Abstract
The results of the ATPCI (efficAcy and safety of Trimetazidine in patients with angina pectoris treated by Percutaneous Coronary Intervention) study showed no significant difference in the incidence of primary endpoint events between trimetazidine and the placebo group in angina patients who recently underwent percutaneous coronary intervention. The study had limitations specific to the design and selection of the target patient population. However, safety outcomes for trimetazidine were reconfirmed in this study. In this article, we discuss the limitations of study design, patient inclusion criteria and their implications in routine practice. We have also dissected the evidence to tweeze out patient groups who are likely to benefit from trimetazidine treatment.

Introduction to the ATPCI
Recently, results of the ATPCI (efficAcy and safety of Trimetazidine in patients with angina pectoris having been treated by Percutaneous Coronary Intervention) study were presented at the ESC 2020, and concurrently published in The Lancet. The ATPCI trial was a randomized, double-blind, parallel-group, placebo-controlled, event-driven study conducted at 365 sites in 27 countries across Europe, Asia and South America in patients with coronary artery disease (CAD) who underwent percutaneous coronary intervention (PCI) due to stable angina (elective PCI) or unstable angina/non-ST segment elevation myocardial infarction (urgent PCI). Within 30 days post-index PCI, patients randomly received trimetazidine (35 mg) or placebo twice daily adjunct to the standard-of-care guideline-recommended treatment included for secondary prevention and antiangiinal therapy. Primary composite endpoint included cardiac death, hospitalization for a cardiac event, recurrent or persistent angina that lead to increasing, switching or adding dose of an evidence-based antiangiinal therapy, and coronary angiography. After a median follow-up of 5 years, which was prolonged from the earlier planned date due to lower rate of events, the incidence of primary efficacy endpoint was not statistically different between trimetazidine (23.3%) and placebo (23.7%) groups. In addition, other endpoints did not differ between the groups. The safety profile of trimetazidine was found to be excellent over the 5-year follow-up duration of the ATPCI study. Number of serious adverse events including frequency of neurological symptoms remained similar between both groups.

Limitations of the ATPCI study design and its implications
The ATPCI study design has certain limitations that can restrict its general applicability in routine clinical management for this patient category. Presence of angina, post-PCI, was not a prerequisite criteria for patient inclusion in the study. Thus, angina was evaluated at neither baseline nor prior randomization thus; there was no scope for assessing antiangiinal efficacy of trimetazidine. Further, in a typical clinical setting, angina episodes increase with time following PCI, whereas in the ATPCI study, only 17.3% of patients were symptomatic at 1 month, which reduced to 13.8% at 12 months and further to 8.0% at the final visit. This could indicate that patients enrolled had very little residual ischemia following successful PCI, as defined in the trial criteria. Moreover, 93% of the patients were on antianginal medications leaving a very limited scope for improvement in symptomatic angina that is in fact the expected effect of trimetazidine. There were no objective assessments using functional testing included that would identify residual ischemia following PCI. Lack of these assessments did not allow correlation of the causes for recurrent angina after PCI, which may include obstructive causes like incomplete revascularization, restenosis, or disease progression to other vessels, or non-obstructive causes like inflammation, spasm or coronary microvascular dysfunction that result in recurring angina despite successful PCI.1,4 Importantly, no antiangiinal agent showed prognostic benefits post-PCI that was also true for trimetazidine in the ATPCI trial.

Overall, the participants of this ATPCI study were at low cardiovascular (CV) risk, and were relatively young with mostly single-vessel CAD (54.6%) and better left ventricular function (LV) function (86%). Achieving satisfactory angiographic and symptomatic response following index PCI was strictly defined in the protocol and was completed as per protocol with no further planned revascularization. Patients included were already well treated with preventive therapies even before they were given trimetazidine. Incidence of diabetes in this study was 28% (much lower than that in patients with CAD in India).3 This led to a much lower rate of events than previously anticipated, thus the trial getting extended by 1 year instead of the pre-
planned duration of 4 years resulting in a 5-year-long trial.

Commonly, the target treatments for angina aim to reduce angina attacks, provide symptomatic relief, improve the quality of life and prevent recurrent CV events. The ATPCI study was designed with the rationale that many patients continued to experience recurrent angina despite successful revascularization and adequate medical therapy indicating an unmet need for finding alternate novel treatment strategies in this patient population but ignored the fact that no antianginal agents showed prognostic benefits in post-PCI settings.8-12

Mechanism of anti-ischemic effect of trimetazidine

Cumulatively, trimetazidine has no role in modifying atherosclerosis. However, it acts directly on the myocardial cells and shifts the cardiac metabolism from β-oxidation of long-chain fatty acids to glucose oxidation thereby providing more efficient oxygen utilization during ischemia.13 Trimetazidine increases the cellular tolerance for ischemia by inhibiting mitochondrial 3-ketoacyl-CoA thiolase and by consequently increasing glucose metabolism. In doing so, trimetazidine directs pyruvate into the mitochondria leading to less production of protons and lactic acid from the ischemic myocardium, and increased anerobic ATP production from the cytosol. The net consequences of these effects include reduction of free fatty acid oxidation and increased glucose utilization by the ischemic myocardium.14 Overall, trimetazidine optimizes energy utilization and maintains a proper energy supply during ischemia.14 Moreover, it is hemodynamically neutral and results in no adverse effects on blood pressure or heart rate unlike other anti-anginal agents. The drug has been found to be effective in reducing anginal symptoms in patients who remain symptomatic despite being treated with conventional anti-anginal agents.15-18 With increasing evidence for microvascular dysfunction as a cause of angina (a situation where conventional antianginal drugs are less effective), a metabolic modulator like trimetazidine promises additional advantages.

Therefore, in addition to the results from the ATPCI trial, trimetazidine also offers clinical benefits in certain patient population as follows:

**Patients with type 2 diabetes, diffuse vessel disease and reduced LVEF**

The TRIMetazidine in POLand-1 (TRIMPOL-1) study provided clinical evidence regarding the tolerability and efficacy of trimetazidine in elderly patients (n=700) with a history of stable, effort-induced angina (for ≥3 months) and documented CAD (either >70% narrowing in at least one coronary artery on coronary angiography or previous myocardial infarction [MI]). Results showed that 4 weeks of treatment with trimetazidine as an add-on to the existing anti-anginal therapy leads to a longer delay in development of 1 mm ST depression (ischemia threshold), significant lengthening of total duration of treadmill exercise, increased total work, longer delay to angina threshold, fewer angina episodes and nitrate usage.19 Similar benefits have also been observed in patients with diabetic CAD, uncontrolled on a single hemodynamic agent in the TRIMPOL-1 sub-study.20 The DIETRIC study reported significant reduction in number of angina episodes and nitroglycerin tablets used per week (all, P < 0.001); improvement in all exercise parameters in patients with prior MI, coronary lesion with >60% occlusion of the main vessel in angiography or with prior PCI or coronary artery bypass grafting (CABG).21 A meta-analysis of 17 clinical trials showed that trimetazidine therapy significantly improved left ventricular ejection fraction (LVEF) in patients with both ischemic and non-ischemic heart failure (HF). Trimetazidine also improved exercise duration and NYHA class.22 In a meta-analysis of 16 randomized controlled trials involving 884 patients with chronic HF, trimetazidine decreased the hospitalization rate for cardiac causes (RR 0.43; P = 0.03), and improved clinical symptoms and cardiac function with LV remodeling.23 These patients with diabetes and diffuse disease were not included in the ATPCI trial.

**Post-PCI patients with CAD who continue to have chest pain or symptomatic angina**

In a prospective study, Xu et al.24 reported significant improvements in the incidence and severity of angina pectoris, silent MI, and angina-free survival with trimetazidine compared with placebo during the 2-year follow-up in elderly patients with multi-vessel chronic heart disease and diabetes mellitus post implantation of drug eluting stent (DES). Trimetazidine reportedly also improved LV function, as measured by LVEF, in a randomized controlled trial in patients (n=138) with acute STEMI without resolution of ST-segment post primary PCI.25 A sub-study of TRIMPOL II also showed similar beneficial effects of trimetazidine in patients with a history of revascularization for CAD.26 The KAMIR registry (Korean Acute Myocardial Infarction Registry) comprising of 13,733 patients with acute myocardial infarction (AMI), where effects of trimetazidine as an add-on to standard treatment were assessed on clinical outcomes.27 A randomized trial assessed the effects of trimetazidine on the release of cardiac markers and improvement in cardiac function in 173 patients with AMI and diabetes who were undergoing PCI.28 On the second day post-PCI, trimetazidine significantly reduced total creatinine kinase (-27%) and creatine kinase myocardial band (CK MB) (-24%) levels compared to the control group. Trimetazidine also significantly reduced cardiac troponin levels by 32% and 31% after days 1 and 6, respectively. Moreover, greater LVEF was seen in patients on trimetazidine (58.4%±8.6%) compared with those on controls (54.9%±8.4%) by 14 days post-MI. A prospective randomized trial in 214 patients with CAD (2/3rd with multi-vessel CAD), and HF undergoing PCI also showed that long-term trimetazidine therapy (two weeks prior PCI and continued for the next 3 years), provided improvements in LVEF and exercise time, reduced arrhythmias and episodes of silent MI.29 As discussed before, only few patients in the ATPCI trial were with symptomatic angina (only 17.3% at baseline, and 8% at final follow-up).

**Patients with LV dysfunction and ischemic heart disease or inducible ischemia with a large area of myocardial ischemia (perfusion defect).**

Belardinelli et al. showed that effects of adjunct treatment with trimetazidine 20 mg on myocardial perfusion and LV systolic function was studied in 34 patients with diabetes mellitus, ischemic heart disease, and LV dysfunction.30 Patients treated with trimetazidine showed significant
Improvements in systolic wall thickening ($P < 0.05$), ejection fraction ($P = 0.007$) and total exercise time (20.5%; $P < 0.05$ vs. controls). The study reported that benefits of trimetazidine were more evident in patients with more severe perfusion defects upon initial evaluation. The ATPCI trial mostly comprised of patients with good LV function (86%), and only 2.5% were with LVEF of < 40%.

**Patients with ischemic heart disease resulting from bad vessel anatomy unsuitable for revascularization; patients with multi-vessel disease not willing to undergo revascularization or patients undergoing partial revascularization.**

Patients suffering from ACS often have severely stenosed vessels where angioplasty or CABG is not technically feasible. Similarly, some patients may not be willing to undergo revascularization, and may opt for a conservative medical therapy and angina relief. Another situation may be diabetes mellitus, which induces microvascular damage within the myocardium, without coexistent changes in the extramural coronary arteries. Trimetazidine prolonged total exercise time and time to 1 mm ST depression compared with placebo. Maximum ST depression was less in patients on trimetazidine than those given placebo. Thus, trimetazidine has beneficial effects in patients with microvascular angina. A randomized trial in 60 patients with microvascular angina showed that addition of trimetazidine to the standard treatment improved angina symptoms, quality of life, and exercise tolerance by improving myocardial perfusion and endothelial function compared to standard therapy alone (all, $P < 0.05$) at 3 months of follow-up. Zang et al. reported trimetazidine also improved heart rate variability and reduced CV events in elderly patients with ACS compared to conventional treatment. Symptomatic angina relief in incomplete/partial revascularization is one of the major benefits of trimetazidine but this was not the target population in the ATPCI trial.

**Patients undergoing procedures for reperfusion or revascularization.**

Patients with symptomatic CAD and significant stenosis are potential subjects for revascularization procedures to improve survival. It may happen in general coronary syndromes cases such as unstable angina, vasospastic angina, myocardial infarction with or without ST elevation, whether or not followed by thrombolysis or angioplasty procedures, as well as in CV surgeries and in elective angioplasties. Trimetazidine was beneficial in improving the myocardial protection during procedures involving reperfusion injury. Trimetazidine proved to be beneficial for myocardial protection during procedures involving reperfusion injury. An open-label randomized controlled trial with trimetazidine pre-treatment in 44 patients undergoing PCI found that the mean ST-segment elevation and the mean amplitude of the T-wave alterations during all balloon inflations were significantly lower in the trimetazidine group ($P = 0.001$). The maximal amplitude of the T-wave alterations was 4.50 mm with trimetazidine versus 9.25 mm in control patients ($P = 0.0005$). Mean time from balloon inflation to onset of angina and the mean time to pain relief after deflation were significantly better with trimetazidine compared to control. Maximal ST-segment elevations and mean ST-elevation values during sequential balloon inflations were also significantly lower with trimetazidine ($P = 0.018$). Angina episodes and rhythm disturbances were more frequent in the control group. A meta-analysis by Li et al. showed beneficial effects of adjunctive trimetazidine therapy in patients with acute MI by reducing (~67%) total major adverse cardiovascular events (defined as composite of death, recurrent non-fatal MI, target vessel revascularization, CABG, recurrence of angina and/or hospitalization for HF).

**Conclusion**

The ATPCI study did not show preventive potential in this well-treated patient population who were at low CV risks, with well-controlled angina. We believe that the clinical utility of trimetazidine in patient populations is diametrically opposite to those included in ATPCI trial. This subgroup may include patients with type 2 diabetes, diffuse vessel disease, reduced LVEF, post-PCI CAD who continue to have chest pain or symptomatic angina, those with multi-vessel disease unwilling to undergo CABG/intervention, inducible ischemia with large perfusion defect, and in those with ACS due to bad vessel anatomy where revascularization is not feasible.

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**References**


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