

Clinical benefits of treating angina directly at the cardiac cell level with trimetazidine

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Abstract

Patients presenting with symptoms of angina and/or signs of ischemia may have no visible coronary stenosis on coronary angiography. Myocardial ischemia as a multifactorial process implies that anti-anginal management should not solely focus on large coronary vessels, but also on the microvessels and cardiac cells. Trimetazidine is an effective and well-tolerated anti-ischemic agent that provides symptom relief and functional improvement, and that offers cytoprotection during ischemia. It has anti-ischemic and antianginal effects directly on cardiac cells. The drug is suitable for use as a monotherapy and also as an adjunctive therapy when symptoms are inadequately controlled by nitrates, β -blockers, or calcium antagonists. Trimetazidine does not affect hemodynamic variables; it may improve left ventricular function in patients with chronic coronary artery disease or ischemic cardiomyopathy and in ischemia during percutaneous coronary intervention or coronary artery bypass grafting. According to the 2013 European Society of Cardiology (ESC) guidelines for the management of stable coronary artery disease, trimetazidine is indicated as a second-line treatment for angina/ischemia relief. In the 2016 ESC guidelines on diagnosis and treatment of heart failure, trimetazidine is considered for the treatment of stable angina pectoris with symptomatic heart failure with reduced ejection fraction. ■

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Introduction

Patients presenting with symptoms of angina and/or signs of ischemia may have no visible coronary stenosis on angiography. In a large registry of 398 978 patients undergoing elective invasive angiography, 37.6% of those without known

heart disease had no obstructive coronary artery disease (CAD).¹ In addition, the analysis of 304 stable angina patients revealed normal or near normal coronary arteriograms in 47%.² Acetylcholine testing triggered epicardial or microvascular coronary spasm, suggesting abnormal coronary vasomotion, in nearly two-thirds of these patients.³

Abbreviations

CABG: coronary artery bypass grafting; **CAD:** coronary artery disease; **CLASSICA:** the Most Effective Combination of Antianginal Drugs in the Treatment of Patients with Stable Angina; **HF:** heart failure; **LV:** left ventricular; **LVEF:** left ventricular ejection fraction; **PCI:** percutaneous coronary intervention; **RITA-2:** second Randomized Intervention Treatment of Angina; **TACT:** Trimetazidine in Angina Combination Therapy; **TRIMPOL II:** second TRIMetazidine in POLand study; **TRIUMPH:** TRImetazidine MR in patients with stable angina: Unique Metabolic PatH; **VASCO:** Efficacy of Trimetazidine on Functional Capacity in Symptomatic Patients with Stable Exertional Angina

On the other hand, when coronary stenoses are documented, a wide variety in the severity of symptoms, exercise intolerance, and stress echo test findings may be demonstrated.² Long-term follow-up studies have shown that patients with coronary stenosis and evidence of ischemia have more adverse events, a poorer quality of life, and higher mortality than those without evidence of ischemia.⁴

Medical therapy is the mainstay of treatment of stable angina. In the Euro Heart Survey, results from the analysis of 3779 patients with stable angina confirmed that the use of antianginal medications was similar or even greater in patients undergoing coronary revascularization. Only 3% of these patients received no antianginal medication, whereas 55% had two medications, and an additional 20% had more than two.⁵ In addition, in the RITA-2 trial (second Randomized Intervention Treatment of Angina) comparing a medical strategy with percutaneous coronary intervention (PCI) in patients with stable coronary disease, 5-year follow-up showed that 70% of patients with coronary angioplasty received more than one antianginal drug.⁶ These data indicate that in patients with stable CAD, antianginal medications are clinically justified, despite the use of myocardial revascularization procedures.

Therefore, besides coronary obstruction, there are other mechanisms influencing myocardial oxygen supply and demand, resulting in ischemia. In addition to disturbances in cardiomyocyte metabolism (often deranged by comorbidities such as arterial hypertension and diabetes), microparticle embolization, and micro- and macrovascular dysfunction could also be responsible for angina symptoms and ischemia. Also,

vessel stiffening, inflammation, thrombosis, and impaired angiogenesis may play a role.^{3,7}

Mitochondrial dysfunction and impaired energy production have been observed in various heart diseases. Increased amounts of fatty acid oxidized by the mitochondria in relation to carbohydrate oxidation can decrease cardiac efficiency and contribute to impairment of myocardial function in heart failure (HF), ischemic heart disease, and diabetic cardiomyopathies.⁸ Therefore, inhibition of mitochondrial fatty acid oxidation is a well-established target for treatment of these diseases.

The recognition of myocardial ischemia as a multifactorial process implies that antianginal management should not focus solely on large coronary vessels, but also on the microvessels and the cardiac cell. A more convenient approach would consist of a comprehensive therapeutic strategy that encompasses all causes of ischemia. Trimetazidine, a reversible competitive inhibitor of 3-ketoacyl coenzyme A thiolase, directly targets mitochondrial fatty acid oxidation enzymes, improves the function of failing hearts, and reduces rates of glycolysis and/or increases glucose oxidation, resulting in reduced proton levels.⁹

Effects of trimetazidine on clinical parameters and exercise tolerance in stable angina pectoris

According to the 2013 European Society of Cardiology (ESC) guidelines for the management of stable CAD, the treatment of angina combines lifestyle changes and drug therapy with revascularization strategies. After initiation of optimal medical treatment, which includes at least one antianginal drug and drugs for event prevention, trimetazidine is indicated as a second-line treatment for angina/ischemia relief (class IIb, level of evidence B).¹⁰

The efficacy of oral trimetazidine, both as monotherapy and adjunctive therapy, in patients with angina pectoris not sufficiently controlled by other antianginal agents has been evaluated in clinical trials.

Trimetazidine has anti-ischemic efficacy that is similar to that of propranolol 20 mg thrice daily.¹¹ When added to standard maintenance therapy (propranolol, aspirin, and statin), trimetazidine improves angina class. This is due to a nonmechanical anti-ischemic mechanism of action, since heart rate and rate-pressure product remain unchanged in the trimetazidine group.¹²

In clinical practice, in the large prospective CLAS-SICA study (the Most Effective Combination of Anti-anginal Drugs in the Treatment of Patients with Stable Angina) cohort of 1213 angina patients, trimetazidine on top of other standard anti-ischemic therapy significantly reduced the number of angina attacks per week regardless of the baseline antianginal therapy.¹³

In the TRIUMPH trial (TRImetazidine MR in patients with stable angina: Unique Metabolic Path), in patients with stable angina, trimetazidine added to conventional therapy decreased the number of angina attacks and use of nitroglycerin tablets per week. It also lessened physical limitation and improved angina stability.¹⁴ Furthermore, in the TACT trial (Trimetazidine

Study	No of pts	Design	Results
Vitale et al, ¹⁵ 2013. (VASCO trial)	645	Randomized double-blinded, placebo-controlled; symptomatic and asymptomatic patients with chronic ischemic heart disease. Treatment with placebo or TMZ (70 mg/d and 140 mg/d) in addition to atenolol (50 mg/d); 12-week follow-up.	Total exercise duration (TMZ: 6% ± 23% vs placebo: 0.7% ± 5%; <i>P</i> =0.0074). Time to 1-mm ST-segment depression (TMZ: 9.6% ± 33% vs placebo: 3% ± 16.8%; <i>P</i> =0.0239).
Makolkin et al, ¹⁴ 2004. (TRIUMPH trial)	846	Open-label, uncontrolled; stable angina patients. Treatment with TMZ (70 mg/d) in addition to conventional therapy; 8-week follow-up.	Weekly number of angina attacks (11.2 ± 0.4 to 3.6 ± 0.2; <i>P</i> <0.0001). Weekly nitroglycerin use (11.9 ± 0.8 to 3.4 ± 0.2; <i>P</i> <0.0001). QOL improvement (<i>P</i> <0.0001) for all five items: Physical limitation score (0.7 ± 0.7 to 61.0 ± 0.6). Angina stability score (57.6 ± 0.9 to 92.5 ± 0.7). Angina frequency score (33.3 ± 0.7 to 55.6 ± 0.8). Treatment satisfaction score (62.3 ± 0.7 to 77.4 ± 0.5). Disease perception score (36.7 ± 0.6 to 55.5 ± 0.7). AE in 2.4% (22/906).
Chazov et al, ¹⁶ 2005. (TACT trial)	166	Randomized, placebo-controlled; stable angina patients resistant to nitrates or β-blockers. Treatment with placebo or TMZ (60 mg/d) in addition to β-blockers or long-acting nitrates; 12-week follow-up.	Total exercise duration (417.7 ± 14.2 s to 506.8 ± 17.7 s in TMZ vs 435.3 ± 14.8 s to 458.9 ± 16.2 s in placebo; <i>P</i> <0.05). Time to 1-mm ST-segment depression (389.0 ± 15.3 s to 479.6 ± 18.6 s in TMZ vs 411.8 ± 15.2 s to 428.5 ± 17.3 s in placebo; <i>P</i> <0.05). Time to onset of angina (417.0 ± 16.9 s to 517.3 ± 21.0 s in TMZ vs 415.1 ± 16.5 s to 436.4 ± 18.5 s in placebo; <i>P</i> <0.005). Weekly number of angina attacks (5.6 ± 0.6 to 2.7 ± 0.5 in TMZ vs 6.8 ± 0.7 to 5.1 ± 0.7 in placebo; <i>P</i> <0.05). Weekly nitroglycerin use (5.2 ± 0.9 to 2.8 ± 0.8 in TMZ vs 5.5 ± 0.8 to 4.1 ± 0.9 in placebo; <i>P</i> =ns).
Szwed et al, ¹⁷ 2001. (TRIMPOL II trial)	347	Randomized, multicenter, double-blind, placebo-controlled; stable, effort-induced angina patients with documented coronary artery disease. Treatment with placebo or TMZ (60 mg/d) in addition to metoprolol (100 mg/d), 12-week follow-up.	Time to 1-mm ST-segment depression (341 ± 114 s to 427 ± 134 s; <i>P</i> <0.01). Total exercise duration (420 ± 108 s to 485 ± 122 s; <i>P</i> <0.05). Total work (8.43 ± 1.90 to 9.65 ± 2.22; <i>P</i> <0.05). Maximum ST depression (1.67 ± 0.46 mm to 1.42 ± 0.71 mm; <i>P</i> <0.01). Time to onset of angina (372 ± 116 s to 465 ± 124 s; <i>P</i> <0.01). Mean weekly number of angina attacks (4.0 ± 3.2 to 2.1 ± 2.4; <i>P</i> <0.01). Mean weekly nitrate consumption (2.8 ± 2.5 to 1.5 ± 1.9; <i>P</i> <0.05). Angina pain intensity (Borg scale); <i>P</i> =ns. Rate-pressure product; <i>P</i> =ns.
Ruzylo et al, ¹⁸ 2004.	94	Subgroup from TRIMPOL II; patients with history of revascularization for coronary artery disease and who are symptomatic after 6 months on metoprolol (100 mg/d). Treatment with placebo or TMZ (60 mg/d) in addition to metoprolol (100 mg/d), 12-week follow-up.	Time to 1-mm ST-segment depression (385.1 s ± 144.6 s vs 465.0 s ± 143.8 s; <i>P</i> <0.01). Exercise test duration (466.9 s ± 144.8 s vs 524.4 s ± 131.5 s; <i>P</i> =0.048). Total workload (9.0 m.e. ± 2.4 m.e vs 10.1 m.e. ± 2.4 m.e; <i>P</i> =0.035). Time to onset of angina (433.6 s ± 164 s vs 508.1 s ± 132.4 s; <i>P</i> =0.031).

Table 1 Trials on exercise tolerance and clinical effects of trimetazidine in stable angina pectoris.

Abbreviations: AE, adverse events; ns, nonsignificant; pts, patients; QOL, quality of life; TACT, Trimetazidine in Angina Combination Therapy; TMZ, trimetazidine; TRIMPOL II, second TRImetazidine in POLand study; TRIUMPH, TRImetazidine MR in patients with stable angina: Unique Metabolic Path; VASCO, Efficacy of Trimetazidine on Functional Capacity in Symptomatic Patients with Stable Exertional Angina.

in Angina Combination Therapy), trimetazidine combined with nitrates or β -blockers improved not only angina symptoms, but also stress echo parameters.¹⁶ Similar evidence comes from trials investigating the addition of trimetazidine to β -blocker monotherapy. The VASCO-angina trial (Efficacy of Trimetazidine on Functional Capacity in Symptomatic Patients with Stable Exertional Angina) gives evidence that standard- and high-dose trimetazidine improves effort-induced myocardial ischemia and functional capacity in patients with chronic stable angina receiving atenolol.¹⁵ In the TRIMPOL II trial (second TRIMetazidine in Poland study), the combination of trimetazidine and metoprolol produced greater improvements in angina symptoms and parameters of exercise testing than metoprolol alone (Table I).¹⁷

A growing proportion of patients with stable angina require combined antianginal medications to control symptoms. Indeed, in the subpopulation of patients with a history of PCI or coronary artery bypass grafting (CABG) included in the TRIMPOL II study, trimetazidine provided antianginal efficacy in post-revascularized patients with recurrent angina despite monotherapy with metoprolol.¹⁸

A meta-analysis including 1628 patients with stable angina pectoris confirmed the efficacy of trimetazidine as an addition to conventional antianginal agents, regardless of treatment duration.¹⁹ The beneficial effects were reflected in a decrease in the number of angina attacks and a lower use of nitroglycerin, longer time to 1-mm ST-segment depression, higher total work, and longer exercise duration at peak exercise. In the meta-analysis by Danchin et al on 19 028 patients with stable angina, trimetazidine mono-

therapy was comparable to non-heart-rate-lowering antianginal treatments, but was significantly better than placebo (Table II).²⁰

Effects of trimetazidine on left ventricular function in stable angina pectoris and ischemic heart disease

A meta-analysis of 11 randomized clinical trials of 545 patients established the efficacy of trimetazidine as monotherapy in the treatment of stable angina pectoris. Trimetazidine monotherapy improved left ventricular (LV) function compared with placebo, with an LV ejection fraction (LVEF) improvement of 6.88%, a reduction in LV end systolic volume by 11.58 mL, and a reduction in wall motion score index (WMSI) by 0.23.²¹

Effects of trimetazidine in patients with ischemic cardiomyopathy

In patients with ischemic cardiomyopathy, trimetazidine treatment has been associated not only with functional improvement and reduction in hospitalizations and mortality, but also with a significant positive effect on LV remodeling.²² Trimetazidine improves LV remodeling processes, levels of natriuretic peptides and cardiac troponin, and arteriolar endothelium-dependent relaxation.²³ Such results have been demonstrated only in ischemic, and not in nonischemic, HF patients.^{24,25}

In the 2016 ESC guidelines on diagnosis and treatment of HF, trimetazidine is considered for the treatment of stable angina pectoris with symptomatic HF with reduced ejection fraction. It can be used to

Meta-analysis	No of RCT/ No of pts	Design	Results
Peng et al, ¹⁹ 2014.	13 / 1628	TMZ combination with antianginal drugs (β -blockers and calcium-channel blockers) vs antianginal drugs alone.	Weekly number of angina attacks (-0.95, 95% CI: -1.30 to -0.61; $P<0.001$). Weekly nitroglycerin use (-0.98, 95% CI: -1.44 to -0.52; $P<0.001$). Time to 1-mm ST-segment depression (+0.30 s, 95% CI: 0.17 to 0.43; $P<0.001$). Total work (+0.82, 95% CI: 0.44 to 1.20; $P<0.001$). Exercise duration at peak exercise (+49.81 s, 95% CI: 15.04 to 84.57; $P<0.001$).
Danchin et al, ²⁰ 2011.	218 / 19 028	TMZ vs placebo. TMZ vs non-heart-rate-lowering antianginal drugs.	Total exercise duration (+46 s, 95% CI: 28 to 66; $P<0.001$). Time to 1-mm ST-segment depression (+55 s, 95% CI: 35 to 77); $P<0.001$). Time to onset of angina (+54 s, 95% CI: 24 to 84; $P<0.001$). Weekly number of angina attacks (-0.28 s, 95% CI: -1.17 to 0.64; $P=ns$). Total exercise duration (+7 s, 95% CI: 12 to 28; $P=ns$). Time to 1-mm ST-segment depression (-1 s, 95% CI: -23 to 22; $P=ns$). Time to onset of angina (+8 s, 95% CI: -22 to 40; $P=ns$).

Table II Meta-analysis of randomized controlled trials on exercise tolerance and clinical effects of trimetazidine in stable angina pectoris. **Abbreviations:** CI, confidence interval; ns, nonsignificant; pts, patients; RCT, randomized controlled trials; TMZ, trimetazidine.

relieve angina in patients with persistent symptoms despite treatment with a β -blocker (or alternative) (class IIb, level of evidence A).²⁶ This recommendation is based on drug effects to improve functional capacity, exercise duration, and LV function in patients with HF with reduced ejection fraction.

Patients with diabetic cardiomyopathy have impaired myocardial glucose handling and a more distal distribution of coronary atherosclerosis. Trimetazidine not only improves myocardial glucose utilization, but also the levels of glycosylated hemoglobin (HbA_{1c}) and glycemia, and it increases forearm glucose uptake.²⁷ In addition, in diabetic patients with ischemic heart disease, trimetazidine added to standard medical therapy has a beneficial effect on LV volumes and LVEF compared with placebo.²⁸

Effects of trimetazidine in patients undergoing revascularization procedures

Elderly patients have an increased incidence of ischemic dilated cardiomyopathy, often related to diffuse CAD. Adjunctive therapy with trimetazidine, added on to standard care, improves reverse remodeling and quality of life in these patients.²⁹ The addition

of trimetazidine to standard care therapy in elderly patients with diabetes mellitus and multivessel CAD after drug-eluting stent implantation can have a beneficial effect on recurrent angina pectoris, as well as on LV function and structure.³⁰

Furthermore, trimetazidine reduces the incidence of stent restenosis and major adverse cardiac and cerebrovascular events in patients undergoing PCI (Table III).³¹

There is some evidence of a positive effect of trimetazidine on myocardial preservation in CABG patients. In a meta-analysis of six trials including 505 patients, preoperative trimetazidine therapy appeared to reduce ischemia-reperfusion injury during and after CABG.³²

Conclusions

Trimetazidine is an effective and well-tolerated anti-ischemic agent, which—in addition to providing symptom relief and functional improvement in patients with angina pectoris—has a cytoprotective action during ischemia. It has anti-ischemic and anti-anginal effects directly at the cardiac cell level, by optimizing adenosine triphosphate (ATP) use and

Study	No of pts	Design	Results
Xu et al, ³⁰ 2014.	700	Single-center, prospective, randomized, double-blind; elderly (aged 68.94 ± 3.54 years) multivessel CHD patients with DM undergoing coronary angiography. Treatment with placebo or TMZ (60 mg/d) in addition to conventional CHD treatment after DES implantation; 2-year follow-up.	LVEF (66.07% ± 4.04% vs 61.94% ± 3.05%; <i>P</i> <0.01). LVEDD (48.07 ± 4.43 mm vs 51.25 ± 3.57 mm; <i>P</i> <0.01). LVESD (30.81 ± 4.27 mm vs 33.48 ± 3.02 mm; <i>P</i> <0.01). Recurrent angina pectoris, n (%): 102 (40.4) vs 130 (51.0); <i>P</i> =0.010. Angina pectoris, n (%): 72 (28.2) vs 96 (37.6); <i>P</i> =0.024. Silent myocardial ischemia, n (%): 88 (34.5) vs 117 (45.9); <i>P</i> =0.009.
Vitale et al, ²⁹ 2004.	47	Randomized, controlled. Treatment with TMZ vs placebo, (mean age 78 ± 3 years); 6-month follow-up.	LVEF (34.4% ± 2.3% vs 27% ± 2.8%; <i>P</i> <0.0001). LVEDD (58.6 ± 1.9 mm vs 64 ± 1.7 mm; <i>P</i> <0.0001). LVESD (44.5 ± 1.1 mm vs 50 ± 0.8 mm; <i>P</i> <0.0001). Smaller wall motion score index (1.24 ± 0.12 vs 1.45 ± 0.19; <i>P</i> <0.01). Improvement in angina and NYHA class and QOL.
Rosano et al, ²⁸ 2003.	32	Randomized, parallel control, (mean age 67 ± 6 years); DM patients with ischemic cardiomyopathy. Treatment with TMZ (60 mg/d) vs placebo; 6-month follow-up.	LVEF improvement (5.4 ± 0.5% vs -2.4 ± 1.1%; <i>P</i> <0.01). LVEDD (63.2 ± 2.1 mm to 58 ± 1.6 mm vs 62.4 ± 1.7 mm to 63 ± 2.1 mm; <i>P</i> <0.01). Improvement in wall motion score index and in the E/A wave ratio.
Chen et al, ³¹ 2014.	635	Randomized, open; patients with DES (on TMZ for at least 30 days after stent implantation). Treatment with TMZ vs control; 1-year follow-up.	Lower incidence of stent restenosis (4.2% vs 11.1%; <i>P</i> =0.001). Higher LVEF (65.4 ± 10.7 vs 63.1 ± 10.4; <i>P</i> =0.006). Lower incidence of MACCEs (6.1% vs 10.8%; <i>P</i> =0.032). TMZ predictor for stent restenosis (OR: 0.376, 95% CI: 0.196 to 0.721; <i>P</i> =0.003).

Table III Trials on left ventricular function parameter effects of trimetazidine in stable angina pectoris and ischemic heart disease.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; DES, drug-eluting stent; DM, diabetes mellitus; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MACCEs, major adverse cardiac and cerebrovascular events; NYHA, New York Heart Association; OR, odds ratio; pts, patients; QOL, quality of life; TMZ, trimetazidine.

opposing deleterious effects of ischemia, maintaining the contractile myocardial function. The drug is suitable for use as monotherapy in patients with angina and as an adjunctive therapy where symptoms are not controlled by nitrates, β -blockers, or calcium antagonists. Trimetazidine does not affect hemodynamic variables, such as heart rate, systolic blood pressure, and the rate-pressure product. In addition, there is some evidence suggesting trimetazidine may improve LV function in patients with chronic CAD or ischemic cardiomyopathy and in patients experiencing ischemia during PCI or CABG. ■

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