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Personalized approach for patients with heart failure and diabetes: responding to current unmet needs

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Presentation of the case

A 67-year-old female hispanic patient presented with effort angina, dyspnea, and fatigue despite pharmacologic therapy.

Clinical history and treatments

- Diabetes mellitus (DM -14 y), obesity (30 y)
- Anterior myocardial infarction with nonobstructive coronary arteries (MINOCA) in 2017 *(Figure 1)*
- Heart failure (HF) since 2018 without HF hospitalizations in the last 12 months
- Current medications: sacubitril/valsartan 200 mg bid, bisoprolol 5 mg od, ivabradine 7.5 mg bid, spironolactone 25 mg od, furosemide 20 mg od, aspirin 100 mg od, atorvastatin 20 mg od, metformin 500 mg bid, empaglifozin 10 mg od

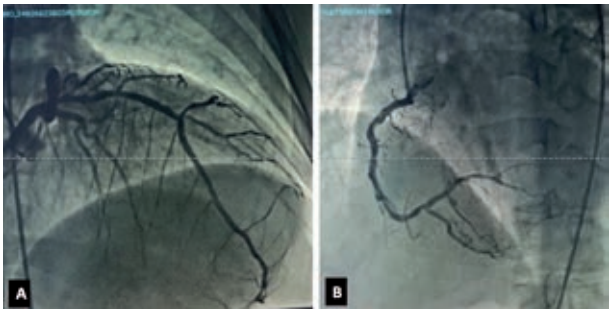

Figure 1 *Coronary angiogram. Coronary angiogram showed no obstructive coronary arteries. A: Right coronary artery, B: Left coronary artery*

Clinical status and symptoms (in consult)

Functional Class II-III NYHA & CSS, heart rate (HR) 60 bpm, blood pressure (BP) 115/80 mm Hg, O_2 saturation 90%, Clear lung fields, holosystolic apical murmur I/IV suggestive of mitral regurgitation (MR), no S3, no hepatomegaly, mild peripheral edema.

Resting electrocardiogram: sinus rhythm, HR 60 bpm, QRS 110 msec, QS in V1-4, cQT 400 msec.

Echocardiogram: Left ventricular (LV) dilation, anteroapical hypokinesis, mild MR, left ventricular ejection fraction (LVEF) 38%, Pulmonary arterial pressure 40 mm Hg, tricuspid annular plane systolic excursion 19 mm.

Laboratory: fasting glucose 89 mg/dL, glycated hemoglobin 7.0%, serum creatinine 1.1 mg/dL, N-terminal-pro- B-type natriuretic peptide (NT-proBNP) 450 pg/mL, serum Na 134 mEq/L, serum potassium 4.5 mEq/L, hemoglobin 13 g/dL, serum ferritin 300 µg/L.

Kansas City Cardiomyopathy Questionnaire (KCCQ): Clinical summary score: 64 pts, total symptom score 65 pts, overall summary score 60 pts.

6-minute walking test (6MWT) distance: 280 meters.

MAGGIC heart failure risk score: 20, risk of dying within 1 year 10.2%, risk of dying within 3 years 24.7%.

At this point we have a patient with ischemic heart disease (IHD), diabetes mellitus (DM), and HF with

reduced ejection fraction (HFrEF) who has received apparent optimized treatment with guideline recommendations including novel therapies like angiotensin receptor–neprilysin inhibitors (ARNIs) and SGLT2 inhibitors. Despite these, the patient persists with moderately severe physical limitation and poor quality of life.

According to the current guidelines and recommendations,[1] the patient is not a candidate for cardiac resynchronization therapy because she has narrow QRS, additional HR control is not necessary because she was already at the HR target of <70 bpm with the treatment with β-blockers and ivabradine, and an implantable cardioverter defibrillator implantation as an alternative for primary prevention of sudden cardiac death is not recommended because the LVEF is over 35%. Other causes for her clinical deterioration such as anemia and/or iron deficiency and renal failure were not present, so iron supplements are not indicated.

The LVEF, the absence of recurrent HF hospitalizations, and the MAGGIC Score reveal a patient with low risk of mortality at 1 year, and for this reason she is not a candidate for a left ventricle assist device.

For all of the above, the guidelines[1] recommend the use of hydralazine–isosorbide dinitrate or digoxin for symptomatic control, but the nitrates and hydralazine have shown maximum efficacy in populations different from our patient. On the other hand, the use of digoxin could be controversial, specifically in patients with polypharmacy and without evidence of atrial fibrillation. Additionally, recent evidence suggests that digoxin could be harmful in many patients with HF.

At this point, we decided to start trimetazidine because of its antianginal effects and some evidence of benefits in HF patients. The patient started the drug with 35 mg bid.

The follow-up at 1, 3, and 6 months showed a significant improvement in symptoms, with angina attacks reduced from 4 per week to 1 per month, and the NYHA Functional Class improved from III to I-II. At 3 months after the start of trimetazidine treatment, the patient increased the distance walked in the 6-min walking test from 290 to 360 meters, and the overall summary score in the KCCQ improved from 60 to 70 points.

After 6 months of follow-up the NYHA Functional Class was I-II, the transthoracic echocardiogram reported LVEF 40%, NT-proBNP 300 pg/mL. The patient had no rehospitalizations during this period.

Discussion

Ischemic heart disease (IHD), HF, and DM are clinical conditions that frequently coexist, and this represents a challenge for the clinicians. The prevalence of diabetes in patients with HF is 20% in outpatients, and could be 40% in HF hospitalized patients. DM increases the risk of major cardiovascular events in HF such as hospitalizations and mortality.[2] The triad of IHD, HF, and DM means the worst-case scenario for this population.

The guidelines of clinical practice are a powerful tool in terms of controlling symptoms and reducing the risk of major adverse events like hospitalizations; even more, the implementation of the guidelines recommendations improve the life prognosis in the majority of HF patients.

Unfortunately, despite these good results, many patients with HF, and/or IHD, and/or DM persist with symptoms that affect their quality of life and constitute a real burden of disease, with negative impact in the evolution of the disease. In those cases it is necessary to reanalyze the case in terms of detecting potential factors that contribute to the persistence of symptoms, and tailor a personalized treatment according to the individual clinical scenarios.

In this particular case, the coexistence of three clinical conditions (HF, IHD with no obstructed coronary arteries, and DM) require an approach that takes account of the diverse pathophysiological pathways that are observed in patients with these conditions.

Recently, the metabolic origins of HF are under profound analysis, especially in ischemic patients. Some of the common pathways are: (i) endothelial dysfunction; (ii) increase in neurohormonal activation (sympathetic nervous system and renin-angiotensin-aldosterone system); (iii) changes in intracellular Ca^{2+} homeostasis; (iv) diastolic dysfunction; (v) altered energy production by cardiac mitochondria.[2]

Many therapeutic targets have been studied, and by now the mandatory use of renin-angiotensin-aldosterone system inhibitors such as angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), β-blockers, and mineralocorticoid antagonists are recommended by the majority of the clinical guidelines. Recently, HR control with drugs such as ivabradine as an adjunctive treatment in selected patients show an additional benefit in terms of reducing the risk of HF hospitalizations and mortality. Moreover,

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the inclusion of ARNIs in patients with persistent symptoms despite the use of ACEIs/ARBs is a good strategy for the optimization of the treatment.[3] With regard to the control of diabetes in HF patients, the use of SGLT2 inhibitors (empaglifozin, canaglifozin, and dapaglifozin) added to metformin have been showing promising results and their use in nondiabetic HF patients is being researched in terms of incorporating another option for the optimized treatment for HF. However, currently, routine use is not recommended.[4]

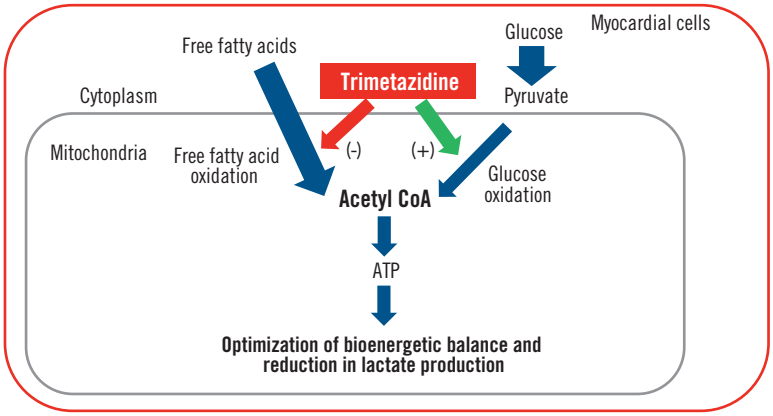

Figure 2 *Trimetazidine – mechanism of action.*

With regard to the metabolic approach for the treatment of IHD and HF, pharmacologic agents such as trimetazidine have been studied because it is clear that in HF and is ischemic heart disease, there is an increase in the uptake of free fatty acids (FFAs) and glucose into cardiac myocytes. The increase in FFA oxidation and decrease in glucose oxidation leads to the accumulation of metabolic intermediates like lactate and promotes cellular maladaptative signaling and cardiomyocyte dysfunction.[5]

Trimetazidine is a metabolic regulating agent that blocks FFA oxidation in the cardiac myocyte mitochondria *(Figure 2).* This blockade allows an increase

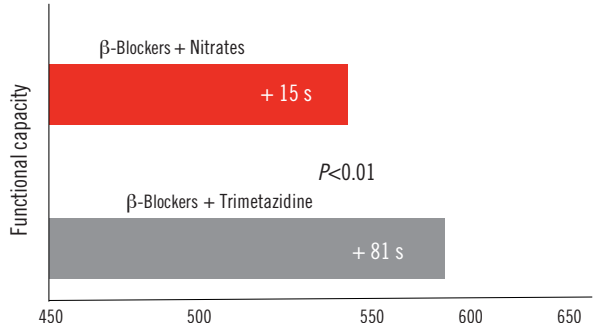

Figure 3 *Effects of combination β-blockers plus trimetazidine on functional capacity in patients with chronic ischemic heart disease. Modified from ref 8: Michaelides AP, Spiropoulos K, Dimopoulos K, Athanasiades D, Toutouzas P. Antianginal efficacy of the combination of trimetazidine-propranolol compared with isosorbide dinitrate-propranolol in patients with stable angina.* Clin Drug Invest. *1997;13:8-14.*

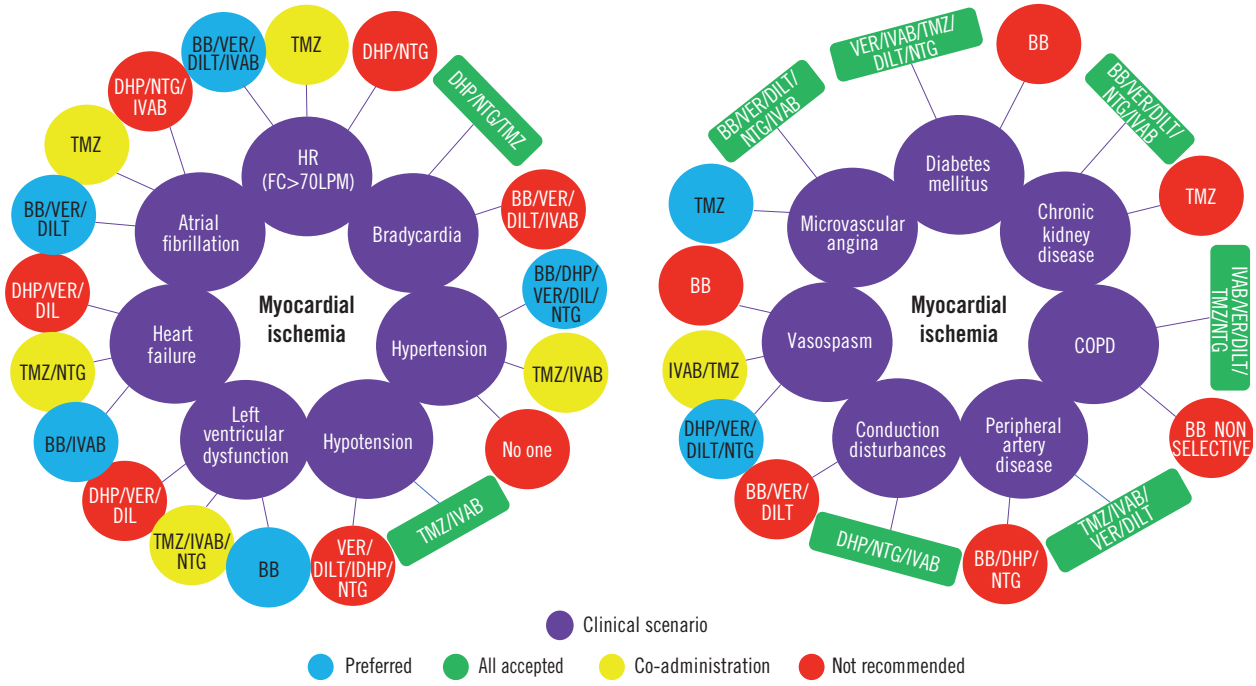

Figure 4 *Individualized treatment for ischemic heart disease.*
Adapted from ref 9: Ferrari R, Camici P, Crea F, et al. A 'Diamond' approach to personalized treatment of angina. Nat Rev Cardiol. *2018;15:120-132.*
Abreviatures: BB, β-blockers, DHP, Dihydropyridines, DILT, Diltiazem, IVAB, Ivabradine, NTG, Nitrates, TMZ Trimetazidine, VER, Verapamil, COPD, Chronic obstructive pulmonary disease

in glucose oxidation, and consequently lactate production is diminished and cell homeostasis could be restored partially. The final result of this metabolic switch is an effective ATP production by the cardiac cells with minimal ATP consumption and better utilization of bioenergetic substrates.[6,7]

In ischemic patients with and without coronary obstructive lesions, the use of trimetazidine has been shown to bring about a significant reduction in angina episodes and increase the functional capacity of patients *(Figure 3).*[8] These results are particularly important in patients with microvascular angina, IHD, and diabetes, with persistent angina after myocardial revascularization procedures (coronary artery bypass graft and/or percutaneous coronary intervention).[7] For this reason the European consensus for the personalized therapeutic approach for the treatment of ischemic heart disease proposes the use of trimetazidine in these specific conditions *(Figure 4).*[9]

In HF, the addition of trimetazidine to standard therapy has been reported to provide slight improvement in LVEF, a significant improvement in NYHA Functional Class, and a reduction of cardiac biomarkers, specifically natriuretic peptides *(Figure 5).*

In our case, the optimization of the treatment with the addition of trimetazidine demonstrated an important improvement in the clinical course of the patient and confirmed the indication of this drug in selected populations in terms to cover some unmet needs and gaps in the treatment of HF, IHD, and diabetes. For this reason, it could be important to have more studies designed specifically to reinforce this data, and possibly add this option in expert consensus, recommendations, and guidelines. ■

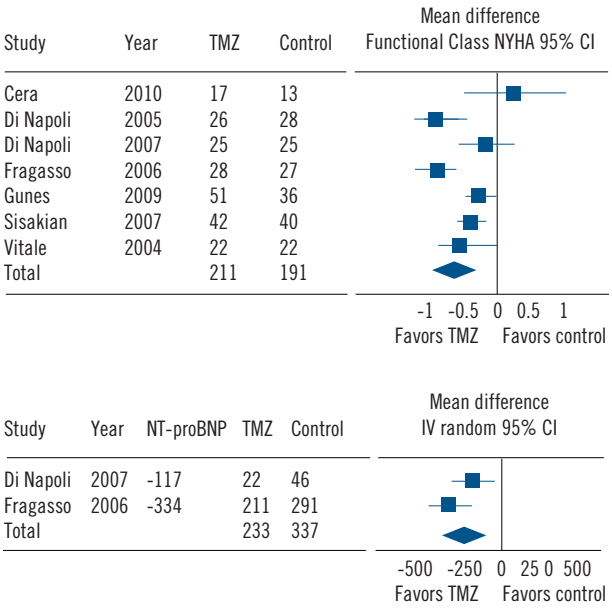

Figure 5 *Efficacy of trimetazidine (TMZ) in heart failure.*
Modified from ref 10: Zhang L, Lu Y, Jiang H, Zhang L, Sun A, Zou Y, Ge J. Additional use of trimetazidine in patients with heart failure: a meta analysis. J Am Coll Cardiol. *2012;59:913-922.*

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