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# Trimetazidine effects on preventing cardiovascular events in diabetic patients

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**Abstract**

Diabetes is one of the main risk factors for cardiovascular disease (CVD), particularly atherosclerotic vascular disease, including coronary artery disease (CAD). In the healthy heart, approximately 60% to 90% of adenosine triphosphate (ATP) production originates from β-oxidation of free fatty acids (FFAs), whereas 10% to 40% is produced through the glycolytic pathway. FFAs are a less efficient fuel, and their oxidation in mitochondria for ATP production results in higher mitochondrial oxygen ($O_2$) consumption compared with glucose oxidation. This leads to a greater decrease in myocardial performance for a given amount of ischemia, diminished energy production, contractile dysfunction, and alterations in calcium homeostasis. Trimetazidine (TMZ) inhibits FFA oxidation and increases glucose oxidation, which leads to ATP production with less $O_2$ consumption. Better angina control, improved quality of life, and increased exercise tolerance as well as improved cardiac function seen in nondiabetic patients have been documented in patients with diabetes with TMZ treatment. Moreover, recent data have shown that the benefits of TMZ extend to reduction in cardiovascular events, such as hospitalizations, contrast-induced nephropathy after percutaneous coronary intervention (PCI), in-stent restenosis after drug-eluting stent (DES) implantation, and all-cause and cardiovascular mortality. Because patients with diabetes represent one of the high-risk groups for cardiovascular events, all the benefits provided by TMZ in the general population should be of particular value to patients with diabetes. ■ *Heart Metab*. 2015;68:27-30

**Keywords:** diabetes; metabolism; myocardial ischemia; prognosis; trimetazidine

## Diabetes and cardiovascular disease

Diabetes is one of the main risk factors for cardiovascular disease (CVD), particularly atherosclerotic vascular disease, including coronary artery disease (CAD).[1] In the United States, according to data from the Centers for Disease Control and Prevention, at least 68% of diabetic patients over the age of 65 die of some form of heart disease.[2] Death rates related to CVD among adults with diabetes are two to four times higher than the rates for adults without diabetes.[2]

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## Abbreviations

**ATP:** adenosine triphosphate; **CAD:** coronary artery disease; **cTnI:** cardiac troponin I; **CVD:** cardiovascular disease; **DES:** drug-eluting stent; **FFA:** free fatty acid; **HF:** heart failure; **LV:** left ventricular; **MACE:** major adverse cardiac event; **NYHA:** New York Heart Association; **PCI:** percutaneous coronary intervention; **TMZ:** trimetazidine

Management of patients with diabetes and CAD usually poses a major clinical challenge: clinically, signs of myocardial ischemia, when present, may be atypical and misleading, and silent myocardial ischemia may occur in one in five asymptomatic patients with type 2 diabetes.[3] Angiographically, the accelerated atherogenesis results in more severe and extensive disease, higher incidence of multivessel disease, and small-sized vessels.[4] Both diabetes mellitus and small vessel size are known to be predictors of restenosis after percutaneous coronary intervention (PCI).[5] In patients with multivessel disease, although bypass surgery may be the preferred therapeutic strategy because of the greater long-term protection compared with PCI,[6] this comes at the expense of a higher rate of complications, including wound healing and sternal dehiscence, compared with nondiabetic patients.[7]

In addition, the involvement of distal coronary artery branches reduces regional coronary perfusion and causes hibernation of myocardium that together with the abnormal glucose utilization decreases left ventricular (LV) function,[8] further increasing the risk for future cardiovascular events.

## Cardiac metabolism in patients with diabetes

Adenosine triphosphate (ATP) is produced via two important metabolic pathways. In the healthy heart, approximately 60% to 90% of ATP production originates from β-oxidation of free fatty acids (FFAs); 10% to 40% is produced via the glycolytic pathway.[9] However, glucose utilization is hampered in the diabetic patient, particularly during periods of stress; thus, FFA oxidation is dramatically increased and can account for almost 100% of the heart's energy production.[10] FFAs are a less efficient fuel, and their oxidation in mitochondria for ATP production results in higher mitochondrial oxygen ($O_2$) consumption compared with glucose oxidation.[11] The increased uptake and use of FFAs during stress and ischemia may lead to important changes in the diabetic heart, such as (i) greater decrease in myocardial performance for a given amount of ischemia, compared with the nondiabetic heart[12]; (ii) diminished energy production and a parallel increase in intermediate metabolic products that are toxic for the cells[13]; (iii) contractile dysfunction and an increased sensitivity of the heart to injury during ischemia[14]; and (iv) alterations in calcium ($Ca^{2+}$) homeostasis, which are responsible for the impaired systolic and diastolic functions of the diabetic heart.[15] Based on these premises, modulation of myocardial FFA metabolism may be a key target for metabolic interventions in patients with CAD with or without diabetes. In the former, the benefits of such metabolic approach should be even greater that those observed in nondiabetic patients.

Trimetazidine (TMZ) selectively inhibits the mitochondrial long-chain 3-ketoacyl-Coenzyme A thiolase, resulting in inhibition of FFA oxidation and increased glucose oxidation, restoring coupling between glycolysis and carbohydrate oxidation, which leads to ATP production with less $O_2$ consumption.[16]

## Effects of TMZ on angina relief and left ventricular function

A recent meta-analysis including 13 studies showed that adding TMZ to other antianginal drugs was associated with fewer weekly angina attacks, less weekly nitroglycerin use, longer time to 1-mm ST-segment depression, higher total work output, and longer peak-exercise duration, compared with treatment with other antianginal drugs for stable angina.[17] Another meta-analysis showed that TMZ improved systolic function and clinical symptoms in patients with chronic heart failure (HF), as shown by a significant change in systolic function, New York Heart Association (NYHA) classification, and exercise duration. A specific analysis performed in patients with diabetes and HF revealed a mean 6.19% absolute increase in LV ejection fraction.[18]

## Effects of TMZ on cardiovascular events

TMZ is effective in reducing mortality and event-free survival in patients with HF, as recently shown by Fragasso et al.[19] In this retrospective study comprising 669 patients with HF, the addition of TMZ on top of

optimal medical therapy showed an 11.3% improvement in global survival and an 8.5% improvement in survival for CVD death. The rate of hospitalization for cardiovascular causes was reduced by 10.4% at 5 years. In a previous meta-analysis, mortality was lower with TMZ than with placebo (7.5% vs 27.5%), yielding a 71% reduction in the risk of death in patients with HF. Finally, TMZ appeared to improve clinical outcomes in patients after acute myocardial infarction by significantly reducing all-cause mortality and major adverse cardiac events (MACEs) over 12 months.[20]

## Cardioprotective effects of TMZ in patients with diabetes

The same benefits offered by TMZ, such as better angina control, improved quality of life, and increased exercise tolerance[21,22] as well as improved cardiac function in nondiabetic patients have been documented in patients with diabetes.[23,24]

Patients with diabetes and any degree of renal dysfunction are at risk not only for cardiovascular events, but also for worsening of renal function after administration of iodine-based contrast media. It is known that the magnitude of the increase in the level of cardiac troponin I (cTnI) directly correlates with irreversible myocardial injury and has an important prognostic signification after PCI. In a recent study performed in patients with diabetes and mild-to-moderate chronic kidney disease,[25] the use of TMZ 72 hours prior to PCI was associated with a lower rate of contrast-induced nephropathy (12% vs 28% in the control group), and lower levels of cTnI after the procedure (*Figure 1*).

Diabetes is one of the strongest predictors of restenosis after successful PCI with stent implantation. The role of TMZ in preventing in-stent restenosis was prospectively assessed in 635 patients (27% with diabetes) after drug-eluting stent (DES) implantation.[26] TMZ given for at least 30 days after the procedure significantly reduced the incidence of stent restenosis from 11.1% to 4.2% on follow-up at 9-13 months. The incidence of MACE was also lower in the TMZ-treated group at the 1-year follow-up (6.1% vs 10.8%). Although the study was not powered enough to allow for subgroup analysis, it is tempting to speculate that patients with diabetes may derive the most benefit with TMZ after PCI, regarding the prevention of in-stent restenosis. In fact, the effect of TMZ on recurrent angina pectoris and LV structure after DES implantation in elderly patients with diabetes and multivessel CAD was recently examined.[27] At the 2-year follow-up, patients in the TMZ group showed a significant improvement in the incidence and severity of angina pectoris, compared with the control group, as well as silent myocardial ischemia and angina pectoris–free survival. LV function and structure were relatively stable in patients receiving TMZ, whereas they deteriorated in the control group.

## Conclusion

An evolution in the understanding of the metabolic disarray in the "diabetic heart" allowed for the emergence of a novel therapeutic target to improve the imbalance in energetic substrate utilization (FFA vs glucose). TMZ, with its unique mode of action, devoid of any discernible hemodynamic effect, may have a favorable impact on the management of patients with diabetes and CAD/HF well beyond what is so easily appreciated by patients and physicians alike: an overall improvement in quality of life, increased exercise tolerance, greater angina relief, and improved cardiac function. Because patients with diabetes represent one of the high-risk groups for cardiovascular events, all the benefits provided by TMZ already documented by clinical studies (many with a significant number of diabetic patients)—such as fewer hospitalizations,

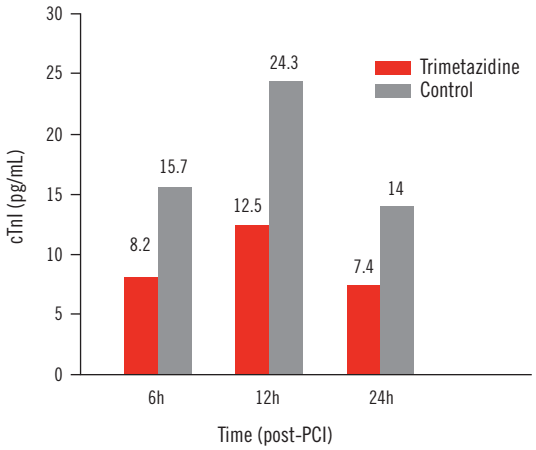


***Fig. 1*** *Graphic presentation showing changes in mean cardiac troponin I levels in patients with diabetes and mild-to-moderate chronic kidney disease undergoing percutaneous coronary intervention.*
**Abbreviations:** *cTnI, cardiac troponin I; h, hours; PCI, percutaneous coronary intervention.*
**Modified from reference 25:** *Shehata.* Am J Cardiol. *2014;114(3):389-394.*

lower rates of in-stent restenosis after PCI, and increased survival—may also be applicable to patients with diabetes. A reappraisal of how patients with diabetes and CVD should be treated is overdue: in dismissing metabolic therapy with TMZ in this scenario, we are needlessly exposing our already high-risk patients to a further increase in their risk of future cardiovascular events. At least where patients with diabetes are concerned, the common saying of "what the eye doesn't see, the heart doesn't grieve over" might not be true. ■

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