Letter to the Editor

ACPTI study: Being positive in a negative situation is not naivety — Trimetazidine still has role in symptomatic CAD patients

ABSTRACT

Keywords:
Percutaneous **c**oronary **i**ntervention
Trimetazidine
Angina pectoris

Results: of the effic**A**cy and safety of **T**rimetazidine in patients with angina pectoris having been treated by **P**ercutaneous **C**oronary **I**ntervention (ATPCI) study showed no significant difference in the incidence of primary endpoint events between trimetazidine and placebo group in angina patients who recently underwent percutaneous coronary intervention. However, the study had limitations specific to both, design and selection of patient population. Here, we present some explanations for the null effects of trimetazidine in the ATPCI study and their relevance in routine clinical practice.

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In the September issue of *The Lancet*, Ferrari et al have detailed and discussed results of the efficacy and safety of trimetazidine in patients with angina pectoris having been treated by percutaneous coronary interventions (ATPCI) study, the most comprehensive trimetazidine study so far conducted in patients who have undergone recent percutaneous coronary intervention (PCI). Results of the study showed no significant difference in the incidence of primary endpoint events between trimetazidine and placebo group. In anticipation of these results being translated into routine clinical practice, the study design needs to be examined to gain further insights into its limitations, and their implications.

Treatment targets for angina commonly aim to achieve relief from symptoms, improve quality of life and prevent recurrent cardiovascular events.[1] The ATPCI study was designed considering that many patients continued to experience recurring angina despite undergoing successful revascularization and adequate medical therapy that indicated an unmet need for finding alternative novel treatment strategies in this patient setting.[2—5]

Trimetazidine 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.[6] Moreover it is hemodynamically neutral with no adverse effects on blood pressure or heart rate unlike other anti-anginal drugs. 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.[7—10] With increasing evidence of microvascular dysfunction as a cause of angina (a situation where conventional antianginal drugs are less effective), a metabolic modulator such as trimetazidine promises additional advantages.

ATPCI was a randomized, double-blind, parallel-group, placebo-controlled, event-driven study in patients with coronary artery disease who underwent PCI due to stable angina (elective PCI) or unstable angina/non-ST segment elevation myocardial infarction (urgent PCI). Within 30 days following index PCI, patients were randomized to receive trimetazidine (35 mg) or placebo twice daily in addition to standard-of-care guideline-recommended treatment that included secondary prevention and antianginal therapy. Patients were planned to be followed-up for 2—4 years. The ATPCI study enrolled patients from 365 sites in 27 countries across Europe, Asia and South America. Primary endpoint was a composite of cardiac death, hospitalization for a cardiac event, recurrent or persistent angina leading to adding, switching or increasing the dose of an evidence-based antianginal therapy and coronary angiography. After a median follow-up of 5 years, which had to be prolonged from the earlier planned date due to very few events, the incidence of primary efficacy endpoint was not statistically different between the groups (23.3% in trimetazidine group and 23.7% in placebo group). In addition, other endpoints did not differ between the groups.

1. Two important reasons for the ATPCI trial not showing a benefit with trimetazidine are outlined below along with their implications

1.1. *An overall low event rate that prompts a re-look at the inclusion criteria*

- The study enrolled a relatively young population (mean age ~60 years) mostly with single-vessel coronary artery disease (54.6%) and following a successful PCI. A stringent definition of successful PCI was used wherein PCI was considered successful when the procedure was uncomplicated with satisfactory angiographic and symptomatic response and was completed as initially planned, with no further planned revascularization.
- Most patients had preserved LV function, and only <2% had LVEF <40%

- While the incidence of diabetes in this study was 28% (much lower than in patients with CAD in India.[11] Surprisingly, 83% of patients were reported to have hypertension. Extrapolating these results to the patient population, each, a variety of prevalence of these two important risk factors would perhaps be an over-reach.
- This was an extremely well treated patient population, with most of them getting guideline-directed medical therapy. Overall, 97% received dual antiplatelet treatment (aspirin + P2Y12 inhibitor); 96.6%, lipid-lowering agents; 82.2%, renin—angiotensin inhibitors; and 83·9% received β-blockers.

What did this translate into: The expected rate of events in the trial was much lower than anticipated, requiring the extension of the follow-up period by another 12 months to a median follow-up duration of 47·5 months (IQR 42·3—53·3). In comparison with post-PCI populations of other studies (COURAGE, ISCHEMIA, RIVER PCI, BERN REGISTRY), patients of the ATPCI study had a lower incidence of all-cause mortality, cardiac mortality and MI. ***Possibly, the decision to enroll patients with predominant single-vessel disease and preserved LV function following a successful PCI without complications unintentionally led the enrolled cohort being at a lower risk of adverse events*** than those in comparable studies.[2,5,12,13] Patients were assigned to receive either trimetazidine or matching placebo, up to 1-month post PCI, and were included regardless of the presence or absence of angina symptoms after the index PCI.

1.2. Little residual ischemia post PCI in the current patient cohort

- Since angina after the index PCI was not a pre-requisite for including patients, therefore it was not evaluated at baseline or prior to randomization, and the design of the ATPCI study prevented correct estimation of the antianginal efficacy of trimetazidine.
- Further, in a typical clinical setting, angina episodes can increase over time following PCI, whereas in the ATPCI study, only 17.3% of patients were found to be symptomatic at 1 month, which reduced to 13.8% at 12 months and further to 8.0% at the final visit.

What did this translate into: The enrolled patient population had very little residual ischemia following successful PCI, as defined in the trial criteria. Apart from β-blockers and calcium channel blockers, nearly 39% were on antianginal medications (~12% were receiving long-acting nitrates or molsidomine, and the other 27% were on other antianginal therapy including open label trimetazidine). Therefore, the potential of any symptomatic angina relief (which is the desired effect of a metabolic modulator like trimetazidine) was perhaps difficult to achieve. There was no objective assessment of the presence or absence of residual ischemia using any functional testing. Recurrent angina after PCI may have diverse causes such as incomplete revascularization, restenosis, or disease progression in other vessels.[14,15] Similarly, myocardial ischemia has a multifactorial pathology, which may not be exclusively due to macrovascular coronary lesions, but also include inflammation, spasm or coronary microvascular dysfunction that results in recurring angina despite successful PCI unrelated to concomitant obstructive CAD.[16—19] Importantly, no antianginal drug has shown prognostic benefits in post-PCI settings, and this was also true for trimetazidine in the ATPCI trial.

An important safety signal from the ATPCI trial: Overall, the safety profile of trimetazidine was found to be excellent during the 5-year duration of the ATPCI study. Number of serious adverse events remained similar between the trimetazidine and placebo groups without any differences in the frequency of neurological symptoms, serious skin disorders, arterial hypotension, falls, hepatic disorders, thrombocytopenia, coagulation disorders, or agranulocytosis were seen.

2. Conclusion

Previous studies and meta-analysis demonstrated the benefits of pre-procedural administration of trimetazidine in preventing ischemic reperfusion injury that occurs during PCI.[20—24] The surge of β-oxidation and fatty acid utilization, harmful effect on mitochondrial membranes and calcium overload that occurs during the reperfusion have shown to be blocked by trimetazidine; and with reduction in numbers of post procedural angina attacks, electrocardiographic changes during PCI, cardiac troponin levels, improved left ventricular ejection fraction and cardiovascular events.[20,24]

While the ATPCI study did not demonstrate the benefits of trimetazidine in this well-treated and low-cardiovascular-risk patient population, ***the data needs to be interpreted in a clinical context of the treated patient population***. The study enrolled a specific subset of patients that may not be representative of the real-world post-PCI population. Given the existing evidence of trimetazidine, it could be speculated that ignoring pre-PCI benefits of trimetazidine together with treatment initiation up to 30 days of PCI in a low-risk patient population might have nullified the potentially beneficial effects of the drug.

Given the limitations of the ATPCI study, it is important to understand that the current clinical position of trimetazidine does not call for ignoring its benefits in ***symptomatic patients*** (***as part of combination therapy***) or in ***prevention of biomarker-detected reperfusion injury in the setting of PCI***. Further sub-analysis of the ATPCI study and ***future trials, which if includes symptomatic patients post PCI, those with LV dysfunction and/or residual disease not amenable to revascularization***, will help further clarify the position of trimetazidine in our therapeutic armamentarium.

Declaration of competing interest

Authors declare no conflict of interest.

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