

# The clinical benefits provided by trimetazidine (Vastarel® MR) in left ventricular dysfunction patients

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## Abstract

Metabolic treatment involves the use of drugs that improve cardiomyocyte function. Trimetazidine (Vastarel® MR) is the most investigated drug in this group with a well-established role in the treatment of chronic angina. The available data suggest that therapy combining trimetazidine and hemodynamic drugs is effective in patients with chronic heart failure, leading to additional benefits such as improvement in left ventricular function, exercise tolerance and quality of life. However, while trimetazidine has shown beneficial effects on surrogate endpoints in several small trials, its effect on cardiovascular events in chronic heart failure subjects needs to be confirmed in further large randomized studies.

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**Keywords:** Chronic heart failure, left ventricular function, metabolic therapy, trimetazidine

## Introduction

Despite treatment with conventional agents, a high proportion of patients with chronic heart failure (CHF) and left ventricular (LV) dysfunction continue to have symptoms and poor quality of life (QOL). Emerging evidence suggests that chronic heart failure is an “energy-deprived” state in which alterations in substrate metabolism of myocardial cells contribute to the development and maintenance of LV dysfunction [1]. Trimetazidine (TMZ) (Vastarel® MR) belong to a group of drugs called “metabolic modulators” that benefit CHF patients by modulating cardiac metabolism without altering hemodynamics. TMZ selectively inhibits the activity of long-chain 3-ketoacyl coenzyme A thiolase (3-KAT), the final enzyme of the fatty acid  $\beta$ -oxidation path.

This leads to a change in substrate energy, partially inhibiting  $\beta$ -oxidation of fatty acids and increasing glucose oxidation, which is more efficient with regards to adenosine- 5'-triphosphate (ATP) pro-

duction per molecule of oxygen consumed. This prevents intracellular acidosis and electrolyte disorders [2] and preserves energy necessary to sustain contractile function.

## Effects on left ventricular function

Several studies published in the last decade have demonstrated significant improvements of LV function during long-term administration of TMZ [3–8]. First observations were made in diabetic patients with ischemic CHF. In a small crossover trial an increase of LV ejection fraction from 36% to 45% was observed in the TMZ group compared with placebo, while exercise time did not change between the two groups [3]. In a similar population, Rosano et al. [4] observed a significant reduction of LV diastolic and systolic diameters (from 63 mm to 58 mm and from 41 mm to 34 mm respectively) and a significant increase of LV ejection fraction (+5.4% U) in the TMZ group, while

no significant changes were detected in the placebo group.

These results have been confirmed and amplified by a larger study reporting improvements in LV volumes, LV ejection fraction, and diastolic function in elderly subjects with post-ischemic CHF, most of whom had multi-vessel coronary disease and large areas of hibernating myocardium, with and without diabetes [5]. According to these data, it has been hypothesized that benefits of TMZ on LV function are related to its metabolic action leading to improved glucose utilization and optimization of myocardial energy metabolism even in the presence of chronic reduction of blood flow. Consequently, the structural and metabolic alterations of myocardial cells related to chronic ischemia may be reversed by TMZ, with a resulting improvement of the mechanical efficiency of areas of viable myocardium. Several studies have been published supporting this hypothesis. In 38 patients with ischemic LV dysfunction, Belardinelli et al. [6] evaluated the contractile response to low-dose infusions of dobutamine at baseline and after 2 months of treatment with TMZ or placebo. At the end of the follow-up period, TMZ significantly improved the rest and peak systolic wall thickening score index, LV ejection fraction, and peak oxygen uptake. The investigators concluded that the improvement in LV contractility was due to the recruitment of stunned or hibernating cells after optimal oxygen utilization by these cells. El-Kady et al. [7] obtained a similar result using gated single photon emission computerized tomography. In this study, there was a significant improvement of summed stress and rest scores, systolic wall thickness, and wall motion score index with TMZ compared with placebo. On the other hand the benefits of TMZ on LV function seem not to be limited to the group of CHF of ischemic origin. In a study by Fragasso et al. [8], ejection fraction significantly increased in patients treated with TMZ, regardless of the etiology of CHF. Tuunanen et al. [9] evaluated 19 patients with idiopathic dilated cardiomyopathy randomized to single-blind TMZ or placebo for 3 months. Interestingly in the TMZ group, EF was increased by 15% during the treatment, whereas in the placebo group, it decreased by 17%.

### **Exercise tolerance**

The usefulness of TMZ to improve the functional status and the exercise capacity of patients with ischemic cardiomyopathy has been assessed in several studies [7,9–12]. Improvements in exercise capacity have been evaluated by a six-minute walking test, change in New York Heart Association (NYHA) functional class, or an ergometric test.

In the study of Brottier et al. [3], 20 patients were randomized to either placebo or TMZ. At 6-month

follow-up, all patients on TMZ reported a considerable clinical improvement in symptoms such as angina and dyspnea, together with a 9% increase of LV ejection fraction. More recently, an Italian study obtained a similar result [5], with a reduced incidence of angina episodes and improvement in NYHA class after 6 months in the TMZ group compared with placebo.

Another trial enlisted 61 patients with a past history of myocardial infarction, a depressed LV ejection fraction (<40%), and coronary anatomy unsuitable for revascularization [10]. The authors demonstrated a significant improvement in functional status (evaluated by NYHA functional class) after 18 months of treatment with TMZ administered at standard doses. El-Kady et al. further confirmed these findings [7] in a larger study involving 200 patients with multi-vessel coronary artery disease and impaired LV function (LV ejection fraction <50%). Patients were randomized to TMZ or placebo in an open-label design, and after 24 months of treatment, the patients receiving TMZ had a significant reduction in the frequency of anginal episodes per week, a reduction in the weekly consumption of nitrate tablets, and a significant increase in treadmill exercise test duration (+75 s with TMZ versus +25 s with placebo,  $p < 0.01$ ).

In the study by Fragasso et al. [8], TMZ was associated with significant improvements in functional capacity assessed by ergometric test. The authors demonstrated a significant increase of peak metabolic equivalent system (from 7.4 to 8.8,  $p = 0.04$ ) and total exercise time (from 314 s to 402 s,  $p = 0.04$ ) in the TMZ group. Conversely, these parameters remained stable in the conventional therapy group. At the same time in the TMZ group there was a significant reduction in plasma natriuretic peptide levels compared with conventional therapy. Interestingly these improvements were equally apparent in patients with non-ischemic and ischemic cardiomyopathy. In another study [11], conducted in patients with stable ischemic CHF, the distance walked in 6 minutes significantly improved in the TMZ group, from 355 m at baseline to 417 m at the end of follow-up. Conversely, the distance walked decreased in the placebo group.

The improvement in exercise tolerance with TMZ may be secondary to its effects on LV systolic and diastolic performance. However, in the study of Di Napoli et al. [11], there was no significant change on LV diastolic and systolic diameter after 6 months of treatment in the TMZ group compared to placebo. Therefore, an additional mechanism of action such as a direct effect of TMZ on skeletal muscle should be taken into account. A recent study by Monti et al. [12] demonstrated that TMZ treatment in diabetic patients with ischemic cardiomyopathy improves forearm skeletal muscle metabolism.

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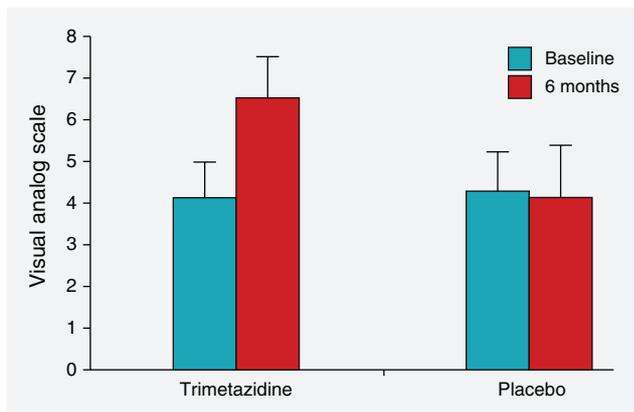


Figure 1. Changes (6 months vs. baseline) in visual analog scale observed in the TMZ and placebo groups.

### Quality of life

Currently, few data are available on the impact of TMZ on QOL. In the study of Vitale et al. [5], QOL, assessed by the visual analogue scale, significantly improved in all patients treated with TMZ, while it remained unchanged in those allocated to placebo. Fragasso et al. [8] assessed QOL with two tests: a visual analogue scale measuring the general well-being and an LV dysfunction questionnaire (LVD-36) in order to measure the impact of LV dysfunction on daily life. The authors showed a significant decrease in LVD-36 score (from 18 to 15,  $p=0.038$ ) and no significant increase of visual analogue scale, which went from 63% to 71% ( $p=0.07$ ). More recently, we investigated the effects of TMZ on different areas of QOL in elderly patients with ischemic dilated cardiomyopathy by using a self-administered questionnaire, the MacNew Quality of Life After Myocardial Infarction. We showed a significant improvement in physical and social areas in patients randomized to TMZ, but not in those allocated to placebo (Fig. 1) [13]. Benefits of TMZ on QOL could be related to several factors. First, in patients with ischemic CHF and recurrent angina, the increased well-being could be a consequence of its anti-angina effects. Moreover, the improvement in exercise tolerance and a direct action on skeletal muscle mass could play a role [14].

### Additional benefits

According to some recent studies, TMZ seems to have a broader spectrum of action at cardiac level than previously thought. TMZ improves several parameters related with the outcome of CHF patients. Gunes et al. [15] demonstrated that the addition of TMZ to optimal medical therapy in patients with CHF of ischemic

origin might improve heart-rate variability that is related to the improvement of LV ejection fraction. Cera et al. [16] showed that long-term treatment with TMZ can yield a significant reduction of Tpeak-Tend-d index, a noninvasive marker of dispersion of ventricular repolarization in post-ischemic CHF patients. A study by Belardinelli et al. [17] demonstrated that TMZ improved endothelium-dependent relaxation (EDR) in patients with ischemic cardiomyopathy. The authors postulated that EDR improvement was significantly related to an antioxidant effect of TMZ because they observed a concomitant reduction in plasma levels of some malondialdehyde and lipid hydroperoxides. Taken together these studies suggest that TMZ has additional mechanisms of action in CHF subjects.

### Conclusion

The available data suggest that therapy combining TMZ and hemodynamic drugs is effective in patients with CHF, leading to additional benefits such as improvement in LV function, exercise tolerance, and QOL. TMZ has shown beneficial effects on surrogate endpoints in several small trials. However, further large randomized studies are needed to answer the question of whether these effects could translate into decreased morbidity and mortality. ■

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