MERIT-HF
MEtoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure

Background

In chronic heart failure, studies have shown that metoprolol improves cardiac function, left ventricular remodeling, capacity for physical exercise, and lessens the symptoms for heart failure. However, the survival benefit with metoprolol has not been proven.

Aim

To investigate whether metoprolol extended-release once-daily added to optimum standard therapy lowers mortality in patients with decreased ejection fraction and symptoms of heart failure.

Patient number

3991

Patient Characteristics

Patients with symptomatic chronic heart failure [New York Heart Association (NYHA) functional class II-IV], ejection fraction of 0.40 or less and stabilized with optimum standard therapy (combination of diuretics and an angiotensin converting enzyme inhibitor/ hydralazine/or angiotensin II receptor antagonist/ digitalis).

Treatment groups and dose titration

Metoprolol extended-release (12.5 / 25 mg once-daily) vs. Placebo. After 2 weeks, dose was titrated to 50 mg once-daily for 2 weeks, then increased to 100 mg once-daily for 2 weeks and finally up to the target dose of 200 mg once-daily. If up-titration of dose was not tolerated, either the drug dose was temporarily decreased or the diuretic dose was increased.

Primary endpoint

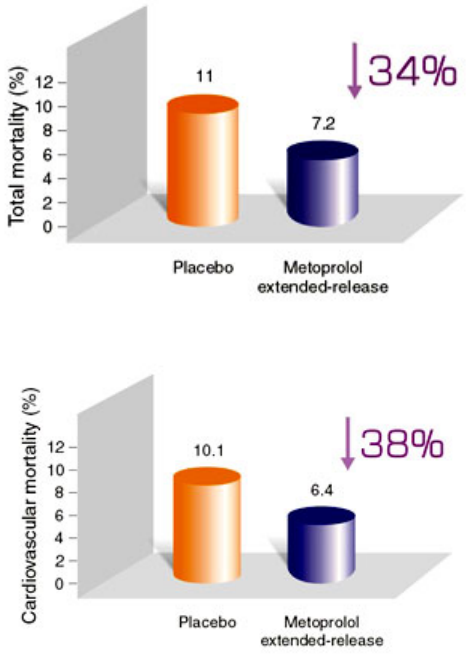
All-cause mortality

Study duration

Mean follow-up was 1 year

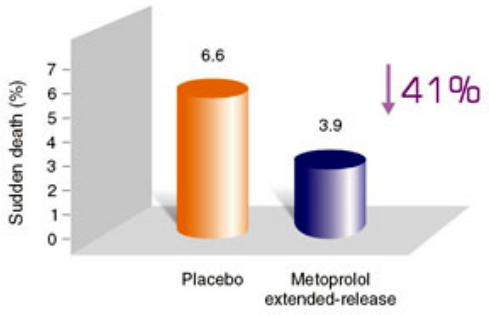
Results

1 Metoprolol extended-release significantly improved survival in chronic heart failure patients.

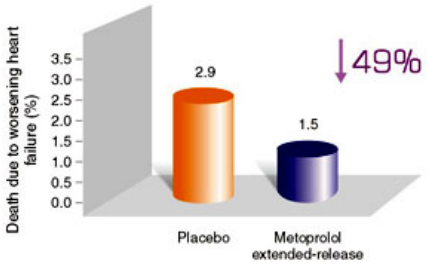


Addition of metoprolol extended-release to ACE inhibitor therapy significantly reduced the risk of sudden death and death due to worsening heart failure. It was equally effective across different subgroups of ejection fraction.

There is no consistent impact of angiotensin converting enzyme (ACE) inhibitor treatment on sudden death in chronic heart failure patients. Also, there is little/no survival benefit of ACE inhibitor treatment in chronic heart failure patients with ejection fraction > 0.30 (New Engl J Med 1991; 325: 293-302; New Engl J Med 1992; 327: 669-677).



This significant reduction in sudden death may be due to the antifibrillatory effect of metoprolol as ventricular fibrillation leads to a substantial proportion of sudden death.



2 Sudden death was more common among patients with a less severe degree of chronic heart failure (NYHA class II) whereas death from worsening heart failure increased with increasing severity of heart failure.

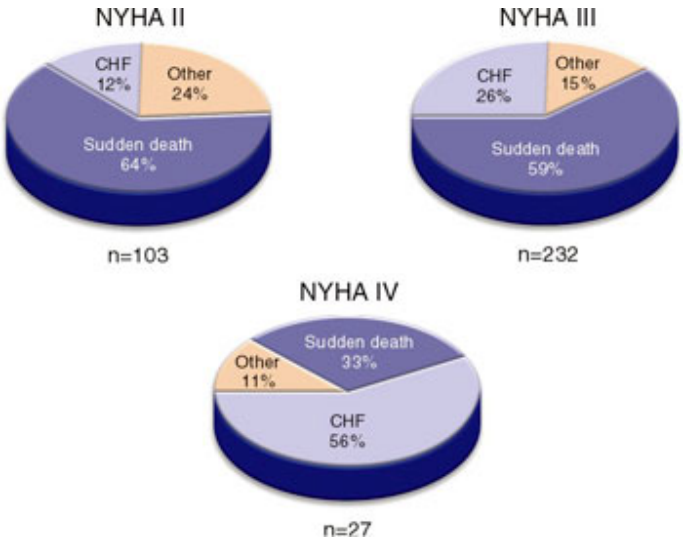


Figure: Severity of heart failure and mode of death, n=number of deaths.

3. Survival benefits with metoprolol extended-release were evident in all subgroups of patients.

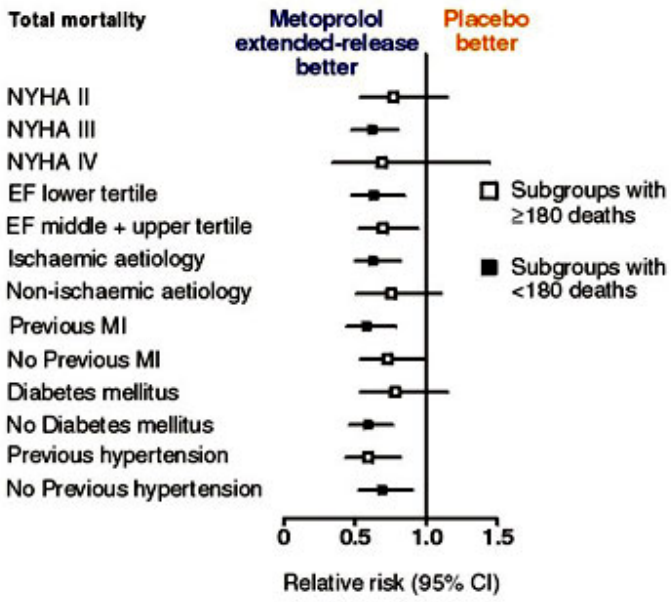


Figure: Relative risk for total mortality in predefined subgroups; EF = ejection fraction; MI = myocardial infarction

4. Total mortality in relation to the NYHA class in each treatment group was as follows:

Heart failure class	Metoprolol extended-release	Placebo
NYHA class II	44 (5.3%)	59 (7.1%)
NYHA class III	90 (8.11%)	142 (13.2%)
NYHA class IV	11 (16.7%)	16 (24.9%)

5. Heart rate reduced from baseline in both metoprolol extended-release (14 beats per min) and placebo (3 beats per min) groups. No difference was evident in the diastolic blood pressure in the two groups. Systolic blood pressure decreased less in the metoprolol extended-release group than in the placebo group (-2.1 vs. 3.5 mmHg). **This shows that metoprolol extended-release improved left ventricular geometry and function.**

6. Mean daily dose at end of study was 159 mg once-daily in the metoprolol extended-release group and 179 mg in the placebo group.

Dose	Patients (%)	
	Metoprolol extended-release	Placebo
≥ 100 mg once-daily	87%	91%
≥ 200 mg		

7. Metoprolol extended-release when added to standard therapy with diuretics and angiotensin converting enzyme inhibitors was well tolerated.

Conclusion

Treatment with once-daily metoprolol extended-release added to standard therapy improved survival and lowered the risk of sudden death and death from worsening heart failure in patients with mild to severe chronic heart failure secondary to left ventricular systolic dysfunction of ischemic or non-ischemic cause.

Reference :

Lancet 1999; 353: 2001-2007