C hronic ischemic heart disease (IHD) and stable angina are a major clinical problem worldwide. The prevalence of stable angina is estimated to be in the region of 20,000 to 50,000 per million in the general population.¹,² According to the REACH (REduction of Atherothrombosis for Continued Health) registry of more than 38,000 patients, 3 in every 20 patients with established coronary artery disease (CAD) has had a major event or been hospitalized within the previous year.³

Despite great advances in the management of CAD patients in recent times, symptoms are still common in many patients, sometimes even after revascularization. In the Heart and Soul Study, over a third (38%) of outpatients with stable CAD had angina, ischemia, or both.¹ A substantial number of patients with typical angina do not have significant coronary atherosclerotic obstructions.⁴ Furthermore, the prevalence of coronary atherosclerotic obstruction in patients with or without typical angina is similar and is age-related in both sexes.

The treatment of stable CAD includes several potential strategies, including revascularization procedures (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]) and pharmacotherapy.⁵ One of the potential strategies for the treatment of CAD consists in targeting cardiac cells directly and in particular the energetic origin of ischemia with the use of a metabolic agent, such as trimetazidine, on top of β-blockers and other vasoactive agents.⁵

Myocardial ischemia is multifactorial and, above all, a deficiency in energy

Recent data clearly show that above and beyond coronary atherosclerotic obstruction, IHD is due to a large number of mechanisms, including coronary vasomotor, microcirculatory, endothelial, and platelet dysfunction and inflammation, among others.⁶ Because myocardial ischemia is multifactorial in nature, it should, above all, be defined as a deficiency in energy (in the form of ATP, adenosine triphosphate) at the cardiac cell level.⁷ Under conditions of energy deficit, drugs that act directly by increasing the energy supply in cardiac cells are of use, whatever the causal mechanism involved, and as such are essential for the optimal treatment of ischemia.

To protect myocardial cells from ischemia, energy supply needs to match energy demand. β-Blockers have a positive impact, reducing energy demand, while metabolic agents, such as trimetazidine, increase energy supply. That is why the use of an agent like trimetazidine fully complements β-blocker therapy.
Trimetazidine + β-blocker: an optimal combination for reducing angina

The TRIMPOL (TRIMetazidine in POLand) II study was one of the first studies to test the use of a metabolic agent on top of β-blockers in 426 patients with stable CAD. It was a randomized, multicenter, double-blind, placebo-controlled parallel-group study. Patients with documented CAD and stable, effort-induced angina uncontrolled by metoprolol received either placebo or trimetazidine 20 mg three times daily in addition to metoprolol 50 mg twice daily. In this study, 12 weeks’ treatment with trimetazidine plus metoprolol significantly improved treadmill exercise test parameters and significantly reduced clinical symptoms compared with placebo plus metoprolol. This was achieved without any further hemodynamic changes in these patients. In addition to its antianginal efficacy, trimetazidine was well tolerated.

Michaelides et al performed a randomized, double-blind, controlled trial in angina patients who were symptomatic despite treatment with propranolol. The trial demonstrated that adding trimetazidine to treatment significantly decreased the mean number of angina attacks (~63%) twice as much as adding isosorbide dinitrate (~31%). This finding might be explained by the mode of action of trimetazidine, which provides a synergistic and complementary approach to hemodynamic agents, such as β-blockers. In a recent meta-analysis of almost 20 000 angina patients, trimetazidine was shown to be as effective as calcium channel blockers or nitrates at reducing ischemia and angina symptoms.

Nesukay demonstrated that directly adding trimetazidine to β-blockers in over 1400 patients with stable angina allowed for a quick reduction in angina symptoms, regardless of whether or not these patients who were on β-blockers were also on nitrates or calcium channel blockers.

Adding trimetazidine to β-blockers: evidence of improved prognosis in ischemic patients

In a recent heart failure registry, approximately 40% of chronic heart failure patients were found to have heart failure of ischemic origin. In a contemporary meta-analysis in nearly 1000 patients with heart failure, of mainly ischemic origin (93%), Gao et al showed that adding trimetazidine significantly reduced all-cause mortality as well as cardiovascular events and hospitalization for heart failure (P<0.01 versus placebo). In post–myocardial infarction patients with stable angina and heart failure, the use of modified-release trimetazidine was related to a significant reduction in major adverse cardiac events (cardiac death, nonfatal myocardial infarction, acute stroke, need for coronary revascularization, and hospitalization for unstable angina or heart failure) after 6 years of follow-up.

Adding trimetazidine to decrease ischemic reperfusion injury during revascularization and angina recurrence afterwards

Labrou et al have investigated whether the administration of trimetazidine before and after PCI minimizes procedure-induced myocardial damage and improves left ventricular function 1 and 3 months after PCI. Twenty-four hours after PCI, troponin I levels were >1 ng/mL in 26% of patients treated with trimetazidine versus 44% of patients in the control group. Forty-eight hours after revascularization, troponin levels remained elevated in 15% vs 32% of patients. About a fifth (22%) of patients in the trimetazidine group had creatine kinase MB (CK-MB) levels >5 ng/mL 24 hours after PCI, compared with 40% in the control group.

The number of patients with an ejection fraction <50% was significantly reduced in the trimetazidine-treated group compared with the control group at 1 and 3 months after PCI: 11% versus 16% (P=0.046) after 1 month and 4% versus 16% (P=0.017) after 3 months. A significant improvement in regional wall motion versus placebo was noted after treatment with trimetazidine. The use of trimetazidine appeared to minimize myocardial reperfusion injury during PCI and improved global and regional wall motion 1 and 3 months after PCI, according to the authors.

The incidence of stent restenosis has risen, as increasing numbers of patients are treated with drug-eluting stents (DES). Chen et al evaluated whether long-term treatment with trimetazidine reduced the incidence of stent restenosis in 768 patients who underwent PCI with DES. The group on long-term trimetazidine treatment had a lower incidence of stent restenosis compared with the control group (4.2% vs 11.1%; P=0.001). At the 30-day follow-up, the trimetazidine patients exhibited a higher left ventricular ejection fraction than control patients (65.4±10.7% vs 63.1±10.4%; P=0.006). The incidence of major adverse cerebrovascular or cardiovascular events (MACCEs) was also lower in the trimetazidine group at 1-year follow-up (6.1% vs 10.8%; P=0.032). Treatment with trimetazidine was found to predict a reduction in stent restenosis (odds ratio [OR], 0.376; 95% CI, 0.196 to 0.721; P=0.003). The authors concluded that trimetazidine treatment effectively reduced the incidence of stent restenosis and MACCEs 1 year after DES implantation.
Xu et al.\textsuperscript{17} also appraised the effects of trimetazidine after DES implantation on recurrent angina pectoris and left ventricular structure in elderly patients with multivessel CAD and with diabetes mellitus and a left ventricular ejection fraction $>50\%$. After 2 years, patients in the trimetazidine group were shown to have significant reductions in the incidence and severity of angina pectoris, compared with the control group, as well as a reduction in silent myocardial ischemia and increase in angina pectoris–free survival. Left ventricular function and structure in trimetazidine-treated patients were relatively stable after 2 years, but in control patients these parameters deteriorated. Adjunctive therapy with trimetazidine after DES implantation appears to have a beneficial effect in preventing recurrent angina pectoris as well as in improving left ventricular function and structure in elderly multivessel CAD patients with diabetes.

**Conclusion**

Chronic IHD is still a significant clinical burden in daily practice, and in stable angina $\beta$-blockers and revascularization procedures are extensively used treatments. Although the current pharmacological treatment of angina with vasoactive agents is effective, the addition to therapy of metabolic antianginal agents that act directly at the cardiac cell level could provide further treatment benefits, by targeting alternative mechanisms of ischemia. Moreover, use of these metabolic agents during and after revascularization procedures may also offer additional benefits, by decreasing ischemic repertusion injury and decreasing angina recurrence. Targeting the cardiac cell directly and addressing the energetic origin of ischemia with metabolic agents—such as trimetazidine—on top of treatment with vasoactive agents—such as $\beta$-blockers—seems a clinically pertinent strategy for managing IHD as effectively as possible. ■

**References**


**Keywords:** $\beta$-blocker; cardiac metabolism; myocardial ischemia; revascularization; stable angina; trimetazidine