Trimetazidine After Coronary Revascularization: Much Ado About Nothing?

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This Commentary relates to the article by S. Park et al on pages 318-326.

Expectation is the root of all heartache - William Shakespeare

Ischemic heart disease (IHD) continues to represent one of the most common causes of death, being the most prevalent cardiac disease.[1] Indeed, despite enormous advances in treatment and in preventive measures, coronary artery disease (CAD) still represents a most fearsome killer, causing every year several million deaths worldwide.[2] In the continuous effort to improve prognosis and quality of life in patients with IHD, substantial research has been conducted in recent years, aimed at different targets in such a multifaceted clinical condition. Antithrombotic therapy has been for years the mainstay to prevent disease relapses, but nowadays several other drugs have proven to be effective in decreasing overall cardiovascular risk and major adverse cardiovascular events, even after an acute coronary syndrome.[3]

Prevention of heart failure (HF) with prompt revascularization when amenable and aggressively tackling risk factors have been shown to be particularly effective, given the detrimental interplay among these clinical entities.[4] Intriguingly, metabolic derangements in myocardiocytes stem from an imbalance in myocardial energy consumption and reduced oxygen supply, because of decreased blood flow in CAD, resulting in myocardial ischemia.[5] As high energy phosphates run off due to impaired metabolism, consequent electrolyte imbalances lead to diastolic dysfunction, rapidly followed by systolic dysfunction and electrocardiographic changes, ultimately resulting in chest pain.

Among the 4 major classes of antianginal drugs (Table 1), metabolic antianginal agents constitute a unicum because they act without affecting hemodynamic parameters, hence providing either a safe add-on therapy or a valuable alternative when other drugs are not tolerated. This class of molecules includes ivabradine, perhexiline, ranolazine, and trimetazidine. Notably, being able to act at the level of mitochondrial long-chain oxidation, trimetazidine shifts myocardial cell metabolism from oxygen wasting fatty acid metabolism toward glucose, improving as well insulin sensitivity, decreasing blood glucose, and improving endothelial function.

Despite its well-established benefits in increasing exercise tolerance and reducting in frequency and duration of anginal episodes, effects of trimetazidine on prognosis are still to be demonstrated because large trials addressing this very relevant issue are missing. To this purpose, Park and colleagues[6] report in this issue of the Journal a timely and important study addressing the effect of trimetazidine in preventing hospitalization for HF in patients who underwent coronary artery revascularization. These investigators used a comprehensive health record database stemming from 8 Korean hospitals, identifying all patients who

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TABLE 1. Comparative Features of Selected Anti-Ischemic Pharmacologic Agents

Agent	Mechanism	Clinical Effectiveness	Side Effects	Contraindications
Beta-blockers	↓ HR ↓ BP ↓ Metabolic demand Inhibit RAS opposing hyperadrenergic state in HF	High; improving symptoms and prognosis	Negative inotropy and BP reduction; rebound effect on therapy cessation (avoid sudden withdrawal)	Asthma; sick sinus syndrome; severe bradycardia; high-degree heart block; peripheral vascular disease (rest ischemia)
Calcium channel antagonists	Block Ca^{2+} entry in cardiomyocytes; arteriolar vasodilatation; afterload reduction (↓ BP)	High for symptoms, modest at best for outcomes	Negative inotropic effect; ankle edema; headache; flushing; tachycardia	Severe aortic stenosis; LV dysfunction; pre-existing hypotension
Ivabradine	If inhibitor; ↓ metabolic demand	High for symptoms control (similar to beta-blockers)	Phosphenes	Not sinus rhythm; HR < 75 bpm; unstable or acute HF; PMK-dependent HF
Nitrates	↓ Oxygen demand secondary to ↓ afterload; epicardial artery vasodilatation	Symptomatic	Headache (most common) responsive to ASA; syncope and hypotension; methemoglobinemia; might worsen endothelial dysfunction	Hypertrophic obstructive cardiomyopathy; PDE-5 inhibitors
Ranolazine	Metabolic effects	Symptomatic; improves glucose sensitivity; reduces calcium overload in HF	Proarrhythmic if QT prolongation	Prolonged QT interval
Trimetazidine	Metabolic effects	Symptomatic; no effects on prognosis; improve glucose tolerance	Clinical worsening in patients diagnosed with Parkinson disease	Parkinson disease

ASA: acetylsalicylic acid; BP: blood pressure; Ca^{2+}: calcium; HR: heart rate; LV: left ventricular; PDE-5: phosphodiesterase type 5; PMK: pacemaker; RAS: renin–angiotensin system.

underwent their first myocardial revascularization without signs and symptoms of HF to assess whether patients assuming trimetazidine had better clinical outcomes. In particular, de novo onset of HF was the primary outcome and the incidence of major adverse cardiovascular events was the secondary outcome. Propensity score matched analysis showed no significant difference in the incidence of hospitalization for HF between the groups, with comparative risk effect estimates (hazard ratios) ranging between 0.88 and 1.31, with similar findings for major adverse cardiac events (effect estimates ranging from 0.98 to 1.16).

Despite its many strengths, this interesting study suffers from some distinct limitations. First, completeness of revascularization was not considered, as well as residual angina after index procedures, both factors that certainly play a role in clinical decision-making.[7] Furthermore, considering only HF hospitalizations, many patients with new-onset HF that were managed as outpatients were not considered in the analysis. Nonetheless, these results, which in fact show that trimetazidine did not improve prognosis in patients with coronary heart disease and no HF at the time of first revascularization, are relevant and add to evidence already present.

Indeed, in a recently published randomized control trial, more than 6000 patients who underwent coronary revascularization were randomized to oral trimetazidine added on top of guideline-directed medical therapy or standard care, showing no effect of trimetazidine in reducing primary end point, a composite of cardiac death, hospital admission for a cardiac event, or recurrence of angina requiring therapy modification or coronary angiography at a median follow-up of 47.5 months.[8] Such data are to be seen in the context of a notably improved treatment of CAD and HF. Indeed, great progresses in the field of interventional cardiology allow nowadays higher rate of success also in case of high coronary complexity, such as severely calcific lesions, coronary bifurcation, or very distal lesions. Furthermore, many antianginal drugs, such as calcium channel blockers and beta-blockers, exert a relevant activity in preventing HF and are complementary to drugs aimed to tackle cardiovascular risk factors such as lipid lowering, antihypertensive, and anti-inflammatory therapies, with relevant impact on patient prognosis, thus contributing to absence of benefit seen with trimetazidine. Nonetheless, in patients with refractory angina, trimetazidine

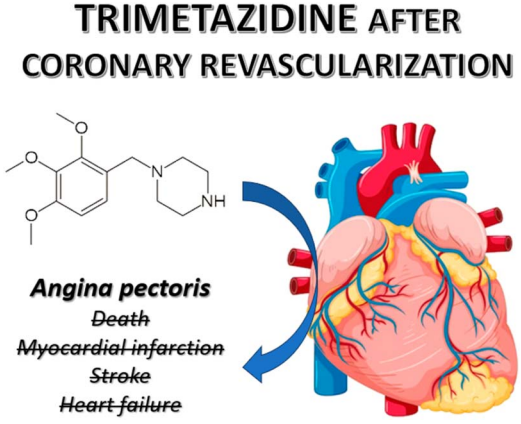

FIGURE 1. Summary of trimetazidine effects in patients with cardiovascular disease undergoing coronary revascularization.

still remains a valuable option because its efficacy in improving quality of life has been clearly demonstrated. As a matter of fact, in a randomized trial involving more than 400 patients, trimetazidine did improve both exercise tolerance and frequency and duration of anginal attack, as well as prolonging total exercise duration and time to ST-depression during exercise stress test.[9,10] Given the molecular mechanism of action of this drug, aimed at counteracting the deleterious effects that ischemia exerts on energy metabolism rather than preventing ischemia itself, it is not surprising the lack of outright efficacy in preventing major adverse cardiovascular events and rehospitalization, and the results of the recent study by Park and colleagues reinforces, probably definitively, this concept (Fig. 1).

In conclusion, although trimetazidine remains a useful treatment option in patients with myocardial ischemia despite guideline-directed medical therapy aimed at preventing major adverse outcomes, its role in preventing HF events or similarly hard outcomes is small, if present at all.

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