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EDITORIAL

Trimetazidine: is there a role beyond angina?

Jason M. Tarkin[1,2]* and Juan Carlos Kaski[3]

[1]Division of Cardiovascular Medicine, University of Cambridge, Box 110, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK; [2]Department of Cardiology, Barts Heart Centre, St. Bartholomew's Hospital, W Smithfield, London EC1 7BE, UK; and [3]Molecular and Clinical Sciences Research Institute, St George's, University of London, Cranmer Terrace SW17 0RE, UK

This editorial refers to 'The role of trimetazidine in cardiovascular disease: beyond an anti-anginal agent', by C.P. McCarthy *et al.*, *Eur Heart J Cardiovasc Pharmacother.* 2016;2:266–272.

Is it time to re-think the use of trimetazidine in cardiovascular disease? In their article 'The role of trimetazidine in cardiovascular disease: beyond an antianginal agent',[1] McCarthy *et al.* consider novel clinical uses for this antiangina drug. American and European guidelines recommend the use of beta-blockers and calcium channel blockers as 'first-line' agents for the treatment of angina pectoris. 'Second-line agents', which include vasodilator agents such as nicorandil, late sodium current inhibitors such as ranolazine, and the piperazine derivative trimetazidine, are considered to represent alternative treatments for patients who remain symptomatic on first-line agents or cannot tolerate the use of conventional antianginals. Interestingly, some of these second-line agents exert their anti-ischaemic effects without affecting major determinants of oxygen consumption such as blood pressure or heart rate. Trimetazidine, for example, improves ischaemic myocardial energetics though direct inhibition of long-chain 3-ketoacyl coenzyme A thiolase activity, shifting myocardial substrate utilization from fatty acid oxidization towards more energy efficient glucose metabolism, thereby reducing oxygen consumption. Unlike most antiangina drugs, trimetazidine does not have negatively inotropic, chronotropic, or vasodilatory properties. Trimetazidine belongs to a unique group of 'metabolic modulators', which target myocardial ischaemia at the level of mitochondrial energetics, rather than the haemodynamic factors controlling oxygen and metabolite supply and demand.

Several clinical trials have demonstrated trimetazidine to be efficacious in patients with stable effort-induced angina, with an overall effect similar to that of other non-heart rate-lowering agents. For example, in TRIMPOL-II (TRIMetazidine in POLand), a randomized double-blind placebo controlled trial of 426 patients with stable angina treated with metoprolol, the addition of trimetazidine significantly improved performance on exercise testing and reduced the frequency of weekly angina attacks and nitrate consumption compared to placebo.[2] Similar antiangina benefits were reported for trimetazidine in the TACT (Trimetazidine in Angina Combination Therapy),[3] VASCO-angina[4], and CHOICE-2 studies.[5]

The *2013 European Society of Cardiology Guidelines* on the management of stable coronary artery disease give trimetazidine a Class IIb, 'may be considered', recommendation for use as a second-line agent for symptom control in patients with persistent angina.[6] However, in this scenario, there is more compelling clinical trial data available to support the use of other second-line angina drugs (i.e. nicorandil, ranolazine, and ivabradine) compared to trimetazidine. Trimetazidine is also not currently licensed in the United States, nor the United Kingdom. Concerns about potential adverse effects of trimetazidine, including the occurrence of Parkinsonian symptoms and other movement disorders, led the *European Medicines Agency* to undertake a review in 2012; this report concluded that movement disorders were rare and typically reversible on discontinuing the medication. Despite its versatility and efficacy reported in many studies, trimetazidine's current use is restricted as an add-on therapy for patients who are not adequately controlled by, or who are intolerant to, other therapies for angina, as recommended by the *2013 European Society of Cardiology Guidelines*.[6]

But, is there a role for trimetazidine in cardiovascular disease beyond angina? In their review, McCarthy *et al.* highlight several possible alternative uses for trimetazidine, including the treatment of heart failure, peripheral vascular disease, ischaemia-reperfusion injury, and even contrast nephropathy. Indeed, there exists an intriguing body of mechanistic and early clinical data to support these novel uses.

In patients with chronic heart failure, trimetazidine has been shown in two meta-analyses to result in significant improvements in left ventricular dimensions, ejection fraction, and New York Heart Association functional capacity, as well as reducing the frequency of hospital admissions.[7,8] While several studies have also shown an association with mortality reduction in patients with heart failure treated with trimetazidine in addition to usual care,[8,9] this potential prognostic benefit has yet to be confirmed in a large prospective clinical outcome trial.

Interestingly, the beneficial actions of trimetazidine in heart failure have not only been observed in patients with an ischaemic aetiology, but also non-ischaemic causes, including idiopathic dilated cardiomyopathy, diabetic cardiomyopathy, and anthracycline-induced cardiotoxicity. Pre-clinical work suggests that in these patients with non-ischaemic heart failure, trimetazidine might inhibit myocardial fibrosis resulting from pressure overload, and angiotensin II-induced fibroblast proliferation and collagen synthesis.[10] Other proposed mechanisms of action

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* Corresponding author. Division of Cardiovascular Medicine, University of Cambridge, Box 110, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK. Tel: +44 1123331504, Fax: +44 1223331505, Email: jt545@cam.ac.uk

for trimetazidine in chronic heart failure include improved endothelium-dependent relaxation[11] and a reduction of whole-body resting energy expenditure.[12]

Trimetazidine has also been shown to reduce infarct size, limit myocardial neutrophil accumulation, and prevent intracoronary platelet aggregation in animal models of ischemia-reperfusion. During ischaemia-reperfusion, trimetazidine reduces intracellular acidosis and protects ATP stores, acts as an antioxidant preventing excess release of oxygen free radicals, inhibits myocardial cell apoptosis, and increases sarcolemma resistance to mechanical stress from soft tissue oedema post-myocardial infarction.[13] Moreover, the cytoprotective properties of trimetazidine during ischaemia-reperfusion injury might also result from inhibition of Ca^{2+}-induced mitochondrial permeability transition pore opening and associated pro-apoptotic mechanisms,[14] as well as increased microRNA-21 expression and its effect on Akt and the Bcl-2/Bax pathway.[15]

There is also some clinical evidence to suggest that trimetazidine might protect against reperfusion arrhythmias in patients undergoing thrombolysis for acute myocardial infarction,[16] and reduce myocardial injury in patients with stable angina undergoing percutaneous coronary intervention,[17] or coronary artery bypass grafting surgery;[18] however, again, these findings have yet to be evaluated in large multicentre clinical trials. In the LIST (Limitation of Infarct Size with Trimetazidine) study, a randomized trial of intravenous trimetazidine in 94 patients undergoing primary angioplasty for acute myocardial infarction, although trimetazidine was associated earlier resolution of ST-elevation, there were no significant differences observed in left ventricular wall motion, enzymatic infarct size, or clinical outcomes compared to placebo.[19] In contrast, the METRO (ManagEment of angina: a retrospective cOhort) study, a retrospective analysis of 353 consecutive patients discharged from an intensive care unit after surviving a myocardial infarction, showed significant reduction in 6-month, all-cause mortality in patients with antecedent stable angina who were treated with trimetazidine in addition to other antiangina drugs prior to their event (odds ratio 0.36, $P = 0.02$).[20]

Taking all of the above together, trimetazidine appears to be an appealing cardiovascular therapeutic agent that could be safely used in different conditions and in patients with multiple comorbidities given its lack of haemodynamic effects and little drug-to-drug interactions. Indeed, trimetazidine can be combined with conventional cardiovascular drugs. However, before we can truly incorporate trimetazidine as a genuine and versatile first-line treatment for cardiovascular disease beyond its current indication as a second-line agent for symptom control in patients with stable angina, large-scale, prospectively designed, randomized controlled trials with long-term clinical endpoints are needed.

In this time and age, when elderly patients with comorbidities, low blood pressure, and drug intolerances represent a very large proportion of those subjects requiring pharmacological treatment for cardiovascular disease, the suggested efficacy and versatility of trimetazidine should be investigated thoroughly and exhaustively.

Conflict of interest: none declared.

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