Research Article

Effectiveness and safety of anti-ischemic trimetazidine in patients with stable angina pectoris and Type 2 diabetes

Journal of Comparative Effectiveness Research

Zsófia Meiszterics[1,3], Attila Kónyi[1,3], Gábor Hild[2], Zsolt Sárszegi[‡,1,3] & Balázs Gaszner[*,‡,1,3]

[1]Coromed Kft., Private Cardiology Practice, Pécs, Hungary

[2]Institute of Biophysics, University of Pécs, General Faculty of Medicine, Pécs, Hungary

[3]Heart Institute, University of Pécs, General Faculty of Medicine, Pécs, Hungary

* Author for correspondence: Tel.: +36 204 984 004; Fax: +36 727 81462; gaszner.balazs@pte.hu

‡ Authors contributed equally

Aim & methods: This 6-month prospective, observational, noninterventional, open-label clinical study assessed the effectiveness/safety of trimetazidine in 737 patients with stable angina pectoris and Type 2 diabetes mellitus (OGYI/51534–1/2014). **Results:** Trimetazidine-based therapy was effective in stable coronary artery disease, with significant improvements from baseline ($p < 0.05$) in: number of angina attacks/week (2.9 ± 2.4 vs 1.1 ± 1.6), angina severity (Canadian Cardiovascular Society Classification 1.9 ± 0.8 vs 1.2 ± 0.8), exercise capacity (metabolic equivalents 6.1 ± 1.7 vs 6.5 ± 1.7), and exercise-induced myocardial ischemia (min 5.5 ± 2.5 vs 6.5 ± 2.6). **Discussion:** Trimetazidine treatment significantly ($p < 0.05$) improved glucose metabolism, lowered HbA1c (7.1 ± 1.1% vs 6.6 ± 1.0%), glucose levels (7.7 ± 2.1 mmol/l vs 6.9 ± 1.6 mmol/l) and decreased arterial stiffness (pulse wave velocity 11.2 ± 2.1 m/s vs 10.4 ± 2.2 m/s). In most patients, the tolerability of trimetazidine was rated as excellent to good, with a low incidence of adverse events.

First draft submitted: 12 February 2017; Accepted for publication: 20 June 2017; Published online: 17 November 2017

Keywords: stable coronary artery disease • trimetazidine • Type 2 diabetes mellitus

According to WHO statistics, cardiovascular diseases are the leading cause of mortality worldwide, and this is not expected to change in the near future [1]. In addition to their impact on mortality statistics, angina attacks occurring in patients with stable coronary artery disease (SCAD) also interfere with the patients' daily activity and eventually lead to an impaired quality of life (QoL). Patients with stable angina pectoris undergo life changes, and the pain, or merely the fear of pain, may render the patient physically inactive. In view of these factors, state-of-the-art therapy aims to slow down disease progression and alleviate symptoms. The 2013 European Society of Cardiology (ESC) guidelines on the management of SCAD propose the use of β-blockers, calcium-channel blockers, and short-acting nitrates as first-line treatments, combined with prophylactic medicinal products (e.g., aspirin, statins, ACE inhibitors) to alleviate the symptoms. If symptoms persist, long-acting nitrates, ivabradine, nicorandil and nonhemodynamic antianginal agents (ranolazine and trimetazidine-based therapy) are recommended [2].

Conservative estimates suggest that the global prevalence of diabetes mellitus is 8.5% in the adult population [3]. The most important complications of this disease include diabetic micro- and macro-angiopathy, and secondary ischemic heart disease. Based on these data, it is not surprising that cardiovascular diseases are the leading cause of death in diabetic patients. Epidemiology studies (DECODE, UKPDS) have demonstrated, that the coexistence of Type 2 diabetes mellitus (T2DM) and ischemic heart disease causes a twofold increase in mortality risk compared with nondiabetic patients with coronary disease [4,5].

Metabolic modulator properties of trimetazidine suggest that it may be useful for patients with T2DM, where energy production is shifted excessively toward the oxidation of fatty acids in ischemic myocardial cells [6–8]. The anti-ischemic effect of trimetazidine is well known and differs substantially from that of other hemodynamically acting agents [9]. Trimetazidine inhibits the oxidation of fatty acids by selectively blocking 3-ketoacyl-CoA thiolase, the enzyme involved in the β-oxidation of fatty acids in myocardial cells, and enhances glucose oxidation. Glucose

Future Medicine

oxidation requires less oxygen consumption in ischemic myocardial cells. Trimetazidine optimizes the energy utilization of myocardial cells, and maintains a proper energy supply during ischemia [9]. Other possible effects have also been proposed to explain trimetazidine's antianginal mechanism, including decreased production of superoxide free radicals; reduced neutrophil-mediated cardiac reperfusion injury; a direct effect on cardiac fast inward Na+ current; decreased cardiac levels of malondialdehyde (a biomarker for oxidative stress), leading to an improvement in endothelial function [10–16].

Several clinical studies have demonstrated the efficacy and safety of trimetazidine in patients with stable angina [17–19]. A meta-analysis of clinical studies conducted in recent years has shown that, of the measurable parameters, treatment with trimetazidine results in a significant improvement in systolic left ventricular function in patients with chronic heart failure, while reducing subjective clinical symptoms [20,21]. The DIETRIC study showed that, in patients with SCAD and coexisting T2DM, the addition of trimetazidine to standard prophylactic and symptomatic therapy significantly reduced the number of angina episodes and the use of short-acting nitrates, and increased the time to the onset of ischemia in the exercise tolerance test [22]. Until recently, however only two small studies have investigated the effect of trimetazidine on glucose metabolism in patients with T2DM and ischemic heart disease. Fragasso *et al.* found that glycated hemoglobin levels remained stable with trimetazidine, while they increased significantly with placebo at 6 months of treatment. In a similar, short-term (15 days) crossover study by the same group, trimetazidine decreased basal glucose and HOMA-IR levels [23,24].

Considering these results, recent ESC guidelines suggest that favorable data in patients with concomitant T2DM and SCAD are available for two nonhemodynamic antianginal agents: ranolazine and trimetazidine [2]. Beside the favorable effects of ranolazine on HbA1c levels in patients with T2DM, only scarce data and low patient sample sizes are currently available on the metabolic effects of trimetazidine in this cohort of patients. Also, it remains unclear how trimetazidine therapy affects inflammatory laboratory parameters; it is also unclear whether trimetazidine can delay the progression of T2DM and how it influences the development of diabetic cardiomyopathy when no documented heart failure exists.

The current large-scale study evaluated the effectiveness and safety of trimetazidine 35 mg administered twice daily in patients experiencing stable angina pectoris while receiving optimal medication. Our study is a 6-month, prospective, observational, noninterventional, open-label clinical study (OGYI/51534–1/2014), with the primary aim of determining the effectiveness of trimetazidine treatment in patients with SCAD and T2DM. Secondary objectives included an assessment of the safety and tolerability of trimetazidine therapy. In our assessment, we evaluated adverse events occurring after the initiation of therapy, their frequency, severity and the proportion of adverse events requiring treatment discontinuation.

Patients & methods

Patient selection

A total of 737 patients with angina pectoris and T2DM were included in the study at 76 sites in Hungary, with an investigator team of internists and cardiologists. Eligibility criteria for inclusion were: age >18 years; T2DM; stable angina pectoris, diagnosed by the clinician based on 2013 ESC guidelines [2], where the investigator decided to initiate treatment with trimetazidine 35 mg tablets (Moduxin® MR, Gedeon Richter, Budapest, Hungary) twice daily in addition to optimal medication; the patient was required to read and sign the patient information and consent form in advance.

Study exclusion criteria were: contraindications included in the trimetazidine (35 mg) Summary of Product Characteristics; heart failure (New York Heart Association stages III or IV); unstable angina pectoris; Parkinson's disease, extrapyramidal symptoms; severe renal impairment (creatinine clearance < 30 ml/min).

Study design, end points

This was a prospective, observational, noninterventional study. All patients included in the study were followed up for 6 months (three visits in total: baseline status, month 3 and month 6). The study end points were:

- Weekly frequency and severity (Canadian Cardiovascular Society Classification [CCSC]) of angina complaints and the amount of short-acting nitrate products used.
- Systolic left ventricular function and estimated left atrial filling pressure.
- Functional status on exercise tolerance test, time to onset of a 1-mm ST-depression, time to onset of angina.
- Changes in arterial stiffness parameters (pulse wave velocity [PWV], augmentation index [AIX]).

- Changes in HbA1c values.
- Clinician's global impression of change (CGIC).
- Documentation of adverse events and other safety parameters.

Study parameters

Pulse rate and blood pressure measurements were performed in accordance with professional guidelines after a 5-min rest period on two consecutive occasions, in the sitting position. Functional stage of angina was determined using the CCSC scale from I to IV [25]. The weekly frequency of short-acting nitrate use was recorded.

The following laboratory tests were performed, in accordance with applicable protocols, at visit one (patient enrollment) and visit three (month 6): blood glucose, HbA1c, serum urea, serum creatinine, GFR, SGOT, SGPT, CK, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, serum sodium, serum potassium, CRP, uric acid.

Echocardiography was used to determine global left ventricular systolic function ejection fraction (EF) and estimated left atrial filling pressure (E/Ea). Results of arterial stiffness (PWV and AIX) were recorded with an oscillometric, occlusive device (Arteriograph, TensioMed, Budapest, Hungary). An exercise tolerance test was used to assess functional status (metabolic equivalents; METs) and time to onset of angina or a 1-mm ST-depression. Each patient's clinical status at visits two and three was compared with that observed at the baseline visit; the change in medical condition was assessed by the clinician using the CGIC (on a scale from 0 to 7).

Medication used during the observational period

After inclusion in the study, patients received trimetazidine (Moduxin MR) 35 mg twice daily in addition to optimal antianginal medication. Patients with moderate renal impairment (creatinine clearance: 30–60 ml/min), received trimetazidine 35 mg once daily. After the final visit, patients continued to receive medication in accordance with professional guidelines.

Data recording

Patient data were recorded in accordance with the study protocol, on web-based electronic case report forms. The structure of the case report forms was created in accordance with applicable data protection and data management requirements, and the form of patient identification met the requirements on protection of privacy rights.

Statistical analysis

Collected data were processed in accordance with EU-GCP/ICH standards. In addition to standard analyses (mean, SD, median, *t*-test), statistical analysis of all clinical and laboratory data was performed using correlation calculations and variance analysis. Changes between the baseline and final visits are described using 95% CIs. In our statistical analyses, we considered a probability level of $p < 0.05$ as statistically significant.

Results

A total of 737 patients were included in the study. Patient demographic data are shown in Table 1. A total of 60% of patients (442 patients) had a history of cardiovascular or cerebrovascular events (acute myocardial infarction, percutaneous coronary intervention [PCI], coronary artery bypass graft, stroke, transient ischemic attack). In addition to stable angina pectoris, patients had the following comorbidities: hyperlipidemia (88%), hypertension (76%) and peripheral vascular disease (35%). The proportions of patients who received previous prophylactic or supportive therapies are presented in Table 1.

Effect of trimetazidine treatment on blood pressure & pulse rate

During 6 months of treatment with trimetazidine, clinically minor, but statistically significant reductions in systolic and diastolic blood pressure, and pulse rate were demonstrated compared with baseline values ($p < 0.05$; Table 2). All of these changes demonstrate a feature of observational studies that allows therapy adjustments during the study period, rather than the metabolic effect of trimetazidine treatment. Results indicating changes in hemodynamic parameters were obtained from data of patients who underwent adjustments of anti-ischemic treatment with a mainly hemodynamic effect (long-acting nitrates, β-blockers, calcium-channel blockers) or any other (antidiabetic, lipid-lowering or blood pressure lowering) therapy adjustments; therefore, data from such patients were excluded from the scientific evaluation. After closing the study, we processed data from 663 patients. In the analysis performed

Table 1. Descriptive parameters of patients included in the study.

Variable	Patients n = 737
Age (years), mean ± SD	69.4 ± 10.2
Male/female, n	358/379
Body weight (kg), mean ± SD	88.0 ± 18.3
Body height (cm), mean ± SD	167.3 ± 12.8
BMI (kg/m^2), mean ± SD	31.6 ± 4.3
Active smoking (%)	15
Quit smoking (%)	36
Hypertension (%)	76
Dyslipidemia (%)	88
Cardiovascular or cerebrovascular events (%)	60
Peripheral vascular disease (%)	35
ACE inhibitor/ARB (%)	85
β-blocker (%)	86
Calcium antagonist (%)	42
Diuretic (%)	25
Statin (%)	83
Aspirin, clopidogrel (%)	86

ARB: Angiotensin receptor blocker; SD: Standard deviation.

Table 2. Changes (mean ± standard deviation) in systolic and diastolic blood pressure, and pulse rate, during treatment with trimetazidine for 6 months.

Variable	Baseline visit	Month-3 visit	Month-6 visit	p-value
Systolic blood pressure (mmHg) n = 737	136.1 ± 19.2	131.5 ± 12.4	131.2 ± 10.6	<0.05
Diastolic blood pressure (mmHg) n = 737	86.4 ± 7.4	78.4 ± 8.5	78.1 ± 7.9	<0.05
Pulse (1/min) n = 737	74.6 ± 10.0	72.5 ± 8.6	71.8 ± 8.0	<0.05
Systolic blood pressure (mmHg) n = 663	136.0 ± 18.8	135.3 ± 11.8	135.6 ± 11.6	0.20
Diastolic blood pressure (mmHg) n = 663	86.2 ± 10.6	85.9 ± 9.7	85.8 ± 9.8	0.33
Pulse (1/min) n = 663	74.5 ± 10.1	74.3 ± 8.7	74.2 ± 8.9	0.41

on the basis of the above criteria, 6 months of trimetazidine treatment was not found to result in any significant change in hemodynamic parameters (systolic and diastolic blood pressure and pulse rate; see Table 2).

Effect of trimetazidine treatment on angina complaints & short-acting nitrate consumption

During trimetazidine treatment, the weekly frequency of angina symptoms showed significant reductions at visit two (month 3) compared with baseline, and there was a tendency toward further reductions during 6 months of treatment ($p < 0.05$). The severity of angina complaints, mean CCSC score, and short-acting nitrate consumption, all showed a clinically meaningful, significant improvement during the 6-month course of treatment with trimetazidine ($p < 0.05$; Table 3).

Effect of trimetazidine treatment on parameters of exercise tolerance test, echocardiography & arterial stiffness

Functional status METs and the time to onset of angina or a 1-mm ST-depression were assessed using an exercise tolerance test. The 6-month course of treatment with trimetazidine resulted in a clinically effective, significant improvement in all three parameters ($p < 0.05$; Table 3).

No significant change was observed in global left ventricular systolic function EF and estimated left atrial filling pressure (E/Ea) during the 6-month period of therapy ($p = 0.22$ and $p = 0.57$, respectively; Table 3). Parameters

Table 3. Changes (mean ± standard deviation) in study parameters during treatment with trimetazidine for 6 months.

Variable	Baseline visit	Month-3 visit	Month-6 visit	p-value
Number of angina complaints per week	2.9 ± 2.4	1.6 ± 1.8	1.1 ± 1.6	<0.05
CCSC	1.9 ± 0.8	1.4 ± 0.7	1.2 ± 0.8	<0.05
Number of nitrate doses used per week	1.8 ± 1.9	1.0 ± 1.1	0.6 ± 1.2	<0.05
Echocardiography EF (%)	55.9 ± 10.8	–	57.0 ± 9.8	0.22
Echocardiography E/Ea	9.0 ± 3.4	–	8.8 ± 3.0	0.57
Functional status (METs)	6.1 ± 1.7	–	6.5 ± 1.7	<0.05
Time to onset of ST-depression (min)	5.5 ± 2.5	–	6.5 ± 2.6	<0.05
Time to onset of angina complaints (min)	5.8 ± 2.3	–	6.4 ± 2.1	<0.05
Arterial stiffness PWV (m/s)	11.2 ± 2.1	–	10.4 ± 2.2	<0.05
Arterial stiffness AIX (%)	41.9 ± 9.6	–	41.0 ± 10.9	0.28

AIX: Augmentation index; CCSC: Canadian Cardiovascular Society Classification; E/Ea: Estimated left atrial filling pressure; EF: Ejection fraction; MET: Metabolic equivalent; PWV: Pulse wave velocity.

Table 4. Changes (mean ± standard deviation) in laboratory parameters during treatment with trimetazidine for 6 months.

Laboratory parameters	Baseline visit	Month-6 visit	p-value
Blood glucose (mmol/l)	7.73 ± 2.10	6.87 ± 1.56	<0.05
HbA1c (%)	7.13 ± 1.10	6.64 ± 0.96	<0.05
Total cholesterol (mmol/l)	4.93 ± 1.21	4.71 ± 1.02	<0.05
LDL cholesterol (mmol/l)	2.80 ± 0.94	2.58 ± 0.78	<0.05
HDL cholesterol (mmol/l)	1.24 ± 0.41	1.26 ± 0.40	0.76
Triglyceride (mmol/l)	2.11 ± 0.98	1.97 ± 0.70	<0.05
SGOT (U/l)	30.13 ± 14.23	30.11 ± 10.73	0.56
SGPT (U/l)	29.54 ± 13.60	30.17 ± 11.21	0.11
Urea (mmol/l)	7.50 ± 2.35	7.45 ± 2.07	0.29
Creatinine (mmol/l)	93.86 ± 29.17	90.65 ± 22.96	<0.05
Sodium (mmol/l)	140.02 ± 3.63	140.46 ± 3.35	0.55
Potassium (mmol/l)	4.36 ± 0.41	4.37 ± 0.39	0.66
CRP (mg/l)	7.42 ± 5.58	5.10 ± 5.01	<0.05
Uric acid (μmol/l)	343.79 ± 80.02	324.82 ± 69.77	<0.05

of arterial stiffness were also determined in a subgroup of 122 patients; PWV showed significant improvement, whereas the AIX remained unchanged ($p < 0.05$ and $p = 0.28$, respectively; Table 3).

Changes in laboratory parameters during trimetazidine treatment

During 6 months of treatment with trimetazidine, a significant and clinically meaningful 31% reduction in CRP, 11% in blood glucose, 7% in HbA1c levels, and a clinically minimal but statistically significant decrease in total cholesterol, LDL cholesterol, triglyceride, uric acid, and creatinine ($p < 0.05$) were shown; no significant change was observed in HDL cholesterol, SGPT, SGOT, urea nitrogen, potassium, and sodium levels (Table 4).

Effect of trimetazidine treatment on the extent of CGIC & tolerability

Trimetazidine therapy resulted in substantial (39.8%), moderate (30.2%) or mild (19.2%) improvement in CGIC questionnaire scores; a small proportion of patients had an unchanged status (8.5%) or minimal impairment (2.3%).

Adverse events

Out of 737 patients included in the study, 1.1% (8 patients) experienced treatment-related adverse events during 6 months of therapy. We recorded five cases of hospitalization: two cases of acute myocardial infarction treated with PCI, two cases of elective coronary angiography and PCI, and one case of atrial fibrillation. No deaths were reported in the study period. Trimetazidine therapy was discontinued in a total of three cases (hand tremor in two cases and gait disturbance in one case).

Discussion

In our clinical study we assessed the effectiveness and safety of trimetazidine in patients with SCAD and T2DM. In addition to the large number of patients, the strength of our study comes from the fact that the effectiveness of trimetazidine as a symptomatic anti-ischemic therapy was evaluated not only by assessing subjective parameters, but also via extended use of objective, noninvasive cardiology testing methods. According to our results, trimetazidine-based therapy proved to be effective in the vast majority of patients. The weekly frequency and severity of angina symptoms and the amount of short-acting nitrate consumption showed significant regression in terms of clinical symptoms; additionally, patients experienced improvements in QoL.

In addition to assessing subjective parameters, we used a noninvasive exercise tolerance test to demonstrate both a significant improvement in the functional status and an extension of the time to onset of provoked ischemia. Our results support the findings of previous clinical studies [17–19]. On echocardiography, no significant changes occurred in either systolic left ventricular function or estimated left atrial filling pressure during the 6-month course of treatment. In contrast to our results, previous clinical studies and meta-analyses demonstrated substantial improvement in EF [20,21]. However, these findings were obtained in a patient population with heart failure and a low baseline EF. Patients included in our study had good baseline systolic left ventricular function and estimated left atrial filling pressure, which explains the apparent contradiction with data in the literature. It is important to highlight that, according to our echocardiography results, no progression suggestive of diabetic cardiomyopathy was detected during 6 months of treatment with trimetazidine.

Until recently, only two small clinical studies and thus scarce data, have been available on the metabolic effects of trimetazidine in patients with concomitant T2DM and SCAD [23,24]. In patients with T2DM, insulin resistance also affects the myocardium. Reduced glucose uptake caused by insulin resistance results in a shift in energy production processes toward β-oxidation of free fatty acids, which is energetically less effective than glycolysis and results in absolute and relative ATP deficiency during ischemia. By selectively blocking the 3-ketoacyl-CoA thiolase enzyme, trimetazidine switches the energy substrate preference from fatty acid oxidation to glucose oxidation [9]. All these pathophysiological mechanisms lead to the improved glycemic status documented during trimetazidine therapy [23,24]. Based on available published literature, our study is the first large-scale clinical trial to investigate the long-term effects of trimetazidine on blood glucose and HbA1c levels in patients with SCAD and T2DM. In our study, significant positive changes were demonstrated in terms of blood glucose and HbA1c levels in patients with T2DM; moreover, this tendency to improvement was sustained during the 6-month course of trimetazidine treatment. In the long term, improving glycemic status may also have a beneficial effect on the occurrence of cardiovascular events. Cardiovascular and overall mortality have been evaluated in two meta-analyses, which currently show contradictory results [20,21]. In order to clarify this issue, large-scale, multicenter, placebo-controlled clinical studies are needed to evaluate the long-term effects of trimetazidine on mortality and major adverse cardiovascular events.

Arterial stiffness parameters, as predictors of vascular target organ damage, were also determined in a subgroup of patients (n = 122) in our study. In addition to increasing the effectiveness of energy production, the metabolic modulator properties of trimetazidine also stabilize intracellular phosphocreatine stores, decrease cellular acidosis and intracellular free calcium levels and protect against damage caused by free radicals. Based on fundamental research, all these pathophysiological mechanisms lead to an improvement in endothelial function [10–16]. Small-scale, placebo-controlled clinical studies with short-term observation periods yielded inconsistent results in terms of the effect of trimetazidine on endothelial dysfunction. A clinical study in patients with heart failure demonstrated a beneficial effect of trimetazidine on the progression of endothelial dysfunction, as measured by flow-mediated vasodilation [26]. Another study found that the regression of angina symptoms in patients with peripheral arterial disease was not accompanied by a positive change in endothelial dysfunction [27]. Our study is the first clinical trial to investigate the long-term effects of trimetazidine on parameters of arterial stiffness, in other words, PWV and AIX. PWV showed significant improvement during 6 months of trimetazidine treatment. AIX data showed no significant

change during the observation period. Previous studies revealed a significant impairment of arterial stiffness in patients with T2DM, measured as increased PWV, which reflects premature arterial damage. However, the clinical significance of AIX as a useful vascular stiffness marker in T2DM was not supported in these study designs [28–30]. Westerbacka *et al.* pointed out that insulin infusion significantly decreases the AIX, and thus hyperinsulinemia in T2DM consequently leads to unchanged AIX results [29–31]. Based on all of these data, contradictory results reported in the trimetazidine studies could be explained by the different durations of trimetazidine treatment (in this respect, our study is outstanding with its long observation period of 6 months), and the different characteristics of arterial stiffness parameters.

During the 6-month course of treatment with trimetazidine in our study, a significant decrease in CRP levels was observed, showing good correlation with findings from previous studies [32]. According to the meta-analysis of Zhou & Chen, the extent of decrease in CRP levels was dependent on variations in patient characteristics: a higher baseline CRP level was associated with a more pronounced CRP reduction [32]. This finding is also supported by the result of our subgroup analysis: patients with coexisting T2DM and peripheral arterial vascular disease had the most benefit from reduced CRP levels, which occurred at a significantly elevated baseline level. It should be noted that, in our study, of the laboratory parameters known to be independent risk factors, uric acid, triglyceride and total cholesterol levels showed a clinically moderate but statistically significant decrease during trimetazidine treatment. However, this effect is presumably not exclusively attributable to the metabolic modulator features of trimetazidine. During treatment, patients with stable angina pectoris undergo life changes involving an increase in physical activity owing to pain relief and an improved QoL. All these factors lead to a moderate (3.5%) reduction in body weight and secondary improvement in metabolic status, which was also demonstrated in our study, and further improves cooperation between the physician and patient, which in turn may also be reflected in improved medication adherence.

Treatment tolerability was considered to be 'excellent' or 'good' in the vast majority of patients, QoL showed significant improvements, and minimal overall impairment was only observed in 2.4% of patients. Treatment-related adverse cardiovascular events were observed in 1.0% of patients, representing a lower proportion compared with statistical data published in the ESC guidelines [2]. The frequency of adverse events affecting the nervous system (hand tremor, gait disturbances) was 0.26%, reflecting a very low incidence consistent with data reported in the literature, and proved to be reversible upon discontinuation of the medicinal product [33]. Also, it needs to be pointed out that patients with severe diabetic nephropathy or neurological symptoms (Parkinson's disease or motion disorders) were excluded from the study.

In summary, according to ESC guidelines and recently published expert documents, the medical treatment of stable angina has to be individualized taking into account comorbidities and risk factors [2,34,35]. In patients with SCAD and T2DM, the optimal antianginal agent should not only relieve anginal symptoms but also improve the glucose profile. Also, the choice of antianginal agents must suit the patient's hemodynamic status (optimal heart rate and blood pressure). In patients with systolic BP levels less than 120 mmHg, drugs with limited impact on BP are preferred. Also, in patients with a HR <60 bpm, drugs with no impact on HR are optimal. In these cohorts of patients, the nonhemodynamic antianginal agents, ranolazine at first- and second-line, and trimetazidine at third-line therapy, are recommended. Currently, trimetazidine may be viewed as a detrimental choice due to limited data for favorable metabolic effects in T2DM patients. However, based on the results of our clinical study and data reported in the published literature discussed above, we conclude that, in diabetic individuals, 6 months of trimetazidine-based therapy improved glucose metabolism, significantly lowered HbA1c and glucose levels, and it could be used effectively and safely in patients with SCAD and T2DM.

Limitations

This observational, multicenter study has several limitations consistent with the noninterventional design. No control group was used in this study; therefore, we cannot compare the effect and complications that occurred with trimetazidine with the effect of placebo treatment. However, our results reflect the situation in routine clinical practice, and the large patient size was adequate to provide representative results for evaluating trimetazidine efficacy and safety. Large-scale, long-term, placebo-controlled clinical trials (such as the ongoing ATPCI trial), assessing clinically relevant important outcomes, are required to refine the role of trimetazidine in clinical management.

Summary points

- Cardiovascular diseases are the leading cause of mortality worldwide and the main cause of death in individuals with diabetes.
- Anti-ischemic antianginal agents such as trimetazidine may be useful in patients with stable coronary artery disease (SCAD) and Type 2 diabetes mellitus (T2DM).
- In this 6-month, prospective, observational, noninterventional, open-label clinical study, we assessed the effectiveness and safety of trimetazidine in 737 patients with stable angina pectoris and T2DM.
- Trimetazidine-based therapy for 6 months was effective in SCAD, with significant improvements from baseline ($p < 0.05$) in: number of angina attacks/week (2.9 ± 2.4 vs 1.1 ± 1.6), angina severity (1.9 ± 0.8 vs 1.2 ± 0.8 [CCSC]), exercise capacity (6.1 ± 1.7 vs 6.5 ± 1.7 metabolic equivalents), and exercise-induced myocardial ischemia (5.5 ± 2.5 vs 6.5 ± 2.6 min).
- Trimetazidine-based therapy significantly ($p < 0.05$) improved baseline glucose metabolism, lowered HbA1c (7.1 ± 1.1% vs 6.6 ± 1.0%), glucose levels (7.7 ± 2.1 mmol/l vs 6.9 ± 1.6 mmol/l) and decreased arterial stiffness (PWV 11.2 ± 2.1 m/s vs 10.4 ± 2.2 m/s).
- The tolerability of trimetazidine was rated as excellent or good in the majority of patients, and the incidence of adverse events was low.

Acknowledgements

Data and information presented in the publication reflect the therapeutic practice used by the investigators. Richter Gedeon Nyrt. assumes no responsibility for any use of Moduxin® (Gedeon Richter) MR that deviates from the summary of product characteristics.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

The authors thank DP Figgitt, Content Ed Net, for providing medical writing assistance, with funding from Richter Gedeon Nyrt., Budapest, Hungary.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

1 WHO library cataloguing-in-publication data, World health statistics. ISBN 978 92 4 156526 4, (2016). www.who.int/gho/publications/world_health_statistics/EN_WHS08_Full.pdf

2 Task Force Members, Montalescot G, Sechtem U *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur. Heart J.* 34(38), 2949–3003 (2013).

3 Rydén L, Standl E, Bartnik M *et al.* Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur. Heart J.* 28(1), 88–136 (2007).

4 Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. *Diabetes Care* 16(2), 434–444 (1993).

5 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with Type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 281(21), 2005–2012 (1999).

6 Belardinelli R, Cianci G, Gigli M, Mazzanti M, Lacalaprice F. Effects of trimetazidine on myocardial perfusion and left ventricular systolic function in Type 2 diabetic patients with ischemic cardiomyopathy. *J. Cardiovasc. Pharmacol.* 51(6), 611–615 (2008).

7 Fragasso G, Salerno A, Spoladore R, Cera M, Montanaro C, Margonato A. Effects of metabolic approach in diabetic patients with coronary artery disease. *Curr. Pharm. Des.* 15(8), 857–862 (2009).

8 Padial LR. Clinical benefits of trimetazidine in patients with coronary artery disease and diabetes mellitus. *Heart Metab.* 45, 26–29 (2009).

9 Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. *Circ. Res.* 86(5), 580–588 (2000).

10 Guarnieri C, Muscari C. Beneficial effects of trimetazidine on mitochondrial function and superoxide production in the cardiac muscle. *Cardiovasc. Drugs Ther.* 4(Suppl. 4), 814–815 (1990).

11 Coetzee WA, Enous R, Opie LH. Trimetazidine: effects on delayed after depolarizations (DADs) and upstroke velocity of the action potential. *Cardiovasc. Drugs Ther.* 4(Suppl. 4), 806–807 (1990).

12 Guarnieri C, Muscari C. Effect of trimetazidine on mitochondrial function and oxidative damage during reperfusion of ischemic hypertrophied rat myocardium. *Pharmacology* 46(6), 324–331 (1993).

13 Tritto I, Wang P, Kuppusamy P, Giraldez R, Zweier JL, Ambrosio G. The anti-anginal drug trimetazidine reduces neutrophil-mediated cardiac reperfusion injury. *J. Cardiovasc. Pharmacol.* 46(1), 89–98 (2005).

14 Lavanchy N, Martin J, Rossi A. Anti-ischemic effects of trimetazidine: 31P-NMR spectroscopy in the isolated rat heart. *Arch. Int. Pharmacodyn. Ther.* 286(1), 97–110 (1987).

15 Lagadic-Gossmann D, Le Prigent K, Feuvray D. Effects of trimetazidine on pH regulation in the rat isolated ventricular myocyte. *Br. J. Pharmacol.* 117(5), 831–838 (1996).

16 Feener EP, King GL. Endothelial dysfunction in diabetes mellitus: role in cardiovascular disease. *Heart Fail. Monit.* 1(3), 74–82 (2001).

17 Szwed H, Sadowski Z, Elikowski W *et al.* Combination treatment in stable effort angina using trimetazidine and metoprolol: results of a randomized, double-blind, multicentre study (TRIMPOL II). TRIMetazidine in POLand. *Eur. Heart J.* 22(24), 2267–2274 (2001).

18 Szwed H, Pachocki R, Domzal-Bochenska M *et al.* Efficacy and tolerance of trimetazidine, a metabolic antianginal, in combination with a hemodynamic antianginal in stable exertion angina. TRIMPOL I, a multicenter study. *Presse Med.* 29(10), 533–538 (2000).

19 Vitale C, Spoletini I, Malorni W, Perrone-Filardi P, Volterrani M, Rosano GM. Efficacy of trimetazidine on functional capacity in symptomatic patients with stable exertional angina – the VASCO-angina study. *Int. J. Cardiol.* 168(2), 1078–1081 (2013).

20 Gao D, Ning N, Niu X, Hao G, Meng Z. Trimetazidine: a meta-analysis of randomized controlled trials in heart failure. *Heart* 97(4), 278–286 (2011).

21 Fragasso G, Rosano G, Baek SH *et al.* Effect of partial fatty acid oxidation inhibition with trimetazidine on mortality and morbidity in heart failure: results from an international multicentre retrospective cohort study. *Int. J. Cardiol.* 163(3), 320–325 (2013).

22 Rodríguez Padial L, Maicas Bellido C, Velázquez Martín M, Gil Polo B. A prospective study on trimetazidine effectiveness and tolerability in diabetic patients in association to the previous treatment of their coronary disease. DIETRIC study. [Article in Spanish]. *Rev. Clin. Esp.* 205(2), 57–62 (2005).

23 Fragasso G, Piatti PM, Monti L *et al.* Short- and long-term beneficial effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy. *Am. Heart J.* 146(5), e18 (2003).

24 Monti LD, Setola E, Fragasso G *et al.* Metabolic and endothelial effects of trimetazidine on forearm skeletal muscle in patients with Type 2 diabetes and ischemic cardiomyopathy. *Am. J. Physiol. Endocrinol. Metab.* 290(1), E54–E59 (2006).

25 Canadian Cardiovascular Society. Angina classification scale. www.ccs.ca/en/

26 Belardinelli R, Solenghi M, Volpe L, Purcaro A. Trimetazidine improves endothelial dysfunction in chronic heart failure: an antioxidant effect. *Eur. Heart J.* 28(9), 1102–1108 (2007).

27 Vitale C, Marazzi G, Pelliccia F *et al.* Trimetazidine improves exercise performance in patients with peripheral arterial disease. *Pharmacol. Res.* 63(4), 278–283 (2011).

28 Lenkey Z, Illyés M, Böcskei R *et al.* Comparison of arterial stiffness parameters in patients with coronary artery disease and diabetes mellitus using Arteriograph. *Physiol. Res.* 63(4), 429–437 (2014).

29 Lacy PS, O'Brien DG, Stanley AG, Dewar MM, Swales PP, Williams B. Increased pulse wave velocity is not associated with elevated augmentation index in patients with diabetes. *J. Hypertens.* 22(10), 1937–1944 (2004).

30 Westerbacka J, Uosukainen A, Mäkimattila S, Schlenzka A, Yki-Järvinen H. Insulin-induced decrease in large artery stiffness is impaired in uncomplicated type 1 diabetes mellitus. *Hypertension* 35(5), 1043–1048 (2000).

31 Zhang M, Bai Y, Ye P *et al.* Type 2 diabetes is associated with increased pulse wave velocity measured at different sites of the arterial system but not augmentation index in a Chinese population. *Clin. Cardiol.* 34(10), 622–627 (2011).

32 Zhou X, Chen J. Is treatment with trimetazidine beneficial in patients with chronic heart failure? *PLoS ONE* 9(5), e94660 (2014).

33 European Medicines Agency. European Medicines Agency recommends restricting use of trimetazidine-containing medicines (press release). (2012). www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/06/news_detail_001541.jsp&mid=WC0b01ac058004d5c1

34 Ambrosio G, Komajda M, Mugelli A, Lopez-Sendón J, Tamargo J, Camm J. Management of stable angina: a commentary on the European Society of Cardiology guidelines. *Eur. J. Prev. Cardiol.* 23(13), 1401–1412 (2016).

35 Manolis AJ, Poulimenos LE, Ambrosio G *et al.* Medical treatment of stable angina: a tailored therapeutic approach. *Int. J. Cardiol.* 220, 445–453 (2016).