-blockers in heart failure are summarized in chronological order in Table 1. Soon after the first report 24 years ago, several small studies were published demonstrating an improvement in cardiac function, clinical deterioration on withdrawal of therapy, and improvement in survival with the use of ß-blockers compared with historical controls.[14-16] The first randomized-controlled trial demonstrating improvement in cardiac function, symptoms, and treadmill exercise tolerance was reported in 1985.[17]

Between 1980 and the present, over 20 randomized controlled trials of ß-blockers in heart failure were reported.[18] More than 9600 patients with heart failure due to ischemic or non-ischemic etiology have now been studied. Most patients were on ACEI therapy. Variable effects on heart failure symp-

Table 1: Chronology of key studies of beta-blockers in heart failure	
	Year
First case report of 7 patients	1975
Improved survival compared to historical controls	1979
First long-term follow up of ventricular function	1980
First study demonstrating clinical deterioration on drug withdrawal	1980
First placebo-control trial on exercise tolerance, clinical symptoms, and ventricular function	1985
First study of mechanisms of actions	1985

Trial	Agent	Patients (N)	Decrease in mortality (p value)	Mortality as primary endpoint	Year
MDC: improved heart function, reduced morbidity	Metoprolol 150 mg	383	No change		1993
CIBIS-I: reduced morbidity	Bisoprolol 5 mg	641	20% p=0.22	X	1994
US carvedilol program: reduced mortality (post-hoc)	Carvedilol 50-100 mg	345	65% p=0.0001		1995
RESOLVD	Metoprolol 200 mg	426	54% p=0.057		1997
CIBIS-II: reduced mortality	Bisoprolol 10 mg	2647	34% p<0.0001	X	1999
MERIT-HF: reduced mortality	Metoprolol 200 mg	3991	35% p=0.00015	X	1999

toms and exercise tolerance were reported. However, left ventricular ejection fraction improved consistently. A meta-analysis of these trials showed a 31% reduction in mortality.[18] Large-scale prospective randomized trials which could confirm these benefits have obviously been eagerly awaited.

Design and analysis of MERIT-HF

The principal aim of the MERIT-HF study was to investigate whether metoprolol CR/XL once daily, added to standard therapy, would reduce total mortality in patients with reduced ejection fraction and heart failure (Figure 1). It was designed as a randomized, double-blind, placebo-controlled study, preceded by a two-week single-blind placebo run-in period. Of note, there was *no* active drug run-in phase. The study medication was up-titrated during eight weeks starting with the lower dosage, 12.5 mg (for patients with NYHA III and IV symptoms) or the higher dosage, 25 mg once daily (for NYHA class II). The target dose was 200 mg daily. Details of the rationale, design, and organization of MERIT-HF have been published previously.[19]

There were two primary endpoints. These, ranked in order of importance, were: total mortality, and the combined endpoint of all-cause mortality and all-cause hospitalization (time to first event). The secondary outcomes were: combined all-cause mortality and hospitalization for heart failure; death and cardiac transplantation; pooled incidence of cardiac death and non-fatal acute MI; and cardiovascular deaths and heart failure deaths. The tertiary outcomes were: combined endpoint of all-cause mortality, hospitalizations and emergency room visits due to heart failure; tolerability; functional status. In two substudies, the impact of metoprolol CR/XL treatment on quality of life and health economics was also examined.

Figure 1: MERIT-HF trial profile

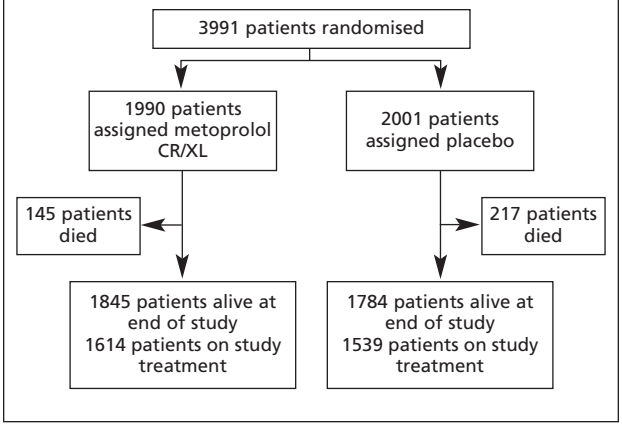
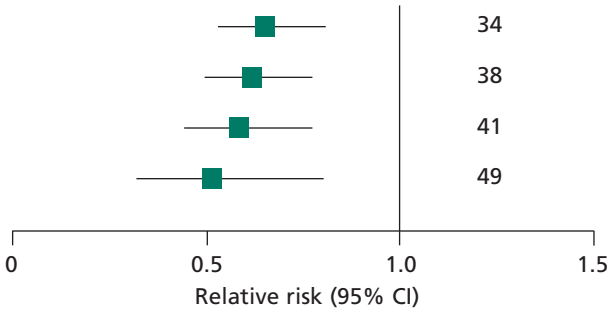


Table 2: Relative risk (95% CI) for total mortality, cardiovascular mortality, sudden death, and death from worsening heart failure in MERIT-HF.

Mortality	Number of deaths	Metoprolol CR/XL better	Risk reduction (%)
Total mortality	362		34
Cardiovascular mortality	331		38
Sudden death	211		41
Death from worsening heart failure	88		49



The main inclusion criteria were: age 40-80 years, symptomatic heart failure (NYHA class II to IV), ejection fraction ≤0.40 and heart rate ≥68 beats/min. The key exclusion criteria were MI within 28 days, planned cardiac transplantation, and use of the calcium channel blockers, diltiazem and verapamil.

The power calculation showed that the mean follow-up time had to be 2.4 years if 1600 patients were randomized to each treatment group during 14 months. This was based on a significance level of α=0.04 for all-cause mortality (intention-to-treat, α=0.01 was set aside for the second primary endpoint) and a power of at least 80% (ß≤0.20). The following assumptions were made: 9.4% annual mortality in the placebo group, mean risk reduction of 30%, withdrawal rate from study medication of 20% the first year and 5% annually.

An Independent Safety Committee monitored safety issues during the study. The predefined stopping rule for efficacy was based on all-cause mortality, analyzed on an intention-to-treat basis, with predetermined interim analyses taking place when 25%, 50%, and 75% of the expected total deaths had occurred. An asymmetric group sequential procedure was used. The cumulative probability of early stopping for benefit was 0.0036 and for harm was 0.015, based on log-rank statistics.

Fourteen countries participated in the study. As patient enrollment was faster than planned, 3991 patients were randomized during the recruitment period, effectively increasing the power of the study. The study was closed prematurely because the second pre-planned interim analysis (50% point) had shown that the pre-defined criteria for termination of study were met and exceeded.

An Independent Endpoint Committee whose members were unaware of treatment status classified all events according to pre-specified definitions using copies of medical records and other documents. Agreement between two members constituted a definite classification.

Results of the primary endpoint of total mortality have recently been published.[4] The rest of the results were presented at the XXIst Congress of the European Society of Cardiology and will be discussed in the following section.

MERIT-HF results: newly available data

The patients – 73% European and the rest from the United States – were randomized to placebo or metoprolol CR/XL. Over 75% of the patients were male and most had NYHA class II (41%) and III (56%) symptoms. Sixty-five percent had ischemic heart disease and 25% had a history of diabetes. ACEIs and diuretics were used in over 90% of the subjects. Most (80%) of patients with NYHA class II symptoms started at the higher dosage, whereas 72% of those with NYHA class III symptoms started with the lower. Target dosage was 200 mg daily.

Table 3: MERIT-HF: combined endpoints (time to first event)

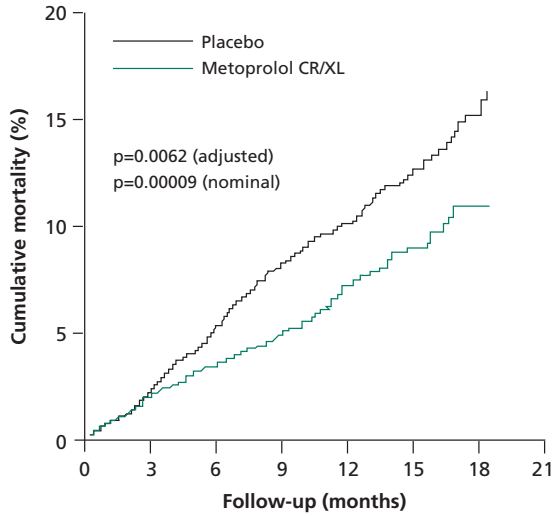
	Metoprolol CR/XL patients (N)	Placebo patients (N)	Risk reduction, 95% CI	P value
All-cause mortality and hospitalizations	641	767	19%, 10-27%	0.00012
All-cause mortality and CHF hospitalizations	311	439	31%, 20-40%	<0.00001
Death and transplant	150	218	32%, 16-45%	0.0002
Cardiac death and non-fatal MI	139	225	39%, 25-51%	<0.00001
All-cause mortality, CHF hospitalization and ER visits	318	455	32%, 21-41%	<0.00001

The median dose received was 159 and 129 mg for metoprolol CR/XL and placebo, respectively. Eighty-seven percent used dosages of metoprolol CR/XL up to 100 mg daily and 64% took up to 200 mg daily. The incidence of permanent drug withdrawal was low – 13.5% and 15.3% for metoprolol CR/XL and placebo, respectively, RR=0.9, 95% CI= 0.77-1.6.

The two primary endpoints of MERIT-HF were total mortality (powered for $p<0.05$) and a combined endpoint of mortality and all-cause hospitalizations (powered for $p<0.01$). Data for all-cause mortality have recently been published.[3] In brief, all-cause mortality was reduced by 34% in the metoprolol CR/XL group compared with the placebo group (145 versus 217 deaths, 95% CI 19-47%, nominal p=0.00009, p adjusted for interim analysis = 0.0062) (Figure 2); cardiovascular mortality was reduced by 38%, sudden death was reduced by 41%, and death from worsening heart failure was reduced by 49% (Table 2). Since publication, additional data on combined endpoints, NYHA functional class and quality of life data have become available. The combined endpoints (time to first event) are shown in Table 3. All-cause mortality and all-cause hospitalizations, the second primary endpoint, were reduced by 19% in the metoprolol CR/XL group. All-cause mortality and hospitalizations due to worsening heart failure were reduced by 31%. These treatment effects were consistent in pre-specified subgroups, including ischemic and non-ischemic etiology, NYHA functional class II and III, ejection fraction less than or > 0.25, male gender, age less than or > 69.4 years, with/without previous MI, diabetes and hypertension, heart rate less than or > 76 beats/min, systolic blood pressure less than or > 120 mm Hg, and diastolic blood pressure less than or > 74 mm Hg. In addition, the rate of hospitalizations due to cardiovascular causes was reduced by 16% (649 versus 773, p=0.029) and that due to worsening heart failure was reduced by 30% (317 versus 451, p=0.0013).

For the tertiary endpoints, NYHA functional class improved significantly from the examination at randomization to the last follow-up visit in the metoprolol CR/XL group compared to the placebo group (p=0.0028). The Overall Treatment Evaluation (OTE) questionnaire, an assessment of quality of life, was obtained in 741 patients. There was a significant overall

Figure 2: Kaplan-Meier curves of cumulative percentage of total mortality.



p value adjusted for two interim analyses.

improvement from baseline to the last follow-up visit relative to the placebo group (p=0.0089). Adverse events resulting in discontinuation of medications occurred in 1990 patients (4.9%) in the metoprolol CR/XL group and 2001 patients (7.3%) in the placebo group.

Conclusions

The results of MERIT-HF demonstrate that in patients with symptoms of heart failure and reduced ejection fraction, the addition of metoprolol CR/XL to conventional therapy decreases mortality, all-cause and heart failure hospitalizations as well as the pooled incidence of cardiac death and non-fatal MI. Metoprolol CR/XL also improves the clinical well-being of patients. MERIT-HF, together with the carvedilol studies and the CIBIS-II study,[3,18,20] clearly establish the evidence for a beneficial effect from ß-blockers in heart failure. However, most of the trials of ß-blockers in heart failure, including MERIT-HF, have involved only small numbers of patients with NYHA class IV symptoms. The role of these agents in patients with advanced heart failure therefore remains undefined. Hopefully, the ongoing COPERNICUS study will help to address this issue. Furthermore, the patients in ß-blocker trials have so far tended to be relatively young with documented systolic left ventricular dysfunction, whereas patients encountered in clinical practice tend to be older, with more co-morbid conditions and relatively preserved systolic function. Finally, it remains unclear whether the non-specific ß-blockers, such as carvedilol, would offer the same level of benefit as metoprolol or metoprolol CR/XL. The ongoing COMET trial will compare carvedilol to immediate-release metoprolol tartrate, but will not address the issue of comparison to metoprolol CR/XL. Not withstanding these caveats, ß-blockers will doubtless become, after ACEI, the next cornerstone of therapy for patients with heart failure.

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