

Implications of ATPCI study on trimetazidine use in clinical practice

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Abstract

The ATPCI (efficacy and safety of Trimetazidine in patients with angina pectoris treated by Percutaneous Coronary Intervention) study reported similar primary outcomes between trimetazidine and placebo groups in patients with angina who recently had a percutaneous coronary intervention, but the results of this study reconfirmed the safety of trimetazidine. The study has certain limitations in terms of design and inclusion of the target patient population. Here, we discuss these limitations and their implications on trimetazidine use in routine clinical practice.

Keywords: Trimetazidine, Percutaneous coronary intervention, Angina pectoris

Abbreviations: ATPCI: efficacy and safety of Trimetazidine in patients with angina pectoris having been treated by Percutaneous Coronary Intervention; CAD: Coronary Artery Disease; PCI: Percutaneous Coronary Intervention; MI: Myocardial Infarction; HF: Heart Failure; SAEs: Serious Adverse Events; CAD: Coronary Artery Disease; CV: Cardiovascular Disease; LVEF: Left Ventricular Ejection Fraction; AMI: Acute Myocardial Infarction; CABG: Coronary Artery Bypass Graft; NYHA: New York Heart Association; MACE: Major Adverse Cardiac Events; ACS: Acute Coronary Syndrome; KAMIR: Korean Acute Myocardial Infarction Registry; TRIMPOL-I: TRIMetazidine in POLand-I

ATPCI Study and its Crux

The ATPCI (efficacy and safety of Trimetazidine in patients with angina pectoris having been treated by Percutaneous Coronary Intervention) study was an international, randomized, double-blind, placebo-controlled event-driven trial assessing the effects of trimetazidine (35 mg BID) added to standard medical therapy in patients with coronary artery disease (CAD) who had successful percutaneous coronary intervention (PCI) 30 days prior randomization [1]. Patients (n=6007) were enrolled irrespective of the presence of angina symptoms after index PCI. At 47.5 months of median follow-up, no difference was observed between the study groups for combined primary endpoints of 4 components, namely, cardiac death, hospitalization for myocardial infarction (MI), angina/ ischemia requiring revascularization, heart failure (HF), sustained ventricular tachycardia (VT) or cardiac arrest, angina leading modification of antianginal drugs and angina leading to coronary angiography observed in patients on trimetazidine and placebo (23.3% vs. 23.7%; HR 0.98; 95% CI 0.88-1.09; P = 0.73) [1]. These individual components of the primary efficacy endpoint did not differ significantly [1]. An excellent safety profile was found with trimetazidine over the 5-year follow-up period; however, the number of serious adverse events (SAEs) remained similar to that of the placebo group [1].

The ATPCI study has limitations restricting the generalization of results for trimetazidine use in routine clinical practice. The presence of angina post-PCI was neither evaluated at baseline nor before the randomization thus, missing the objective for determining the antianginal efficacy of trimetazidine. In clinical settings, post-PCI angina episodes usually increase with time but, in the ATPCI study, only 17.3% of patients were reported symptomatic at 1 month, which reduced to 13.8% at 12 months and 8.0% at the final visit. This explains the minor residual ischemia in the enrolled patients post-PCI [1]. Participants were relatively young and had low cardiovascular (CV) risk, mostly (54.6%) with single-vessel CAD. After index PCI, achievement of satisfactory angiographic and symptomatic responses was completed strictly as defined in the protocol without any further planned revascularization. Moreover, enrolled patients already had received preventive

therapies even before trimetazidine treatment was given. As 93% of patients were on antianginal medications, there was limited scope for symptomatic angina improvement with trimetazidine [1]. Moreover, no objective assessment using functional testing that could identify residual ischemia post-PCI was performed. Therefore, there was a lack of correlation between the causes for recurrent angina post-PCI, which may be as obstructive as incomplete revascularization, restenosis, or progression of the disease to other vessels or non-obstructive like inflammation, spasm, or coronary microvascular dysfunction despite successful PCI [2-7]. The incidence of diabetes was 28% in this study (much lower than reported in a patient with CAD) [1,8]. This led to much lower rates of events than predicted and led to trial extension for 1 additional year, from 4 years (pre-planned) to a 5-year long trial. Moreover, no antianginal agent showed prognostic benefits after PCI, and this can also be implicated for trimetazidine from the ATPCI trial.

Target treatments for angina are aimed to reduce angina episodes, provide symptomatic relief, improve patients' quality of life and prevent angina recurrence [9]. The rationale for the ATPCI study was designed to fulfill an unmet need for finding alternative treatment strategies in patients who continued to experience angina recurrence despite successful revascularization and adequate medical therapy. However, the fact that antianginal agents did not show any prognostic benefits after PCI was overlooked [10-13].

Overall, the ATPCI study showed no preventive potential among the well-treated patient cohort with low CV risks and well-controlled angina [14]. Clinical utility of trimetazidine in patients with comorbidities like type 2 diabetes, post-PCI symptomatic CAD, diffuse vessel disease, those unwilling to undergo or not suitable for revascularization, those undergoing reperfusion or revascularization, those with inducible ischemia, and large perfusion defect has been well reported [14]. However, these patient subsets have not been addressed by the ATPCI study. Clinical evidence of trimetazidine offering benefits in this patient population is briefed below.

Clinical Evidence for Ideal Patient Indications for Trimetazidine

In the TRIMPOL-1 study, trimetazidine was assessed for its tolerability and efficacy in elderly patients with stable, effort-induced angina and documented CAD. Four weeks of adjunctive trimetazidine therapy delayed the development of 1 mm ST depression (ischemia threshold) and angina threshold, significantly lengthens total exercise duration, had fewer angina episodes, and nitrate usage [15]. Similar benefits were also observed in the TRIMPOL-1 sub-study conducted in a cohort with diabetes and CAD uncontrolled on a hemodynamic agent [16]. The DIETRIC study also showed that trimetazidine use significantly reduced angina episodes and usage of nitroglycerin (all, $P < 0.001$), improved all exercise parameters in patients with prior MI, coronary lesion (with $>60\%$ main vessel occlusion) in angiography or with prior PCI or CABG [17]. A meta-analysis reported significant improvement in left ventricular ejection fraction (LVEF) in patients with HF (ischemic and non-ischemic) and improvement in exercise duration and the New York Heart Association (NYHA) class with trimetazidine therapy [18]. Another meta-analysis, including studies in patients with chronic HF, showed decreased hospitalization rate (for cardiac causes RR 0.43; $P = 0.03$) and improved clinical symptoms and myocardial function with LV remodeling with trimetazidine use [19]. This sub-group of patients has not been addressed in the

ATPCI study. Moreover, Belardinelli et al. showed that adjunctive usage of trimetazidine in diabetes patients with LV dysfunction and ischemic heart disease has significant improvement in systolic wall thickening, ejection fraction, and total exercise time (all $P < 0.05$ vs. controls) [20]. Contrastingly, the ATPCI trial had a target patient population with good LV function (EF $>50\%$ in 86%) and only 2.5% with LVEF of $<40\%$.

A prospective trial reported that trimetazidine significantly improved angina incidence and severity, silent myocardial ischemia, and provided angina-free survival compared to placebo at 2-year follow-up in elderly patients with multi-vessel chronic heart disease and diabetes post-drug-eluting stent implantation [21]. Trimetazidine use also showed improvement in LV function in patients with acute ST-segment elevation myocardial infarction (STEMI) and without ST-segment resolution after primary PCI [22]. The TRIMPOL II sub-study also showed similar beneficial effects with trimetazidine use in CAD patients with revascularization history [23]. The KAMIR included patients with acute myocardial infarction (AMI) and reported beneficial effects of add-on treatment with trimetazidine to standard therapy on clinical outcomes [24]. Beneficial effects of trimetazidine use on the release of cardiac markers and improvement in cardiac function were reported in patients with diabetes and AMI who were undergoing PCI [25]. Long-term trimetazidine therapy (2 weeks before PCI until 3 years) in a patient with CAD and HF undergoing PCI showed improvement in LVEF, exercise time, arrhythmias, and silent MI [25]. Contrastingly this evidence, fewer patients with symptomatic angina (baseline: 17.3%; final follow-up: 8%) were targeted in the ATPCI trial.

Patients with symptomatic angina and significant stenosis are candidates for revascularization to improve survival. Trimetazidine provided myocardial protection during procedures for reperfusion injury [26-31]. To reduce reperfusion injuries, trimetazidine needs to be given prior to the intervention. In the ATPCI study, trimetazidine was given mainly post-procedure, beyond the time frame for reperfusion injury benefits. In an RCT, trimetazidine pre-treatment in patients undergoing PCI was shown to reduce maximal ST-segment elevations and mean ST-elevation values during sequential balloon inflations ($P = 0.018$) whereas, frequent angina episodes and rhythm disturbances were observed in the control group [32]. A meta-analysis by Li et al. showed that adjunctive treatment with trimetazidine in patients with AMI has benefits in terms of reducing (-67%) total major adverse cardiac events (MACE) [33].

Patients suffering from acute coronary syndrome (ACS) are often found with severely stenosed vessels where angioplasty or coronary artery bypass grafting (CABG) is not feasible. In addition, patients may not be willing to undergo revascularization and may opt for conservative medical therapy. Another condition may be diabetes mellitus, which induces microvascular damage without coexistent changes in the extramural coronary arteries [34]. Trimetazidine prolonged total exercise time and time to 1 mm ST depression and reduced maximum ST depression compared with placebo in patients with microvascular angina [35]. In patients with microvascular angina, add-on trimetazidine to the standard therapy was shown to improve angina symptoms, quality of life, and exercise tolerance by improving myocardial perfusion and endothelial function (all, $P < 0.05$ vs. standard therapy alone) at 3-month follow-up [36]. Zang et al. reported that trimetazidine improved variability of heart rate and reduced cardiac events compared to conventional treatment

in the elderly with ACS [37]. Evidence proves the benefits of trimetazidine use in the cohort not willing to or not suitable for revascularization; however, this cohort has not been the target population in the ATPCI trial.

Conclusion

The ATPCI study had limitations in showing beneficial effects of trimetazidine in terms of preventive potential in the well-treated cohort and those at low CV risks and well-controlled angina. The population enrolled in ATPCI was a well-treated cohort with low cardiovascular risk and well controlled angina pectoris, which might have nullified the potentially beneficial effects of the drug. The results obtained with this specific subset of patients may not represent the real-world population. Based on the existing evidence for trimetazidine, this communication points out that the benefits of using trimetazidine in a cohort with symptomatic CAD with comorbid conditions should not be ignored as these are likely to be the ideal patient indication for trimetazidine.

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Conflict of Interest

Authors declare no conflict of interest.

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