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A patient with stable angina and mild ischemia: do I have the COURAGE not to stent the lesion?

Luis Henrique Wolff Gowdak, MD, PhD, FESC

Laboratory of Genetics & Molecular Cardiology, Heart Institute, São Paulo, Brazil

Correspondence: Luis Henrique Wolff Gowdak, MD, PhD, FESC, Heart Institute (InCor), University of São Paulo Medical School, Avenida Dr. Enéas de Carvalho Aguiar, 44, São Paulo, SP – 05403-000 Brazil
Email: luis.gowdak@incor.usp.br

Abstract: For many years, physicians worked on the assumption of a linear, straightforward link: angina ⇒ myocardial ischemia ⇒ coronary stenosis; therefore, it also seemed straightforward that to treat angina, we should tackle the culprit element, coronary stenosis, by fixing it with a stent. Advances in our understanding of the complex, multifactorial process leading to myocardial ischemia allowed us to appreciate that coronary stenosis is just one among many elements concurring to provoke myocardial ischemia. Moreover, clinical trials that challenged the "PCI-first approach" in the management of patients with stable angina demonstrated unequivocally that, for patients with nonlimiting symptoms, a run with a combination of antianginal drugs and disease-modifying agents could be safely offered before considering a myocardial revascularization procedure. Based on those premises, we present a clinical case that highlights the role of optimal medical therapy (OMT) in the management of a patient with stable angina as the initial therapeutic strategy as opposed to immediate PCI strategy. ■ *Heart Metab*. 2019;78:24-27

Keywords: angina; treatment; coronary artery disease; trimetazidine; myocardial revascularization; angioplasty

Introduction

This issue of *Heart & Metabolism* focuses on the subject of coronary stenting in patients with stable angina according to current guidelines and the most recent trials. For many years, physicians worked on the assumption that there was a linear, straightforward link connecting angina ⇒ myocardial ischemia ⇒ coronary stenosis, and that therefore, it was also straightforward that to treat angina, we should tackle the culprit element, coronary stenosis, by fixing it with a stent. Thus, coronary stenosis ⇒ percutaneous coronary intervention (PCI) with stent implantation ⇒ angina relief and prognostic benefit. A careful read of this issue should enlighten us and help us see this from a different perspective.

Advances in the understanding of the complex, multifactorial process leading to myocardial ischemia have allowed us to appreciate that coronary stenosis is just one among many elements concurring to provoke myocardial ischemia, clinically translated as angina and/or myocardial dysfunction[1,2] in stable patients. Moreover, clinical trials that challenged the "PCI-first approach" in the management of patients with stable angina demonstrated unequivocally that, for patients with nonlimiting symptoms, a run with a combination of antianginal drugs and disease-modifying agents

could be safely offered before considering a myocardial revascularization procedure.[3] The role of PCI in improving symptoms has been further challenged with the publication of the ORBITA trial.[4] But even before that, in FFR-guided PCI compared with medical treatment, as in the FAME-2 trial, the rate of clinically significant end points such as death or myocardial infarction was not affected by PCI.[5]

Based on these premises, we present a clinical case that highlights the role of optimal medical therapy (OMT) in the management of a patient with stable angina as the initial therapeutic strategy as opposed to immediate PCI strategy.

Clinical presentation

A 70-year-old woman was seen for recently diagnosed stable angina. She had a history of stage I hypertension, type 2 diabetes mellitus, and hypercholesterolemia for which she was taking perindopril-arginine 10 mg od, indapamide 1.5 mg od, rosuvastatin 20 mg od, metformin XR 1 g od, and empagliflozin 25 mg od. Six months before seeking medical attention, she noticed exertional angina during her morning walks, especially if uphill, quickly relieved by resting. Three months later, angina appeared to have progressed, because even walking two blocks on level ground would cause chest discomfort; just 1 week prior to her first appointment with a GP, during an argument with her daughter, prolonged angina occurred at rest and troubled her. When first seen, her heart rate (HR) was 76 bpm and BP 132/70 mm Hg. Physical examination was unremarkable. A resting ECG revealed mild left ventricular hypertrophy. Lab assessment and an echocardiogram were ordered; the patient was advised to start using the Angina Control app (from Servier) to record angina attacks by logging them and filling in the conditions associated with their onset (at rest or during effort) and whether or not nitroglycerin was required for relief. Aspirin (100 mg od) was added.

One month later, she attended with the results of the lab tests *(Table I)* and the echocardiogram, as well as the number of angina attacks. The echocardiogram revealed a normal-sized heart with preserved left ventricular (LV) function (LV ejection fraction [EF] = 56%), concentric remodeling (LV mass index = 95g/m^2 and a relative wall thickness of 0.49), and hypokinesis of the lateral wall. Metoprolol succinate (50 mg od) was added.

On her next appointment, she was slightly better, with a decrease in the number of angina attacks and better exercise tolerance, although angina was still worrisome to her. She avoided social engagements and a long-awaited overseas trip was postponed. She was feeling fatigued but with no shortness of breath. HR dropped to 68 bpm and BP to 126/66 mm Hg. At this point, her GP referred her to see a cardiologist.

At her first appointment with the cardiologist, medication was not changed and a myocardial perfusion scan with dipyridamole stress was ordered. She returned another month later, and the cardiac scintigraphy revealed stress-induced ischemia in the anterior wall of the LV (extension 7%), a fixed perfusion defect in the mid- and apical portions of the inferolateral wall with a globally preserved LV function (LVEF = 50%). Invasive coronary angiography was ordered *(Figure 1).*

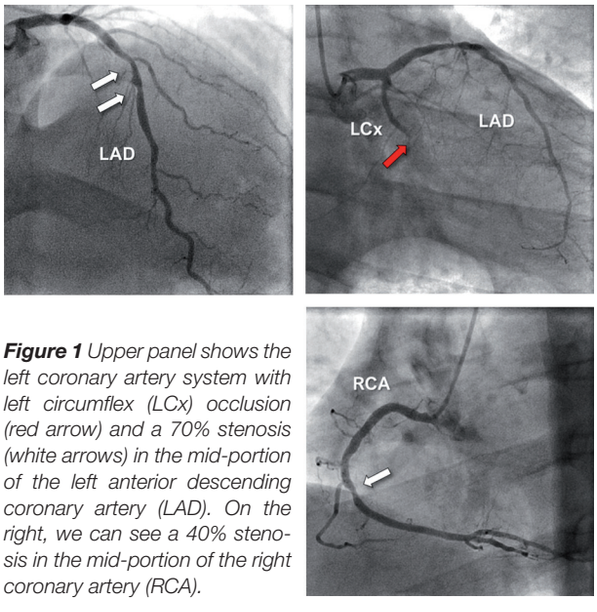

Figure 1 *Upper panel shows the left coronary artery system with left circumflex (LCx) occlusion (red arrow) and a 70% stenosis (white arrows) in the mid-portion of the left anterior descending coronary artery (LAD). On the right, we can see a 40% stenosis in the mid-portion of the right coronary artery (RCA).*

Laboratory tests			
Hemoglobin	13.2 g/dL	Hematocrit	39%
Glucose level	116 mg/dL	HbA_{1c}	7.1%
Total cholesterol	153 mg/dL	LDL-cholesterol	76 mg/dL
HDL-cholesterol	40 mg/dL	Triglycerides	185 mg/dL
Creatinine	0.9 mg/dL	GFR	66 mL/min/1.73 m^2

Table I *Results of selected laboratory tests.*

What should be done now?

All major guidelines agree that a myocardial revascularization procedure should be pursued for improving symptoms and/or prognosis *(Figure 2).* The Heart Team convened and, although PCI with drug-eluting stent (DES) or coronary artery bypass graft (CABG) were both technically feasible, decided to further optimize medical treatment.

The patient was already on a β-blocker at the time a cardiologist assessed her and still complaining of angina with demonstrable stress-induced myocardial ischemia. Among the many options available as add-on therapy, there was a firm recommendation by the Heart Team to add trimetazidine. The patient was well medicated with disease-modifying agents including a high-intensity statin, an antiplatelet agent, and an ACE inhibitor; blood pressure and heart rate were adequately controlled and there was a fear of increasing the adverse effects (such as fatigue) with an increased dose of β-blocker. Moreover, recent studies have raised concerns about an increased risk of death with the use of β-blockers in patients with diabetes and coronary artery disease.[6] Therefore, the choice of trimetazidine, an anti-ischemic agent free of any significant hemodynamic effect, was based on the available evidence of clinical benefit in terms of decreasing the number of angina attacks and the need for short-acting nitrates, increasing exercise tolerance and improving quality of life[7]; additionally, the use of trimetazidine is usually safe and well-tolerated, with no known major drug interactions, including in patients with diabetes[8] and/or heart failure.[9]

The patient was informed about the results of the coronary angiography and the benefits/risks of leaving her on OMT, instead of referring her immediately to revascularization, to which she fully consented. Therefore, and because glomerular filtration rate was above 60 mL/min/1.73m^2, trimetazidine 35 mg bid was started on top of metoprolol, and she continued to use the Angina Control app.

Figure 2 shows the decrease in the number of angina attacks before treatment, after the β-blocker was started, and after trimetazidine was added. When last seen, she was free of angina, having experienced only two angina attacks in the previous month during a more brisk walk in the park on a cold morning. This individual response was also found in a large trial in which the use of trimetazidine on top of any antianginal background (including monotherapy with a β-blocker) provided a fast and significant decrease in the number of weekly angina attacks and improvement in the quality of life,[10] including in patients with newly diagnosed angina pectoris.[11]

If we look carefully at the indications for myocardial revascularization in patients with stable angina[12],

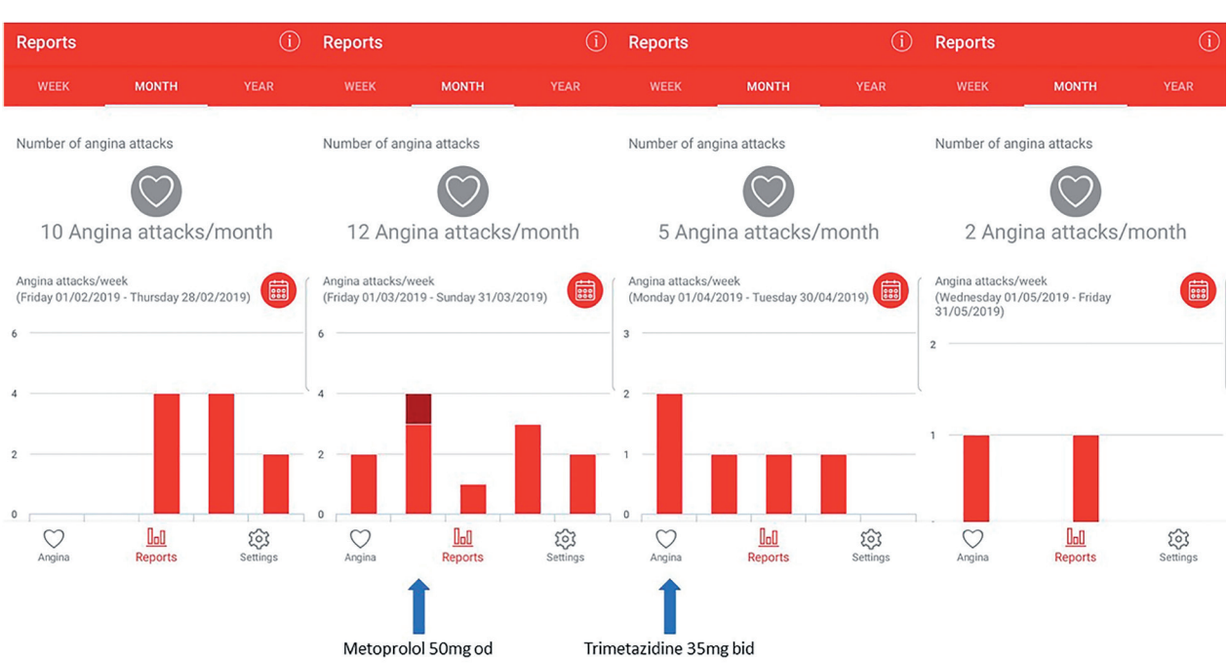

Figure 2 *Angina Control® app showing the number of angina attacks during 4 months of follow-up of a patient with a recent diagnosis of stable angina and the impact of medical treatment.*

we have to consider whether a procedure should be indicated to improve prognosis and/or to relieve angina. For the former, this patient does not fit into any major criteria in which evidence favors the intervention, like LM disease >50%, multivessel disease in the presence of LV dysfunction, or large (>10% LV) area of ischemia; so, we are left to consider revascularization for better symptom control.

However, the guidelines stated quite clearly that revascularization should be considered *in the presence of limiting angina with insufficient response to optimized medical therapy*, which is by far not the case. So, I believe the Heart Team chose wisely to not recommend revascularization as the initial therapeutic strategy.

Conclusion

In conclusion, in this newly diagnosed patient with stable angina with multivessel disease (with no proximal LAD disease), nonlimiting angina, preserved LV function, with less than 10% of myocardial ischemia, although myocardial revascularization either by PCI or CABG was feasible, OMT with a combination of a conventional antianginal agent (β-blocker) with a non-BP lowering agent such as trimetazidine provided excellent control of angina and increase in exercise tolerance, with good tolerability and no side effects. ■

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