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REVIEW ARTICLE

Defining the Role of Trimetazidine in the Treatment of Cardiovascular Disorders: Some Insights on Its Role in Heart Failure and Peripheral Artery Disease

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Abstract Trimetazidine is a cytoprotective drug whose cardiovascular effectiveness, especially in patients with stable ischemic heart disease, has been the source of much controversy in recent years; some have gone so far as to treat the medication as a ‘placebo drug’ whose new side effects, such as Parkinsonian symptoms, outweigh its benefits. This article is an attempt to present the recent key studies, including meta-analyses, on the use of trimetazidine in chronic heart failure, also in patients with diabetes mellitus and arrhythmia, as well as in peripheral artery disease. This paper also includes the most recent European Society of Cardiology guidelines, including those of 2013, on the use of trimetazidine in cardiovascular disease.

Key Points

Trimetazidine is well established in stable coronary artery disease

Preliminary evidence suggests that trimetazidine might be an effective drug in diabetic and non-diabetic patients with chronic heart failure and in those with peripheral artery disease

Trimetazidine has been generally well tolerated in clinical trials but some recently reported adverse drug reactions require careful evaluation in studies with longer follow-up

1 Trimetazidine Mechanism of Action

Trimetazidine is a cytoprotective drug that normalizes metabolic disturbances in low-flow ischemia via several—not yet fully understood—mechanisms of action. The best known trimetazidine mechanism of action is its capacity to inhibit β -oxidation of free fatty acid (FFA) [1]. FFA oxidation provides more energy, but it is associated with increased oxygen consumption. When oxygen is in low supply, the oxidative processes of FFA and glucose are disrupted—paradoxically leading to an increased rate of FFA β -oxidation associated with even greater oxygen consumption—while glucose metabolism decreases, which results in lactate accumulation and, in extreme cases, development of metabolic acidosis [1, 2]. By selectively inhibiting the enzyme long-chain 3-ketoacyl coenzyme A

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thiolase (LC 3-KAT), which is the final enzyme in the FFA β -oxidation pathway, trimetazidine increases the metabolic rate of glucose [2]. Trimetazidine also increases pyruvate dehydrogenase activity, which starts restoring homeostasis between glucose oxidation and glycolysis, imbalanced during ischaemia [1–3]. This results in decreased oxygen consumption during adenosine-5'-triphosphate (ATP) synthesis, hydrogen ion production, limited increase of intracellular acidosis, and reduced calcium ion accumulation [1, 3, 4]. Correcting energy insufficiency leads to reduced accumulation of sodium in cardiomyocyte cytoplasm, decreased formation of reactive oxygen species (ROS), and reduced neutrophil infiltration [5, 6]. This results in cellular membrane stabilization [7, 8].

Another trimetazidine mechanism of action that may be important for cardiovascular disease patients, including subjects with chronic heart failure (CHF), is its direct inhibition of cardiac fibrosis [9]. Compensatory cardiac hypertrophy eventually leads to fibrosis and heart failure (HF). This mechanism may be promoted by the connective tissue growth factor (CTGF), which has been confirmed in an experimental model in rats with valvular HF [9]. In comparison with placebo (physiological saline), trimetazidine reduced collagen accumulation, CTGF expression in cardiac fibroblasts, nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) levels, and ROS production [9]. The phenomenon of trimetazidine effects on endothelin 1 (ET-1) metabolism and release by non-selective blockade of ET-1 receptors has also been observed (still undocumented in clinical studies) (Table 1) [10].

Another trimetazidine mechanism of action, particularly relevant in acute myocardial ischemia, is an improved mechanical resistance of the sarcolemma [11, 12]. During reperfusion following an acute ischaemic episode, the sarcolemma is subjected to significant reoxygenation-induced mechanical stress due to tissue oedema. Increased sarcolemmal resistance of living cells in the reperfused

zone reduces the area of myocardial infarction-related necrosis, which protects myocardial cells against apoptosis [11, 12]. Trimetazidine may also restore mitochondrial function, impaired following ischaemia, since the trimetazidine binding site to the mitochondrial membrane has been identified. This confirms anti-ischaemic properties of the drug (Table 1) [13, 14].

2 Trimetazidine in Stable Coronary Artery Disease

Many patients with angina pectoris do not receive adequate antianginal therapy because of haemodynamic intolerance or chronotropic incompetence. Trimetazidine as an additional therapy may represent an optional treatment to be used in association with first-line antianginal drugs, especially in those patients for whom optimal control of symptoms cannot be achieved with other antianginal drugs. The TRIMetazidine in POLand (TRIMPOL)-II study [15], which was the continuation of the TRIMPOL-I study [16], the study by Sellier and Broustet [17] and the most recent—the VASCO (Efficacy of trimetazidine on functional capacity in symptomatic patients with stable exertional angina) study [18]—were the studies providing evidence generated in support of trimetazidine as an add-on to beta-blockers in symptomatic patients with angina pectoris. Two other studies by Manchanda and Krishnaswami [19, 20] and Manchanda [19, 20] supported the efficacy of trimetazidine as an additional therapy to calcium channel blockers.

In the double-blind, placebo-controlled TRIMPOL-II study, trimetazidine 60 mg/day was added to metoprolol (50 mg bid) for 12 weeks in a group of 426 patients with stable angina pectoris [15]. The authors observed a significant improvement in the trimetazidine group (as compared with placebo) for the following parameters: total exercise duration (+20.1 s, $p = 0.023$), total workload (+0.54 metabolic equivalents [METs], $p = 0.001$), time to 1-mm ST-segment depression (+33.4 s, $p = 0.003$), time to onset of angina (+33.9 s, $p < 0.001$), angina attacks/week (−0.73, $p = 0.014$), and the necessity of short-acting nitrates administration per week (−0.63, $p = 0.032$) [15]. The TRIMPOL-II study showed that trimetazidine added to metoprolol significantly improved exercise capacity and exercise-induced myocardial ischaemia. The efficacy was also confirmed in patients at maximal dose of metoprolol and in patients with recurrent angina [15]. In another important double-blind, placebo-controlled study, Sellier and Broustet evaluated the efficacy of trimetazidine modified release (MR) 70 mg/day in a group of 223 patients with angina pectoris who were insufficiently controlled with 50 mg/day of atenolol after 2 months of therapy [17]. After

Table 1 The main cytoprotective mechanisms of trimetazidine

FFA breakdown inhibition and glucose breakdown stimulation
Reduction in the amount of oxygen necessary for ATP production
Reduction in the cellular accumulation of lactic acid and H^+
Reduction in the cellular accumulation of Na^+ and Ca^{2+}
Reduction in ATP losses for maintaining ion homeostasis
Reduction of adverse effects of overloading cells with calcium
Anti-radical effect
Reduction of granulocyte infiltration to the ischaemic and reperfused area of the myocardium
Cardiomyocyte apoptosis inhibition

Adapted and modified from Banach [3]

ATP adenosine-5'-triphosphate, FFA free fatty acid

8 weeks, the authors observed a significant increase in the time to 1-mm ST-segment depression in exercise tests (+34.4 s, $p = 0.03$) in the trimetazidine group in comparison with the placebo group [17]. Finally, the above-mentioned VASCO study was the largest randomized controlled study conducted with trimetazidine [18]. The patients with stable angina receiving 50 mg of atenolol were randomized to the addition of trimetazidine MR 70 or 140 mg or placebo for a 12-week period. In the cohort of all chronic stable angina patients, trimetazidine significantly improved total exercise duration (TED) compared with baseline and placebo. Both doses of trimetazidine significantly increased TED ($p = 0.0044$ and $p = 0.0338$ for trimetazidine 140 mg/day and trimetazidine 70 mg/day, respectively). A greater TED improvement was observed in trimetazidine 140 mg/day than in trimetazidine 70 mg/day, although the difference was not significant. Amongst patients with limiting angina during exercise test, both doses of trimetazidine significantly improved both time to 1-mm ST-segment depression and TED [18].

The role of trimetazidine in angina pectoris patients was also analysed in the meta-analyses. In 2003, Marzilli and Klein [21] published the first meta-analysis of 12 trials including 868 patients. Trimetazidine was found to significantly increase exercise duration to 1-mm ST-segment depression on the exercise test, and to reduce weekly episodes of angina, both as monotherapy and as add-on therapy [21]. Ciapponi et al. [22] conducted a meta-analysis of 23 trials with 1,378 patients with stable angina. The authors showed that trimetazidine reduced the number of weekly angina attacks ($p < 0.0001$) and weekly nitroglycerine tablet consumption ($p < 0.0001$) and improved exercise time to 1-mm segment depression on the exercise test ($p = 0.0002$), compared with placebo [22]. In the largest meta-analysis conducted on the effects of trimetazidine in stable angina pectoris patients, Danchin et al. [23] evaluated 218 trials with a total 19,028 patients, including the results of the VASCO trial. Trimetazidine significantly improved exercise tolerance, weekly angina episodes, and use of short-acting nitrates when compared with placebo [23]. Finally, for the comparison of trimetazidine with other antianginal agents without an effect on heart rate, network meta-analyses were performed [24]. In these analyses, trimetazidine had similar anti-ischemic effects to dihydropyridines, long-acting nitrates, nicorandil, and ranolazine, both as monotherapy and as add-on therapy. The findings of this robust meta-analysis strongly supported the indication of trimetazidine as an effective agent for the management of stable angina [24]. These results also provided strong arguments for the position of trimetazidine in the current guidelines for the management of patients with stable angina (see below).

3 Trimetazidine in Chronic Heart Failure

Trimetazidine has a rather well documented effect on improving the left ventricular systolic and diastolic function, although properly designed and controlled large clinical trials with sufficient follow-up are still scant [17, 25, 26]. A number of available reports have also demonstrated clinical improvement in patients based on various parameters—improved exercise tolerance, improved quality of life, or reduced New York Heart Association (NYHA) HF class [25–28]. Brottier et al. [26] showed that 6-month therapy with trimetazidine at 20 mg three times a day in patients with NYHA class III/IV resulted in improved left ventricular ejection fraction (LVEF) by 9 % measured via radioactive isotope method, with simultaneous LVEF reduction by 16 % demonstrated in the placebo group ($p = 0.018$). Subsequent studies in CHF patients showed similar results [27–31]. Recent publications do little to challenge these results. The 2006 paper by Morgan et al. [32] based on an experimental HF model additionally demonstrated that 12-week treatment with trimetazidine reduced the levels of the atrial natriuretic peptide (ANP), another biomarker of HF, admittedly not measured in clinical practice. Fragasso et al. [33] assessed the effect of adding trimetazidine ($n = 20$) or placebo ($n = 27$) to conventional treatment in CHF patients followed for a mean period of 13 months. The trimetazidine group showed improvement in the NYHA HF class ($p < 0.0001$), left ventricular end-diastolic volume (LVEDV) (from 98 ± 36 to 81 ± 27 mL; $p = 0.04$) and LVEF (from 36 ± 7 to 43 ± 10 %; $p = 0.002$) [33]. Meanwhile, the placebo group showed deterioration of these parameters, with increased left ventricular end-systolic volume (LVESV) (from 142 ± 43 to 156 ± 63 mL; $p = 0.20$) and LVEDV (from 86 ± 34 to 104 ± 52 mL; $p = 0.10$) as well as reduced LVEF (from 38 ± 7 to 34 ± 7 %; $p = 0.02$). As emphasized by the authors, despite the small number of subjects enrolled in the study, the results suggest a beneficial effect of trimetazidine treatment; that is, inhibition of the natural course of CHF that involves gradual deterioration of cardiac function on conventional therapy alone [33]. In a subsequent study involving 50 patients with ischaemic cardiomyopathy, 25 patients were assigned to receive conventional treatment plus trimetazidine, while the remaining 25 patients constituted the control group [34]. After a 6-month follow-up, both groups achieved an insignificant reduction in NYHA class. The group receiving trimetazidine demonstrated a considerable reduction in brain natriuretic peptide (BNP) levels (135 ± 22 vs 252 ± 44 pg/mL; $p < 0.001$) and cardiac troponin T (cTNT) ($p < 0.001$), while the control group showed increased plasma BNP levels (288 ± 46 vs 239 ± 59 pg/mL; $p < 0.02$), with no significant changes in

cTNT levels. Trimetazidine administration also resulted in a significant improvement in exercise tolerance assessed with a 6-min walk test (6MWT) ($p < 0.01$); however, it was not associated with a significant improvement in LV systolic function (with LVEF values: $28 \pm 4\%$, $29 \pm 5\%$, and $32 \pm 5\%$, at baseline, after 1 month and 6 months, respectively) [34]. Similar results were achieved by Sisakian et al. [35], who achieved even more promising results of trimetazidine use in patients with ischaemic cardiomyopathy. A total of 82 patients were included in that study, with 42 patients (study group) receiving 35 mg trimetazidine twice a day for 3 months on top of their conventional treatment, and the remaining 42 patients constituting the control group. Exercise test-based physical capacity improved by 30 ± 20.7 m (from 215 ± 17.5 to 245 ± 20.7 m) in the trimetazidine group, versus 2.0 ± 18.85 m (from 208.2 ± 12.4 to 210.2 ± 14.2 m) in the control group ($p < 0.001$) [35]. An echocardiographic examination in the trimetazidine group showed improved LV systolic function (LVEF) by a mean of $3.5 \pm 6.72\%$ (to $38.0 \pm 4.8\%$ from the baseline value of $34.5 \pm 3.8\%$), with the improvement in the control group of only $0.8 \pm 8.06\%$ (to $33.2 \pm 5.8\%$ from the baseline value of $32.4 \pm 5.6\%$) ($p = 0.05$) [35]. Belardinelli et al. [36] additionally demonstrated the effect of trimetazidine in essentially improved endothelium-dependent LV relaxation, assessed on the basis of reduced levels of plasma malondialdehyde (MDA) (from 3.98 ± 0.69 to 2.15 ± 0.59 mmol/L) and lipid hydroperoxides (LOOHs) (from 3.72 ± 0.9 to 2.06 ± 0.6 mmol/L) in comparison with the placebo group ($p < 0.001$ for both), which constitutes some evidence for antioxidative properties of the drug [36].

A very interesting study was published by Tuunanen et al. in 2008 [37]. However, it was also very limited due to the small number of included patients. The Finnish group included 19 patients with dilated cardiomyopathy. A total of 12 patients were included in the trimetazidine group and seven patients from the control group received placebo. In comparison with the placebo group, the trimetazidine group demonstrated a greater improvement in LVEF (from 30.9 ± 8.5 to $34.8 \pm 12\%$; $p = 0.027$); moreover, interestingly, an 11% increase in high-density lipoprotein (HDL) levels and reduced insulin resistance reflected in lower blood glucose ($p = 0.047$) and blood insulin levels ($p = 0.031$). However, the power of that study was insufficient to discuss any possible effects of trimetazidine on the reduction of inflammatory processes or oxidative stress, and thus, on any changes in HDL functionality either [38–40]. In another study by Fragasso et al. [41] patients with LV systolic dysfunction ($n = 44$) were randomized to receive either conventional treatment ($n = 19$) or conventional therapy plus trimetazidine ($n = 25$). At 3 months of

follow-up, trimetazidine administration versus conventional treatment alone showed improved LVEF (from 35 ± 8 to $42 \pm 11\%$ and from 35 ± 7 to $36 \pm 6\%$, respectively; $p = 0.02$), reduced NYHA class ($p = 0.0001$) and improved quality of life ($p < 0.0001$). The use of trimetazidine also led to a reduced rate of energy expenditure (from $1,677 \pm 264$ to $1,580 \pm 263$ kcal/day; $p = 0.038$) [41].

Of note, the available data indicate that trimetazidine treatment may be particularly important in patients with CHF and concomitant diabetes mellitus [42, 43]. Similarly to the data presented in the paper by Tuunanen et al. [37], Fragasso et al. [29] demonstrated, by analysing 16 diabetic patients with ischaemic cardiomyopathy, that the use of trimetazidine 20 mg three times a day led to a significant reduction in fasting blood glucose compared with placebo after a 6- and 12-month follow-up (121 ± 30 vs 136 ± 40 mg/dL, respectively; $p = 0.02$ and 125 ± 36 mg/dL vs 140 ± 43 mg/dL; $p = 0.19$) with a simultaneous reduction in insulin resistance [20]. However, these results have not been confirmed in all available papers. Indeed, Swedish investigators demonstrated that the use of trimetazidine for over 1 month in diabetic patients with CHF NYHA class II or III failed to show superiority over conventional treatment [42]. Moreover, there were no statistically significant differences between trimetazidine and placebo groups in terms of exercise tolerance or LV function (LVEF assessment via tissue Doppler imaging at rest and on exertion showed only a slight change in favour of the study group) [42]. Despite being a randomized, double-blind, controlled study, like most of the earlier trimetazidine studies, it included only a very small group of patients ($n = 20$), hence the authors' statement should be treated with caution [42]. Conversely, Gunes et al. [43] demonstrated more beneficial effects. The authors emphasized the benefits of trimetazidine in terms of improved LV systolic function in patients with diabetes and ischaemic CHF. The paper demonstrated that the use of trimetazidine resulted in improved LVEF both in the diabetic ($n = 14$) and non-diabetic ($n = 37$) patients at 3 months of follow-up; however, the improvement of LV systolic function was significantly greater in the group with abnormal glucose metabolism ($p < 0.001$) [43]. The study consistently demonstrated beneficial effects of the drug, particularly in this group of patients. Nonetheless, there is still a question around the mechanism of action of trimetazidine that improves carbohydrate metabolism. Further studies are needed to ultimately determine whether such a relationship really exists. A very interesting suggestion was presented by a group of Chinese authors who believe that the use of trimetazidine at an early stage of abnormal glucose metabolism in the form of impaired glucose tolerance or even at the pre-diabetes stage may prevent

diabetic cardiomyopathy [44]. This results from the fact that patients with abnormal glucose metabolism have significantly reduced glucose and lactate metabolism as well as increased fatty acid β -oxidation [45, 46]. The use of trimetazidine at early stages of the disease could contribute to glucose metabolism normalization, and the drug itself could no longer be considered only in CHF treatment but also in diabetic cardiomyopathy prevention [44]. Naturally, these results must be confirmed in further studies.

Another important aspect is the effect of trimetazidine treatment on electrocardiographic changes in CHF patients and the associated reduction in electrophysiological risk factors of atrial and ventricular arrhythmias, including sudden cardiac death (SCD) [47–49]. Gunes et al. [47] described the effect of trimetazidine on sinus rhythm variability. Adding trimetazidine 20 mg three times a day to conventional HF treatment for 3 months in a group of 30 patients resulted in improved ambulatory 24-hour EKG parameters, such as the standard deviation of normal-to-normal R-R intervals (SDNN) (97.3 ± 40.1 to 110.5 ± 29.2 ms; $p = 0.049$) and standard deviation of the averages of normal-to-normal R-R intervals (SDANN) (80.5 ± 29.0 to 98.3 ± 30.5 ms; $p = 0.008$). Moreover, improved LV systolic function (increase in LVEF from 33.5 ± 5.1 to 42.5 ± 5.8 %; $p < 0.001$) and an increase in SDNN correlated with the increase in LVEF. In another study of the same authors [48], they presented the effect of 6-months' treatment with trimetazidine at 20 mg three times a day in CHF patients ($n = 36$) on the P-wave duration and dispersion—predictors of atrial fibrillation, which is a factor increasing postoperative mortality in patients undergoing coronary artery bypass grafting (CABG) [49]. The authors demonstrated that added to conventional treatment, trimetazidine results in reduced P-wave duration (from 106.7 ± 15.8 to 102.2 ± 11.5 ms; $p = 0.006$) and dispersion (from 57.2 ± 15.4 to 48.9 ± 10.1 ms; $p < 0.001$), with a decrease in left atrial size (from 41.5 ± 6.7 to 40.3 ± 6.1 mm; $p < 0.001$) and improved LVEF (from 32.7 ± 6.5 to 37.2 ± 5.5 %; $p = 0.036$). Zemljic et al. [50] described the effect of trimetazidine on the corrected QT (QTc) interval duration in patients with ischaemic CHF. This study included a total of 42 HF patients with NYHA class II and III, with 20 patients receiving the conventional treatment and 22 subjects receiving an additional 35 mg of trimetazidine two times a day. At baseline, the groups did not differ significantly in terms of the QTc intervals ($p = 0.62$); however, after 1 month of treatment, a statistically significant QTc interval reduction was observed only in the trimetazidine group (404 ± 36 ms; $p = 0.0002$) [50]. Cera et al. [51] studied the effects of trimetazidine on the change in QTc duration in CHF patients. The study included 13 patients receiving conventional treatment and 17 patients additionally

receiving trimetazidine. The QTc interval was significantly reduced in both groups, QT peak increased only in the control group, $T_{\text{peak}}-T_{\text{end}}$ dispersion ($T_{\text{p}}-T_{\text{e}}-d$) decreased only in patients receiving trimetazidine. Based on CHF aetiology, $T_{\text{p}}-T_{\text{e}}-d$ reduction was found to be statistically significant only in patients with underlying ischaemic CHF (65.00 ± 27.14 vs 36.67 ± 11.55 ms; $p = 0.001$). The authors emphasize that the trimetazidine mechanism of action responsible for this phenomenon is still unknown; nonetheless, they indicate the possible benefits of trimetazidine in this group of patients, such as a decreased incidence of ventricular arrhythmias [51].

None of the previous studies answered the question most burning to physicians—whether trimetazidine reduces overall mortality in CHF patients; that is, whether it is a drug that may prolong survival. A post hoc analysis of the Villa Pinid' Abruzzo Trimetazidine Trial [52] showed that, in comparison with conventional therapy alone, the addition of trimetazidine significantly reduced the hospitalization rate due to HF exacerbation (by 47 %; $p = 0.002$) and overall mortality (by 56 %; $p = 0.0047$) at month 48 of follow-up. Moreover, the trimetazidine group demonstrated improvement in LVEF ($p < 0.001$ at month 48 of follow-up), increased exercise tolerance and reduction in NYHA HF class [48]. However, the study was based on a small group of 61 patients and, therefore, was not powered enough to allow these results to be reliable [52]. In 2011, Gao et al. [53] published a meta-analysis which covered 17 randomized studies from the period between 1966 and May 2010, including a total of 955 patients with CHF. In comparison with placebo, trimetazidine administration was associated with increased exercise tolerance (weighted mean difference [WMD] 30.26 s; $p < 0.01$), NYHA class reduction (WMD 0.41; $p < 0.01$), improved LVEF in ischaemic HF (WMD 7.37 %; $p < 0.01$) and non-ischaemic HF patients (WMD 8.72 %; $p < 0.01$). Moreover, the use of trimetazidine in the group of CHF patients reduced the rate of CV events and hospitalizations (RR 0.42, 95 % CI 0.30–0.58, $p < 0.00001$), and most importantly, reduction in overall mortality was demonstrated (RR 0.29, 95 % CI 0.17–0.49, $p < 0.00001$) (Table 2). It must be emphasized that the studies included in that meta-analysis were insufficiently powered to assess the effect of trimetazidine on pre-determined endpoints, and therefore, the results of this meta-analysis must not be considered as decisive [53]. One year later, Zhang et al. [54] presented another meta-analysis on the use of trimetazidine in CHF patients. This time, 16 randomized studies were evaluated, with 884 patients in the study group. Like the earlier meta-analysis, this one demonstrated that the use of trimetazidine was associated with improved LVEF (WMD 6.46 %, $p < 0.0001$), increased exercise tolerance (WMD 63.75 s, $p < 0.0001$), reduced NYHA class (WMD -0.57 ;

Table 2 Major studies with trimetazidine use in CHF patients

Authors	Year	Materials and methods	Results
Gao et al. [53]	2011	17 randomized studies from the period between 1966 and May 2010; 955 CHF patients	In comparison with placebo, the use of trimetazidine results in: <ul style="list-style-type: none"> • Increased exercise tolerance (WMD 30.26 s, $p < 0.01$), • Reduced NYHA class (WMD 0.41, $p < 0.01$), • Improved LVEF in ischaemic HF (WMD 7.37 %, $p < 0.01$) and non-ischaemic HF patients (WMD 8.72 %, $p < 0.01$), • Reduced rate of cardiovascular events and hospitalizations (RR 0.42, 95 % CI 0.30–0.58, $p < 0.00001$), • Reduced overall mortality (RR 0.29, 95 % CI 0.17–0.49, $p < 0.00001$)
Zhang et al. [54]	2012	16 randomized studies; 884 CHF patients	Trimetazidine treatment results in: <ul style="list-style-type: none"> • Improved ejection fraction (WMD 6.46 %, $p < 0.0001$), • Increased exercise tolerance (WMD 63.75 s, $p < 0.0001$), • Reduced NYHA class (WMD -0.57, $p = 0.0003$), • Decreased LVESV (WMD -6.67 mm; $p < 0.0001$) and LVEDV (WMD -6.05 mm, $p < 0.0001$), • Lowered BNP levels (WMD -203.40 pg/mL, $p = 0.0002$), • Reduced rate of cardiovascular hospitalization (RR 0.43, $p = 0.03$) Trimetazidine continues to have no effect on overall mortality (RR 0.47, $p = 0.27$)
Fragasso et al. [55]	2013	A multicentre retrospective study; 669 CHF patients, including 362 patients receiving trimetazidine. Follow-up period: 38.76 ± 15.66 months in the trimetazidine group and 40.17 ± 15.53 months in conventional therapy alone group	Addition of trimetazidine in comparison with the conventional treatment alone is associated with: <ul style="list-style-type: none"> • Reduced rate of cardiovascular hospitalization (adjusted HR 0.524, 95 % CI 0.352–0.781, $p = 0.001$), • Reduced cardiovascular mortality (HR 0.072, 95 % CI 0.019–0.268, $p = 0.0001$), • Reduced overall mortality (HR 0.102, 95 % CI 0.046–0.227, $p = 0.0001$)

BNP brain natriuretic peptide, CHF cardiovascular heart disease, HF heart failure, LVEDV left ventricular end-diastolic volume, LVEF left ventricular ejection fraction, LVESV left ventricular end-systolic volume, NYHA New York Heart Association, WMD weighted mean difference

$p = 0.0003$), decreased LVESV (WMD -6.67 mm, $p < 0.0001$) and LVEDV (WMD -6.05 mm, $p < 0.0001$), lowered BNP levels (WMD -203.40 pg/mL, $p = 0.0002$), and reduced the rate of CV hospitalization (RR 0.43, $p = 0.03$). However, no reduction in overall mortality was observed (RR 0.47, $p = 0.27$) (Table 2) [54]. This meta-analysis had similar limitations to those of the analysis conducted by Gao et al. [53]. Very recently, in March 2013, Fragasso et al. [55] published the results of a large, multicentre, retrospective study, including 669 CHF patients (including 362 patients receiving trimetazidine). A follow-up of 38.76 ± 15.66 months in the trimetazidine group and 40.17 ± 15.53 months in the group receiving conventional therapy alone demonstrated that the addition of trimetazidine versus conventional therapy alone is associated with reduced CV hospitalization rate (adjusted hazard ratio [HR] 0.524, 95 % CI 0.352–0.781, $p = 0.001$), CV mortality (HR 0.072, 95 % CI 0.019–0.268, $p = 0.0001$), as well as overall mortality (HR 0.102, 95 % CI 0.046–0.227, $p = 0.0001$) (Table 2) [55].

Despite these important results presenting trimetazidine efficacy in CHF patients, we cannot recommend using trimetazidine in this group of patients as a result of the significant limitations connected with these studies—meta-analyses based on unpowered studies and the retrospective character of the analysis by Fragasso et al. A well designed, randomized clinical study, placebo-controlled, with well selected endpoints, appropriate patient group, and follow-up duration is still needed to possibly recommend the use of trimetazidine in HF patients.

4 Trimetazidine in Peripheral Artery Disease (PAD)

The benefits of using trimetazidine in peripheral artery disease have not been well documented and are based on individual studies. Several studies have reported a beneficial effect of this drug on extending the intermittent claudication distance [56–58]. One such study published in 2003 described anti-ischaemic effects of trimetazidine both

via coronary vessels (reduced rate of ischaemic attacks), and peripheral vessels (expressed exactly in the extended distance of intermittent claudication) [56]. The same effect was described by other authors in 2006; they observed a longer pain-free walking distance during an exercise test on ranolazine treatment [57]. In the recent double-blind study by Vitale et al. [58], 100 patients with intermittent claudication randomized to receive trimetazidine or placebo with a subsequent 3-month follow-up were included. During the study, the patients exercised regularly, and the assessment was based on measuring the length of maximal walking distance (MWD) and the assessment of ankle-brachial index (ABI), which were measured at baseline and after 3 months of treatment. In a comparison of the trimetazidine and placebo groups, the groups did not differ at baseline or at 3 months of follow-up in terms of ABI (0.83 ± 0.04 vs 0.85 ± 0.03), while the value of MWD at 3 months of treatment was decisively greater in the group receiving trimetazidine (23 vs 14 %, $p < 0.0001$). However, the study was based on a relatively small group of patients (although larger than in the previous reports) and the follow-up period was insufficient to unequivocally confirm beneficial effects of trimetazidine in this group of patients [58]. On the other hand, however, that study was the stepping stone to further trials on a larger group of patients, with a longer follow-up, to finally evaluate the potential role of trimetazidine in patients with atherosclerotic lesions in peripheral arteries.

Among other interesting studies on peripheral arteries, one noteworthy trial was conducted on an animal model, which demonstrated a protective effect of trimetazidine on retinal cells during ischaemia [59]. The authors showed that the thickness of the overall retina from the outer to the inner limiting membrane and outer retinal layers was significantly greater after 15 and 30 days of reperfusion in those rats that were treated with trimetazidine before the retinal ischaemia incident, induced by increasing intraocular pressure to 160 mmHg for 60 minutes [59].

Moreover, there has been a recent study [60] suggesting, based on experiments in diabetic rats, that the use of trimetazidine may decrease the intima-media ratio (IMR) in the carotid artery after only 4 weeks of treatment, and this effect was dose-dependent. In comparison with the control group, trimetazidine at 20 mg/kg/day caused a greater IMR reduction than at 10 mg/kg/day ($p = 0.046$ and $p = 0.002$, respectively). Moreover, trimetazidine was demonstrated to reduce the incidence of restenosis, via reduced smooth muscle cell proliferation and enhanced rate of endothelialization following a carotid artery injury due to balloon expansion during angioplasty, with the proliferation index of 34.2 ± 4.1 % in the control group, 29.4 ± 2.0 % in the trimetazidine 10 mg group, and 15.4 ± 3.2 % in the trimetazidine 20 mg group ($p < 0.01$) [60].

Based on these limited data, trimetazidine still cannot be recommended or any conclusion drawn as to its effectiveness in the treatment of peripheral artery disease. Nonetheless, these results are promising and they offer hope that some patients with peripheral artery disease could also benefit from this drug; however, this requires conducting further, large, and carefully designed studies.

5 Trimetazidine Adverse Drug Reactions

Trimetazidine has been generally very well tolerated in clinical trials and usually only isolated cases of adverse events (ADRs—adverse drug reactions) were observed during trimetazidine treatment (mainly gastrointestinal disturbances, vomiting, nausea) [61]. Some other very rare and reversible adverse effects have also been described, such as thrombocytopenia, agranulocytosis and liver dysfunction [62]. Other minor adverse effects (episodes of headache) were also reported. Most of them were not considered to be directly related to trimetazidine [62].

However, some recently reported ADRs require careful evaluation in longer follow-up. The main identified trimetazidine-induced serious ADR is connected to Parkinson syndrome and related symptoms (tremor) [61]. According to available data, trimetazidine may worsen previously diagnosed Parkinson's disease and gait disorders in some patients [61]. In the study of Martí Massó et al. [61], in 56 of the 130 patients who were treated with trimetazidine (43 %), an adverse effect on motor function was detected that had been induced or aggravated by one of the withdrawn drugs. Drug-induced parkinsonism was detected in 20 of these patients (10 patients were being treated with trimetazidine only, while the remaining 10 were simultaneously receiving other drugs potentially capable of inducing parkinsonism). Treatment with trimetazidine worsened previously diagnosed Parkinson's disease in 12 patients, and gait disorders coupled with disequilibrium was observed in 15 patients. Trimetazidine induced tremor in nine patients [61].

The risk related to Parkinson syndrome that has been identified in the postmarketing setting and in literature is based on positive dechallenge of Parkinson symptoms after the withdrawal of trimetazidine only, positive rechallenge, essentially higher co-prescription of antiparkinson drugs in trimetazidine group compared with control group and significantly higher number of patients that begin antiparkinson drugs after the introduction of trimetazidine compared with control group [24]. It is worth emphasizing that extrapyramidal symptoms reported in patients receiving trimetazidine have a very low prevalence (incidence of 0.36/100,000 person-years) and are generally reversible after trimetazidine withdrawal. According to the European

Medicines Agency (EMA), if trimetazidine-related parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist's opinion should be sought [24]. Parkinsonian symptoms (tremor, akinesia, hypertonia) should be regularly investigated, especially in elderly patients on trimetazidine. Patients receiving the treatment over a very long time, mainly in cardiology indications, aged more than 75 years old are from the group at the highest risk of this complication occurrence. They may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with severe renal impairment (creatinine clearance <30 ml/min), trimetazidine should not be used [24].

6 ESC Recommendations on the Use of Trimetazidine in Cardiovascular Disease

The European Society of Cardiology (ESC) guidelines of 2013 take into consideration the possibility of using trimetazidine as treatment for stable coronary artery disease—however, this is a IIb recommendation [63]. The current recommendations do not consider this treatment in other cardiovascular diseases, such as CHF [64], acute coronary syndromes [65, 66], or peripheral artery disease [67].

7 Conclusions

The most documented effect of trimetazidine has been in stable coronary artery disease, which has been demonstrated by inclusion of this drug into the recommendations, as well as in both diabetic and ischaemic CHF, which still requires confirmation in large clinical studies. There are still no answers to key questions as to the role of this drug in selected cardiovascular conditions as well as whether this drug can reduce mortality in any group of patients with cardiovascular disease [68–72].

Conflict of interest Dr Banach, Dr Chrusciel and Dr Rysz have no conflicts of interest to declare.

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