

# Clinical overview of trimetazidine (Vastarel MR) in patients with heart failure

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## Abstract

Myocardial energy metabolism may be normal in the early stages of heart failure but, as failure progresses, mitochondrial oxidative metabolism is reduced and glycolysis is increased, with downregulation of glucose oxidation. Reducing free fatty acid oxidation and a concomitant increase in glucose oxidation improve cardiac contraction and slow the progression of left ventricular failure. Trimetazidine (TMZ) acts as a partial inhibitor of fatty acid oxidation and in turn stimulates glucose oxidation. In several studies, treatment with TMZ was found to result in a significant improvement in functional ability, left ventricular function, and the remodeling process in non diabetic, diabetic, ischemic, and non ischemic left ventricular dysfunction. Therefore, there is a compelling argument to advocate the use of TMZ in addition to conventional evidence-based treatments in the management of heart failure.

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The failing heart has been described as an energy-starved organ. Through several mechanisms, modulation of cellular energetics has the potential to improve cardiac performance and reduce symptoms in patients with heart failure, without relying on alterations in hemodynamics or further modulation of neurohormones [1]. Inhibition of free fatty acid oxidation with trimetazidine (TMZ) shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase [2], which can decrease the consequences of recurrent ischemia, facilitating the maintenance of myocardial function and enhancing left ventricular performance [3]. By decreasing fatty acid oxidation, TMZ stimulates glucose utilization, restoring coupling between glycolysis and carbohydrate oxidation, and leading to the production of ATP with the consumption of less

oxygen [2]. It has also been demonstrated that TMZ has antioxidant properties and improves endothelial-dependent vasorelaxation in heart failure [4]. In conditions of high oxidative stress, such as chronic heart failure, production of free radicals is increased and contributes to endothelial dysfunction. In this setting, TMZ decreases plasma concentrations of both free radicals and endothelin-1\*. In addition, in patients with heart failure, improvement in the phosphocreatine (PCr)/ATP ratio has been observed in response to TMZ, indicating preservation of intracellular concentrations of myocardial high-energy phosphate [5]. These results deserve interest, especially in view of previous evidence suggesting the PCr/ATP ratio to be a significant predictor of mortality in the patients with heart failure [6]. Although the exact mechanism of action is not fully understood, experimental and clinical results have shown that TMZ has a number

of potentially useful cytoprotective features [3,7]: it has been reported to limit intracellular acidosis and the accumulation of sodium and calcium, preserve contractile function, and limit cytolysis and membrane damage caused by oxygen free radicals. Protection of the cell against the changes induced by oxygen deficit, by preservation of mitochondrial function and energy metabolism, may reduce ischemic left ventricular dysfunction [3].

To date, TMZ has been studied extensively in heart failure predominantly of ischemic origin [5,8–15]. Apart from the well known antianginal effect of TMZ [2,3,16], several clinical studies have demonstrated consistently that TMZ improves left ventricular function and quality of life in ischemic patients with left ventricular dysfunction [5,8,10–15]. The improvement in left ventricular function estimated by echocardiography has been confirmed in several short- or medium-term studies [10–13,17]. The first observation of functional benefit in patients with ischemic cardiomyopathy with TMZ came from Brottier et al [17]. Fragasso et al [12] and Rosano et al [13] reported a relevant improvement in clinical status and left ventricular ejection fraction after 6 months of treatment with TMZ in diabetic individuals with ischemic cardiomyopathy. This effect was associated with enhanced left ventricular diastolic filling and systolic function [12,13]. Belardinelli et al [11] demonstrated that, compared with placebo, 2 months of treatment with TMZ in 44 patients with ischemic cardiomyopathy resulted in a significant improvement in left ventricular ejection fraction at rest and enhanced left ventricular wall motion during dobutamine stress test in those with New York Heart Association (NYHA) class II–III heart failure.

In a blinded crossover study of 15 patients with chronic coronary artery disease, TMZ has been shown, not only to protect from dobutamine-induced ischemic dysfunction, but also to improve resting regional left ventricular function [10]. These results could indicate that TMZ may make the myocardium less vulnerable to ischemic myocardial dysfunction. In all studies, the beneficial effects of TMZ have been shown to occur without any significant changes in systemic hemodynamics as assessed by heart rate and arterial blood pressure [10–15,18]. The explanation for this is that TMZ does not depend on alterations in oxygen supply or demand, acting directly on the ischemic cell [18]. In addition, 6 months of treatment with TMZ in ischemic cardiomyopathy resulted in significant improvement in functional capacity associated with a relevant reduction in plasma concentrations of brain natriuretic peptide (BNP) [19]. The same was demonstrated in left ventricular dysfunction of various etiologies [14]. Taking into consideration that BNP is a marker of myocardial load, these findings confirm that treatment with TMZ has a positive effect on the neurohormonal pathway in patients with ischemic cardiomyopathy and reduces the cellular damage that characterizes chronic evolution of left ventricular remodeling [20]. Improvement in left ventricular remodeling by TMZ is noteworthy as, in the progression of heart failure, left ventricular remodeling is considered to be the pivotal mechanism linked to neurohormonal activation and contributing to the evolution from left ventricular dysfunction to irreversible heart failure [21] (*Figure 1*).

In patients with coronary artery disease, left ventricular dysfunction is the result of myocardial fibrosis, or hibernating and stunned myocardium [16].

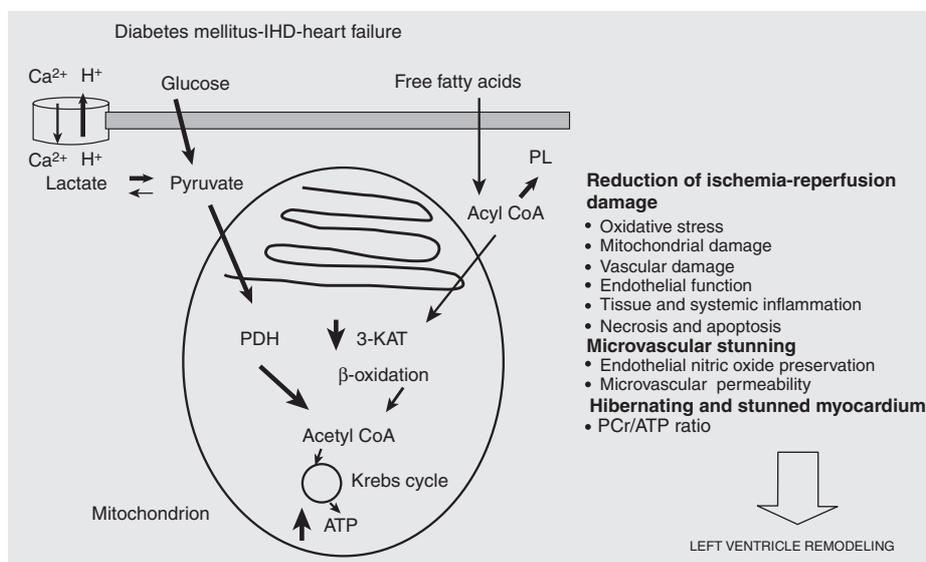


Figure 1. Biological and metabolic effects of trimetazidine in patients with ischemic heart disease [16]. CoA, coenzyme A; IHD, ischemic heart disease; 3-KAT, 3-ketoacyl coenzyme A thiolase; PCr/ATP ratio, phosphocreatine/adenosine triphosphate ratio; PDH, pyruvate dehydrogenase; PL, phospholipids.

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## Focus on Vastarel MR

### *Vastarel MR in patients with heart failure*

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The therapeutic management of hibernating and stunned myocardium is fundamental in ischemic cardiomyopathy, because they are potentially reversible conditions. In a recent study, a more marked improvement has been observed with TMZ in patients with more severe reversible perfusion defects at entry, suggesting that a crucial requirement for the effects of TMZ is the amount of ischemic/hibernating myocardium [22]. In the study by El-Kady et al [9] of 200 patients with ischemic left ventricular dysfunction as a result of multivessel coronary artery disease, the addition of TMZ to conventional treatment improved ischemic attacks clinically and also improved both exercise performance and perfusion as assessed by single photon emission computed tomography (SPECT). From the standpoint of viability testing, an important study was performed in 12 patients with previous myocardial infarction who underwent technetium-99m sestamibi SPECT and echocardiography before revascularization [23]. Patients taking TMZ showed a significant increase in tracer uptake, mainly in viable segments that improved function postoperatively [23]. These results suggest that viable ischemic segments benefit from treatment with TMZ. All these data could explain the reduction in left ventricular remodeling and the preservation of left ventricular function that are observed during treatment with TMZ.

Apart from the studies in ischemic heart failure, the effects of TMZ on cardiac performance and left ventricular function have been estimated in patients suffering from non ischemic dilated cardiomyopathy [14,24]. Fragasso et al [14] conducted a prospective, open-label, parallel group, randomized study comparing add-on TMZ against conventional treatment in 65 consecutive, mostly non diabetic and well-treated patients with symptomatic chronic systolic heart failure. The results were promising: TMZ was associated with significant improvement in functional capacity, quality of life, and plasma natriuretic peptide concentrations compared with conventional treatment; the improvement was equally apparent in patients with non ischemic and ischemic cardiomyopathy. The mean improvement in left ventricular ejection fraction was 7%, which is consistent with prior observations [25]. As in previous studies, TMZ was well tolerated and did not induce any hemodynamic changes [14]. In the more recent study by Tuunanen et al [24], TMZ was shown to improve left ventricular function in idiopathic dilated cardiomyopathy in which overt myocardial ischemia had been excluded. In addition, the positive effects of TMZ on left ventricular function were especially evident in patients with a high degree of  $\beta$ -blockade as estimated by a  $\beta_1$ -adrenoreceptor occupancy test, strongly suggesting a synergistic effect of these two modalities of treatment [23]. TMZ and  $\beta$ -blockers partially inhibit

different enzymes in the free fatty acid pathway [2,26], so their metabolic effects could be additive.

The finding that, in idiopathic dilated cardiomyopathy, TMZ decreases cardiac free fatty acid oxidation modestly, by only 10% [24], raises the possibility of additional mechanisms of action TMZ. In support of this, recent studies have found that TMZ improves whole-body insulin sensitivity and glucose control in insulin-resistant idiopathic dilated cardiomyopathy [26] and in diabetic patients with ischemic heart failure [12]. This is of particular note given the high prevalence of diabetes in patients with idiopathic dilated cardiomyopathy. Enhanced glucose metabolism improves cardiac function and prevents the development of systolic dysfunction in patients with diabetes [27]. Overall, such extracardiac metabolic changes may indirectly improve myocardial glucose metabolism and glycolysis with TMZ, amplifying the effects mediated by the modest decrease in free fatty acid oxidation observed in cardiac tissue.

Lately, in view of the positive effects of TMZ on left ventricular remodeling in patients with non ischemic cardiomyopathy, some authors have challenged the long-standing working hypothesis that TMZ counteracts the “metabolic switch” in the setting of myocardial ischemia [28]. However, the finding may be consistent with those of a prior study in animal models that suggested that there is a down-regulation of the enzymes of fatty acid oxidation; the switch to carbohydrate oxidation may be only a late-stage phenomenon in the heart failure phenotype, and may not be present in otherwise chronic compensated states [7]. Accordingly, the exact phenotype for those who had a response to TMZ remain to be clearly identified.

The question of whether TMZ has prognostic benefits in patients with heart failure needs to be addressed, given the evidence of an improved left ventricular ejection fraction in these patients. Various studies have provided evidence that TMZ could positively influence the prognosis and quality of life in patients with heart failure [14,16]. To date, reduction in cumulative events when TMZ was added to standard therapy has been reported in ischemic heart failure [8,9]. In the study by El-Kady et al [9], survival at 2 years was 92% among patients treated with TMZ and 62% among those treated with placebo. Clearly, this observation is of significance, given the poor prognosis in cardiac failure even when all evidence-based treatment has been deployed. In the post-hoc analysis obtained from the 48-month extension of Villa Pini d’Abruzzo Trimetazidine Trial, it was found that TMZ treatment reduced all-cause mortality and admission to hospital because of heart failure, improved NYHA functional class and exercise tolerance, and reduced left ventricular remodeling in ischemic heart failure [15].

## Summary

There is increasing evidence that TMZ, an approved drug for which there is long-standing clinical experience in treating angina, has the potential to improve cardiac performance and reduce symptoms in patients with heart failure, without relying on alterations to hemodynamics or further modulation of neurohormones. Agents acting via the “metabolic” approach are likely to complement modern pharmacotherapy, and hold a possibility for clinical benefit in patients with heart failure. Larger, long-term randomized trials with TMZ looking at clinically relevant outcomes such as overall mortality are warranted.

\* see glossary for definition of this term. ■

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