

# Clinical benefits of trimetazidine (Vastarel® MR) in the changing scenario of ischemic heart disease

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## Abstract

Despite many advances in medical therapy, ischemic heart disease (IHD) remains a major health challenge worldwide. Moreover, the prevalence of IHD is growing and physicians have to face an increasing number of challenges raised by the changing profile of the patients. Trimetazidine (TMZ) (Vastarel® MR), by specifically acting to improve cardiac energy metabolism, provides benefits complementary to those of classic hemodynamic therapy that, as a result, lead to greater clinical improvement across the wide range of ischemic heart diseases. This article addresses the relevance of a cardiac energetic approach with TMZ in the treatment of stable IHD by highlighting its major clinical benefits in several subsets of high-risk patients, who are encountered more and more frequently in everyday practice, namely patients with diabetes, left ventricular dysfunction, revascularization, and the elderly.

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**Keywords:** Cardiac energy metabolism, cardioprotection, diabetes, IHD, LV dysfunction, trimetazidine MR

## Introduction

Despite many advances in medical therapy, ischemic heart disease (IHD) remains a major health problem worldwide. Moreover, with the aging of the population and the worldwide epidemic of diabetes, the prevalence of IHD is growing and physicians have to face an increasing number of challenges raised by the changing profile of the patients [1].

Fortunately, advances in the understanding of the pathophysiology of IHD have helped identify new pharmacological targets increasing the optimization of medical therapy. Of special interest, increasing evidence implicates altered cardiac energy metabolism at every stage of IHD, from stable angina to heart failure [2–5].

Although conventional drugs for stable angina indirectly address the basic problem of an imbalance

between oxygen supply and demand, they do not act directly on energy metabolism in cardiomyocytes. This is addressed by the metabolic approach, which counteracts the deleterious consequences of ischemia by optimizing cardiac energy metabolism.

By specifically acting to improve cardiac energy metabolism, trimetazidine (TMZ) (Vastarel® MR) provides benefits complementary to those of classic hemodynamic therapy that, as a result, lead to greater clinical improvement across the wide range of ischemic heart diseases.

This article addresses the relevance of a cardiac energetic approach with TMZ MR in the treatment of stable IHD by highlighting its major clinical benefits in several subsets of high-risk patients, who are encountered more and more frequently in everyday practice, namely patients with diabetes, left ventricular (LV) dysfunction or revascularization, and the elderly.

### Trimetazidine MR: an anti-ischemic treatment particularly suited to diabetic coronary patients

Diabetic patients have exacerbated metabolic disturbances of ischemia, increased vulnerability to ischemia and early decreased myocardial performance compared with non-diabetics, thus a therapeutic approach designed to improve cardiac energy metabolism is very well suited to these patients.

TMZ MR shifts cardiac energy metabolism from free fatty acid oxidation to glucose oxidation by selectively inhibiting the mitochondrial long-chain 3-ketoacyl coenzyme A thiolase (3 KAT), which catalyzes the terminal reaction of fatty acid beta-oxidation [6]. A shift toward glucose oxidation is likely to be beneficial during ischemia because adenosine-5'-triphosphate (ATP) production per mole of oxygen consumed is about 12% higher when glucose is the energy substrate rather than fatty acids.

Also, by decreasing fatty acid oxidation and consequently re-activating the glucose pathway, TMZ MR prevents calcium overload and cell acidosis, and thus maintains cell homeostasis. In this way, ATP produced can mainly be used for contraction, so cardiac function is preserved.

Several studies in clinical practice have confirmed the major anti-ischemic and anti-anginal efficacy of TMZ MR in diabetic ischemic patients. In the DIETRIC study [7], which involved 580 diabetic patients with angina, a 6-month treatment with TMZ significantly reduced the incidence of angina episodes, improved results in the exercise tolerance test, and increased the time to ST-segment depression.

Moreover, a trial conducted with 24-hour ambulatory ECG monitoring showed that in diabetic coronary patients, treatment with TMZ significantly reduced the number of silent episodes of myocardial ischemia and the total duration of silent myocardial ischemia over 24 hours [8] (Fig. 1).

These results confirm the suitability of prescribing TMZMR to reduce not only symptomatic ischemic episodes, but also silent ischemia, a particularly important burden in diabetic ischemic patients.

In addition, TMZ MR has been shown in various trials to provide diabetic coronary patients with cardioprotective benefits by preserving their cardiac function, which is frequently impaired due to severe metabolic disturbances.

Fragasso et al. [9] studied the short- and long-term beneficial effects of TMZ in patients with diabetes and ischemic cardiomyopathy, and found that the drug consistently improved patients' functional capacity and LV function. These benefits were recently confirmed in a randomized double-blind study by using gated single-photon emission computed tomography myocardial scintigraphy. The results showed that TMZ

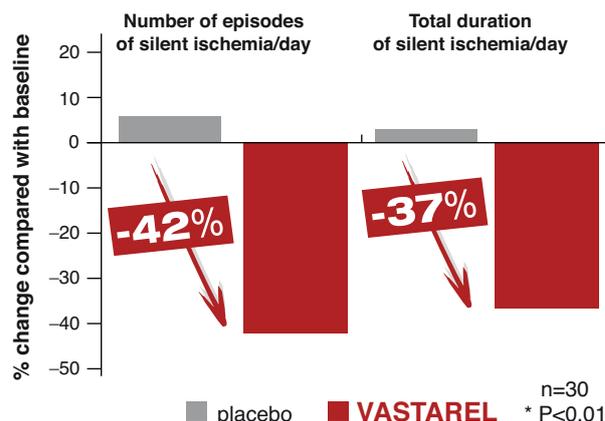


Fig. 1. Changes (6 months vs baseline) in number of episodes and total duration of silent ischemia/day in the TMZ and placebo groups.

significantly improved the left ventricular ejection fraction (LVEF) (by 16%,  $p < 0.007$  versus control group) and exercise tolerance (by 20.5%,  $p < 0.05$  versus controls) of diabetic patients with ischemic cardiomyopathy.

These improvements were even more marked in patients with more severe reversible perfusion defects on initial evaluation [10].

### Trimetazidine MR: clinical benefits in elderly ischemic heart disease patients

Elderly IHD patients have been shown to have a higher incidence of multivessel disease and silent ischemia than younger patients and often present a decrease in LV function. Furthermore, because of increased comorbidity and frequently atypical presentation of the disease, the diagnosis and management of elderly IHD patients is even more challenging. The clinical benefits of TMZ MR in elderly coronary patients have been confirmed in terms of efficacy, tolerability and improvement in quality of life.

The TRIMPOL I study confirmed the efficacy and acceptability of TMZ in a group of 71 elderly patients (age >65 years) with stable angina uncontrolled by other treatments [11]. The Trimetazidine In GERiatric patients (TIGER) multicenter study [12] in 141 angina patients aged 65 to 86 years showed similar results, with significant improvement in symptoms and exercise capacity in the TMZ treatment group. Finally, the study by Vitale et al. [13] showed the beneficial effect of TMZ in 47 elderly patients (average age, 78 years) with LV dysfunction and ischemic cardiomyopathy in comparison with placebo.

TMZ added to standard medical therapy significantly reduced angina attacks, and LVEF increased from 29% at baseline to 34.4% in the TMZ group, while no improvement was observed in the placebo group ( $p < 0.0001$ ).

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Moreover, a recent study by Marazzi et al. [14] assessed the effect of TMZ on the quality of life of elderly patients with ischemic cardiomyopathy. The overall assessment of quality of life using the visual analog scale showed a significant improvement in patients treated with TMZ (from 4.1 to 6.4,  $p < 0.01$ ), whereas no change was seen in patients receiving placebo.

In all these studies featuring frail patients, TMZ MR was well tolerated and safe. These additional attributes of TMZ MR ensure excellent compliance with treatment and contribute to the improvement in the quality of life of elderly patients.

### Trimetazidine MR: effective myocardial protection in revascularized patients

Patients who have undergone myocardial revascularization constitute a growing proportion of patients with stable angina. TMZ MR has a documented anti-ischemic effect during myocardial revascularization procedures. Administration of TMZ MR prior to an intervention, whether percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), results in a reduction in plasma troponin release indicating a significant reduction in ischemic reperfusion injury of the heart.

Bonello et al. [15] reported the beneficial effects of pretreatment with an acute loading dose (60 mg) of TMZ before percutaneous transluminal coronary angioplasty (PTCA) in 266 patients with coronary artery disease (CAD). Prior to intervention, 136 patients were randomly assigned to the Vastarel group, and 130 to the control group. Troponin I (cTnI) levels were measured before and 6, 12, 18 and 24 hours after PTCA. Post-procedural cTnI levels were significantly reduced in the TMZMR-treated group at all time points (6 hours:  $4.2 \pm 0.8$  versus  $1.7 \pm 0.2$ ,  $p < 0.0001$ ; 12 hours:  $5.5 \pm 1.5$  versus  $2.3 \pm 0.4$ ,  $p < 0.0001$ ; 18 hours:  $9 \pm 2.3$  versus  $3 \pm 0.5$ ,  $p < 0.0001$ ; and 24 hours:  $3.2 \pm 1.2$  versus  $1 \pm 0.5$ ,  $p < 0.0001$ ).

New data have come from Iskesen et al. [16], who investigated the protective effects of the preoperative use of TMZ MR on myocardial injury during open-heart surgery in a double-blind, parallel-controlled randomized study. Pretreatment with TMZMR in the treatment group began 2 weeks before the operation, while the control group did not receive this medication. The following biochemical markers were used to detect myocardial injury and therefore the degree of myocardial protection with TMZ MR: creatine kinase (CK), CK isoenzyme MB (CK-MB), troponin T, myoglobin and a lactate extraction calculation. The results show that post-operative levels of all these markers of myocardial injury were significantly lower in the Vastarel group than in the control group ( $p < 0.05$ ).

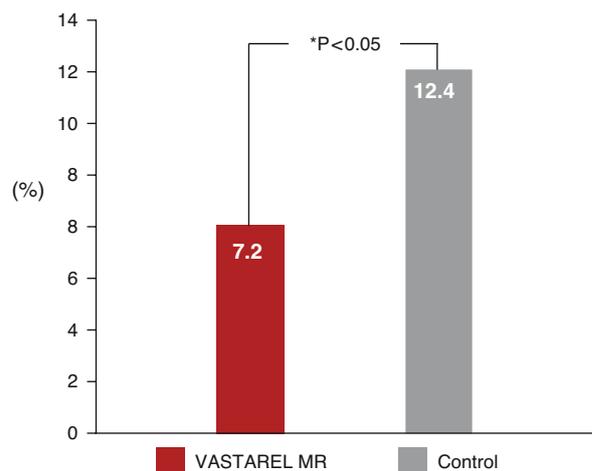


Fig. 2. Recurrence of angina episodes in patients treated with TMZ compared with controls (3-year follow-up).

Lately, a 3-year study [17] has been investigating the early and long-term effects of TMZ MR in 306 patients with CAD undergoing CABG. Patients in the treatment group were randomly allocated to receive TMZ MR 2 weeks prior to CABG, which was continued for 3 years ( $n = 153$ ); the trial included a control group without TMZ MR ( $n = 153$ ).

In the early post-operative period, significantly lower plasma levels of creatine phosphokinase (CPK) and MB-CPK were found in the TMZ MR group (6 hours after CABG). Over the 3 years of follow-up, recurrence of angina was significantly lower in the TMZ MR group than in the control group (7.2% versus 12.4%,  $p < 0.05$ ) (Fig. 2).

Treatment with TMZ MR was also associated with a 15% increase in LVEF ( $p < 0.05$ ) versus no change in the control group (+1.5%, NS).

These results complement those from a subgroup analysis of the TRIMPOL II study. Ruzzylo et al. [18] identified 94 patients with a history of revascularization for the treatment of CAD who were still symptomatic after 6 months in spite of treatment with metoprolol.

Compared with placebo, the 12-week treatment with TMZ MR significantly reduced the weekly number of angina attacks and nitrate consumption compared with placebo ( $p < 0.05$ ).

In all these studies conducted in patients undergoing revascularization, TMZ MR given prior to, during or after the intervention consistently had major anti-ischemic and cardioprotective effects.

### Trimetazidine MR: long-term cardioprotective benefits in patients with LV dysfunction

The presence of systolic LV dysfunction is a key event in the course of IHD patients, worsening the prognosis and requiring adapted management. Unfortunately, in

many patients (50%–60% of cases) systolic LV dysfunction is asymptomatic and thus sometimes diagnosed when already severe and irreversible.

Data from the INDYCE survey, which evaluated systolic LV function prospectively in 3119 patients with stable IHD patients ( $68.4 \pm 11.0$  years; 80% men), show that the prevalence of LV dysfunction is quite high, with one patient in 3 presenting with moderate to severe LV dysfunction (LVEF < 50%) [19]. It is therefore necessary to consider the preservation of cardiac function when treating IHD patients.

The crucial role of myocardial energetic deficiency in LV dysfunction and the pathophysiology of heart failure, and the consequent rationale for treating this energy deficiency clinically by metabolic modulation has gained more and more recognition [2–5]. Moreover, numerous studies have highlighted the beneficial role of TMZ MR in IHD patients with LV dysfunction in various patient profiles, with different evaluation parameters and in short- and long-term follow-up.

Very recently, a publication in *Heart* grouped most of these studies into a large meta-analysis, which confirmed the beneficial effect of TMZ on top of standard therapy, in patients with LV dysfunction, mainly of ischemic origin [20]. This meta-analysis, which included 955 patients from 17 studies, shows that TMZ MR treatment is associated with a significant improvement in symptoms, cardiac function and clinical outcomes in patients with LV dysfunction of ischemic or non-ischemic origin.

TMZ MR significantly increases LVEF in patients with both ischemic (weighted mean difference

(WMD) with placebo, 7.37%; 95% CI, 6.05 to 8.70;  $p < 0.01$  [Fig. 3]) and non-ischemic heart failure (WMD, 8.72%; 95% CI, 5.51 to 11.92;  $p < 0.01$ ). In addition, LV endsystolic volume was significantly reduced (WMD, 10.37 ml; 95% CI, 15.46 to 5.29;  $p < 0.01$ ) and New York Heart Association classification was improved (WMD, 0.41; 95% CI, 0.51 to 0.31;  $p < 0.01$ ), as was exercise duration (WMD, 30.26 s; 95% CI, 8.77 to 51.75;  $p < 0.01$ ).

Moreover, the results of subgroup analyses of long-term studies show that preservation of cardiac function with TMZ MR over time may have a potentially beneficial prognostic effect. Cardiovascular events and hospitalization data reported for four trials revealed a significant decrease in these conditions with TMZ treatment (RR, 0.42; 95% CI, 0.30–0.58;  $p < 0.01$ ).

## Conclusion

In the context of major modern cardiology issues with regard to the continuing increase in the number of high-risk ischemic patients, such as the elderly, diabetics and revascularized patients, the main aim of clinicians is to optimize patient management and patient well-being. Most of the agents used in the treatment of myocardial ischemia address the basic problem of an imbalance between oxygen supply and demand, while TMZ MR optimizes myocardial energy production by targeting cardiomyocytes directly.

That is why TMZ MR provides benefits that are complementary and synergistic to those of classic hemodynamic therapy, which lead to greater clinical improvement across a wide range of contemporary, high-risk subsets of patients, as a result. It is therefore a key player in the challenge of effectively managing the changing scenario of IHD. ■

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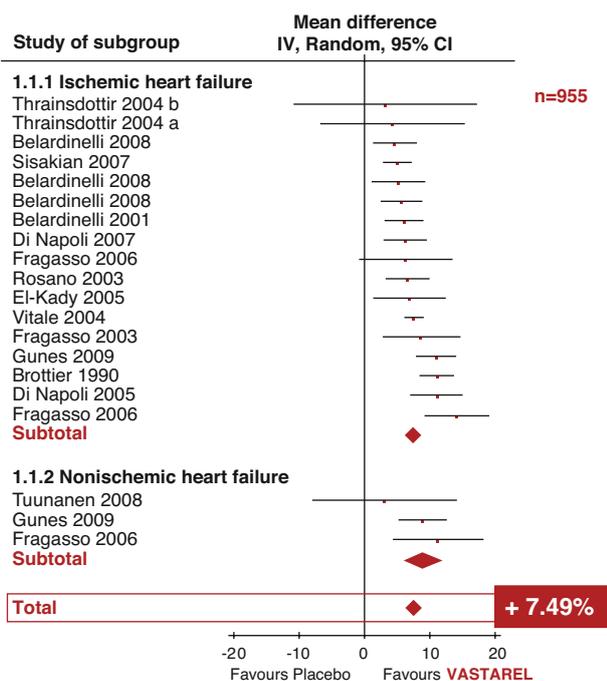


Fig. 3. Improvement in left ventricular ejection fraction in patients treated with TMZ.

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