



CASE SERIES

# The Role of Ivabradine in Managing Symptomatic Patients with Chronic Coronary Syndromes: A Clinically Oriented Approach

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## ABSTRACT

Angina is a significant contributor to disability and impairment in quality of life in patients with chronic coronary syndromes (CCS). An elevated heart rate (HR) may trigger myocardial ischemia by increasing oxygen consumption and decreasing the diastolic time, compromising the coronary flow. HR-lowering strategies offer symptom control and prevent cardiovascular events in subgroups of patients with CCS. However, the best therapeutic approach to achieve the desired HR in patients with CCS can be challenging based on efficacy and tolerability. Guidelines usually propose  $\beta$ -blockers and/or non-dihydropyridine calcium channel blockers (CCB) for angina patients with elevated HR. Nonetheless, there is no clear evidence of greater antianginal efficacy of this strategy versus an alternative HR-lowering agent. Ivabradine reduces the HR by blocking the  $I_f$  current in the sinoatrial node without affecting myocardial contractility or vascular tone. The magnitude of the HR reduction by ivabradine is proportional to the initial HR, which decreases the risk of significant bradycardia. Ivabradine increases the diastolic time and the coronary flow reserve to a greater extent than  $\beta$ -blockers

and favors collateralization, improving the regional blood flow. We present two clinical cases of patients with symptomatic CCS in whom HR control with ivabradine was fundamental for symptom control and improvement in left ventricular (LV) function. An earlier combination of ivabradine plus  $\beta$ -blockers would have provided more rapid symptom control and improved LV function in the first case. In the second case, the primary mechanism responsible for angina was most likely a coronary vasomotor abnormality, in which the use of  $\beta$ -blockers aggravated the discomfort. The combination of a dihydropyridine CCB plus ivabradine was highly influential in symptom control. Due to its effects beyond HR reduction and good tolerability, ivabradine should be considered an essential ally in managing patients with angina and high HR with or without LV dysfunction.

**Keywords:** Angina; Chronic coronary syndromes; Heart rate; Ivabradine; Symptomatic; Treatment

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### Key Summary Points

Angina is a significant contributor to disability and impairment in quality of life in patients with chronic coronary syndromes (CCS).

Heart rate (HR) is one major determinant of myocardial oxygen consumption and, when elevated, may trigger myocardial ischemia and angina.

The best therapeutic approach to achieve the desired HR in patients with CCS based on efficacy and tolerability can be challenging.

Ivabradine is a unique agent, distinct from  $\beta$ -blockers and calcium channel blockers. It reduces HR without affecting myocardial contractility or vascular tone by acting on hyperpolarization-activated cyclic nucleotide-gated channels, a key player in the control of HR by the sinoatrial node.

We present two clinical cases in which a tailored approach towards more effective angina control was provided using ivabradine.

## DIGITAL FEATURES

This article is published with digital features, including a talking head video, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.19583809>.

## INTRODUCTION

Angina is a significant contributor to disability and impairment in quality of life in patients with chronic coronary syndromes (CCS) [1], regardless of its precipitating mechanism [2].

Heart rate (HR) is one major determinant of myocardial oxygen consumption and, when elevated, may trigger myocardial ischemia and angina [3]. An elevated HR also decreases the diastolic time, compromising the coronary flow [4]. The combination of both effects leads to the appearance of myocardial ischemia and a proportional decrease in contractility. An elevated HR correlates linearly with cardiovascular events [5], and HR-lowering strategies may not only offer reliable symptom control but also prevent cardiovascular events in specific subgroups of patients with CCS. However, the best therapeutic approach to achieve the desired HR in patients with CCS based on efficacy and tolerability can be challenging.

The latest guidelines on CCS [6] propose  $\beta$ -blockers or non-dihydropyridine calcium channel blockers (CCB) alone or in combination for patients with angina and an elevated HR, despite the lack of evident greater antianginal efficacy versus an alternative HR-lowering agent such as ivabradine. Nevertheless, the same guidelines allow for a more patient-tailored approach, in which in selected patients, combining a  $\beta$ -blocker or a CCB with a second-line agent may be considered for first-line treatment according to HR and blood pressure (BP).

Ivabradine is a unique agent, distinct from  $\beta$ -blockers and CCB; it reduces HR without affecting myocardial contractility or vascular tone [7] by acting on hyperpolarization-activated cyclic nucleotide-gated channels, a key player in the control of HR by the sinoatrial node [8]. The following cases are real-life clinical examples of how optimal medical therapy was implemented in symptomatic patients with CCS using ivabradine. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics committee approval was not required because patients' identities were kept confidential and no personal information was provided that could potentially break the doctor–patient confidentiality. Informed consent was obtained from all individual participants included in the study.

## CLINICAL CASE #1: A MIDDLE-AGED MAN WITH A LONG HISTORY OF CCS ON $\beta$ -BLOCKERS AND WITH RECURRENT ANGINA

Mr. S. is a 56-year-old man who suffered a myocardial infarction in 2003 that was treated by percutaneous coronary intervention (PCI). In 2007, he underwent bypass surgery for worsening angina and multivessel disease. He has a long history of type 2 diabetes mellitus, hypertension, hypercholesterolemia, and was previously a smoker. He was referred to our center in 2017 because of limiting, progressive angina in the previous 6 months.

When first seen, he was on aspirin 100 mg once daily (od), atorvastatin 80 mg od, bisoprolol 2.5 mg od, olmesartan 20 mg od, metformin 850 mg twice daily (bid), and empagliflozin 25 mg od. He used to play tennis but eventually had to stop because of the worsening angina, which bothered him considerably.

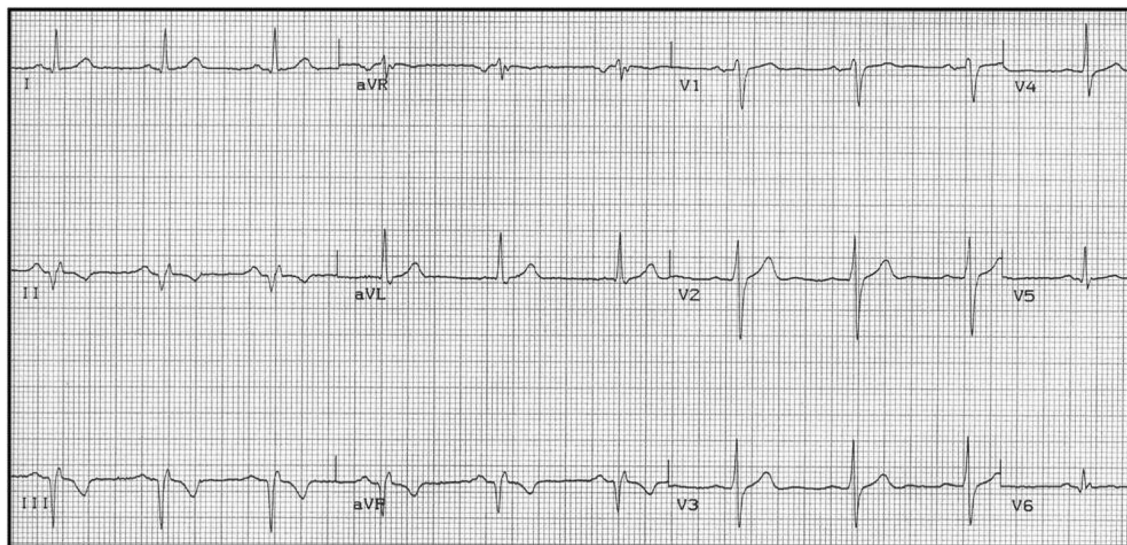
On examination, his HR was 72 beats per minute (bpm) and BP was 126/74 mmHg. His physical examination was unremarkable. Electrocardiogram (ECG) showed sinus rhythm with Q waves noted in inferior leads (Fig. 1); a transthoracic echocardiogram revealed

moderate hypokinesis of the inferior wall and a global left ventricular ejection fraction (LVEF) of 40%.

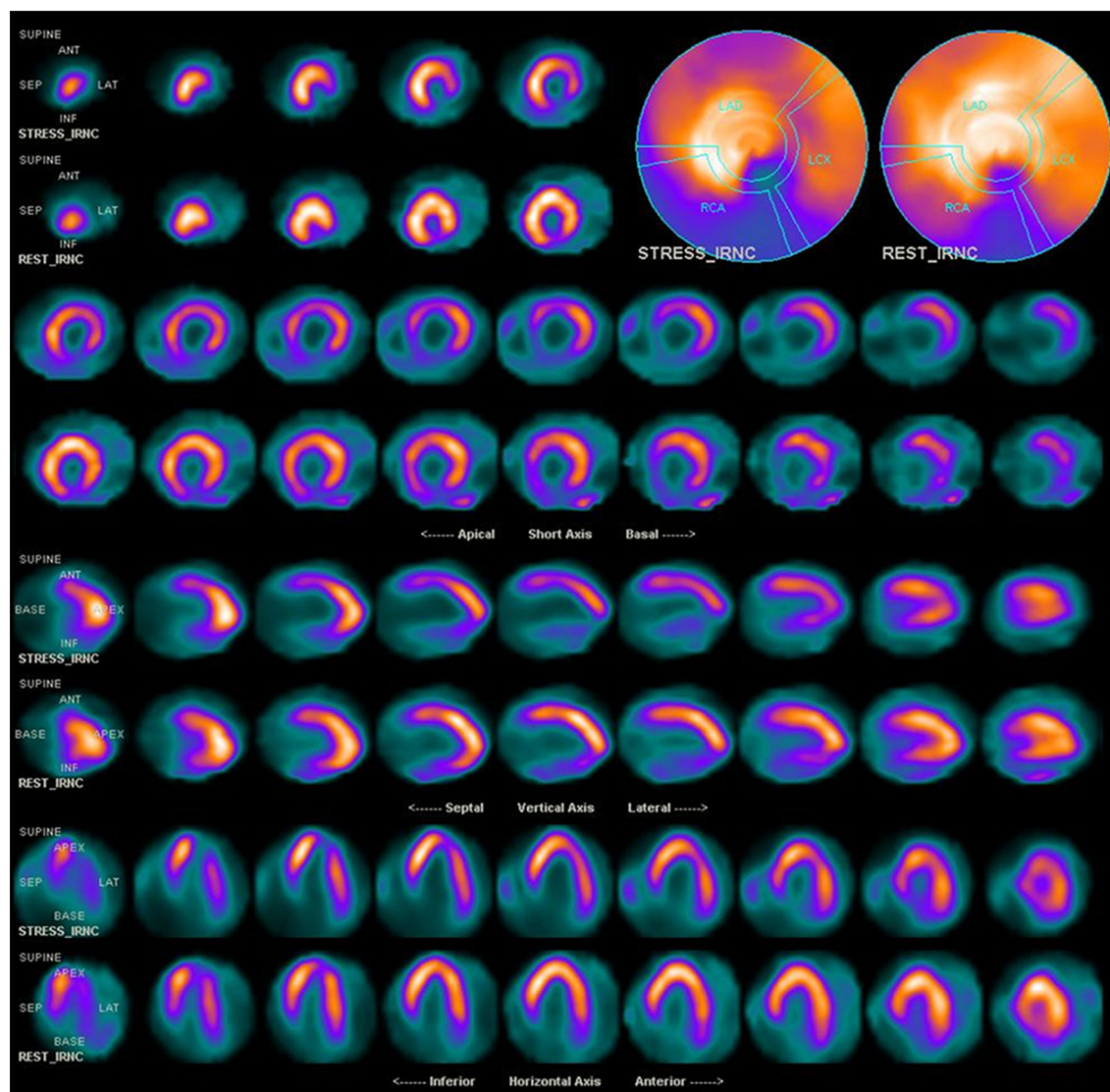
A diagnosis of recurrent angina on a previously asymptomatic patient with long-standing CCS was made. The dose of bisoprolol was increased to 5 mg od. One month later, the patient complained of fatigue, dizziness, and lightheadedness upon standing, and angina had not improved. Bisoprolol was reduced to 2.5 mg od, amlodipine 5 mg od was added, and a myocardial perfusion scan was ordered (single-photon emission computed tomography [SPECT]).

Six weeks later, symptoms had improved very modestly. HR was up to 80 bpm, and BP dropped to 114/64 mmHg. Figure 2 shows the results of the myocardial perfusion scan.

Medical therapy was considered a “failure,” and coronary angiography (CA) was ordered (Fig. 3). The heart team assessed the angiography and judged the patient to be ineligible for another myocardial revascularization procedure: left internal mammary artery to the left anterior descending (LIMA-LAD) was patent, but the distal portion of the native vessel was severely diseased; there was also a chronic total occlusion of the right coronary artery (RCA). As the patient was still symptomatic, with



**Fig. 1** Resting ECG showing a sinus rhythm (heart rate  $\cong$  75 bpm), Q waves in inferior leads (D2, D3, and aVF) with ST-T abnormalities



**Fig. 2** Myocardial perfusion scan by SPECT (sestamibi) with dipyridamole performed in 2017 revealed moderate-to-severe stress-induced myocardial perfusion abnormality in the anterior and lateral segments (reversible defect) and

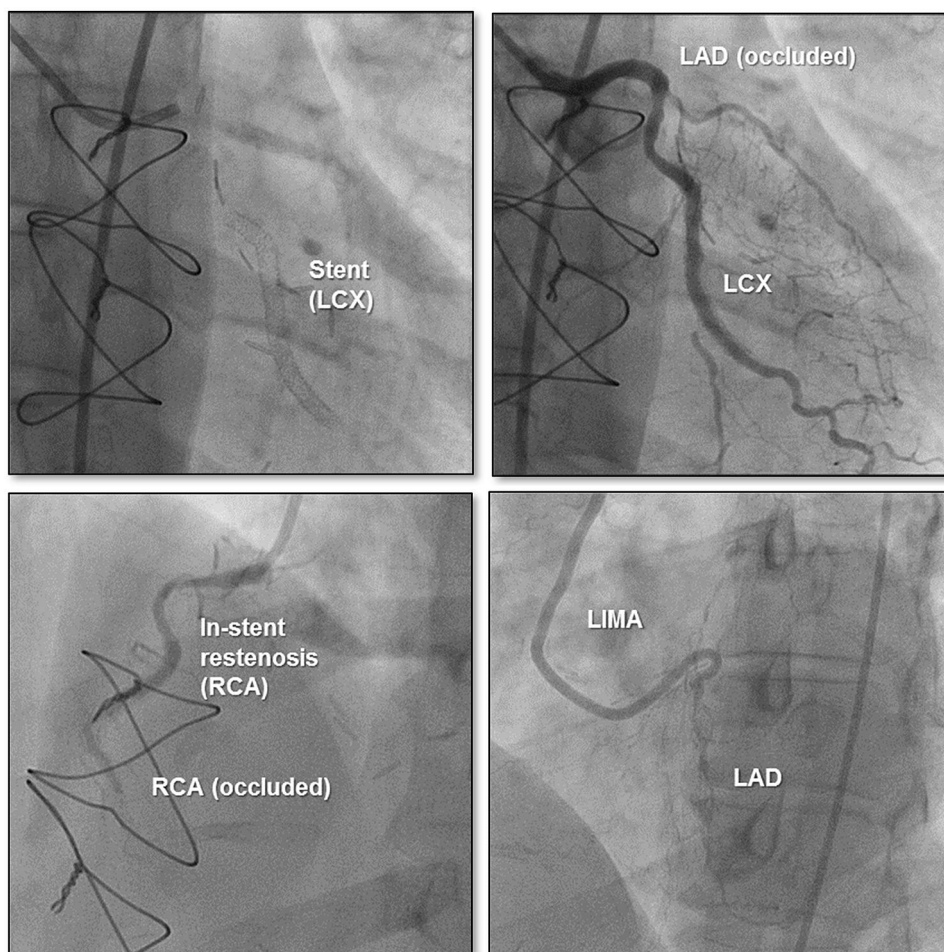
inferior segments (fixed defect). The extension of myocardial ischemia was estimated to be 21% of the LV. The resting LVEF was 36%

borderline BP and sustained elevated HR on  $\beta$ -blockers, ivabradine 5 mg bid was added.

One month later, the patient reported a significant clinical improvement, although he still experienced chest pain during more vigorous exercise. His HR was down to 68 bpm, and BP 118/72 mmHg. Ivabradine was up-titrated to 7.5 mg bid. Three months later, the patient remained free of angina, having experienced a single episode during intercourse, which was

quickly relieved by resting. He was pleased with the treatment, with no side effects noted. HR was 60 bpm, and BP 120/74 mmHg.

Three years later, the patient was still free of angina in his daily activities. Notably, he did not experience any cardiovascular events. Another myocardial perfusion assessment revealed a reduction in stress-induced myocardial ischemia from 21 to 6%, with a corresponding increase in LVEF from 36 to 51% (Fig. 4).



**Fig. 3** Coronary angiography revealed a patent stent placed in the left circumflex coronary artery (LCX) and occlusion of the left anterior descending coronary artery (LAD) and the right coronary artery (RCA). There was a

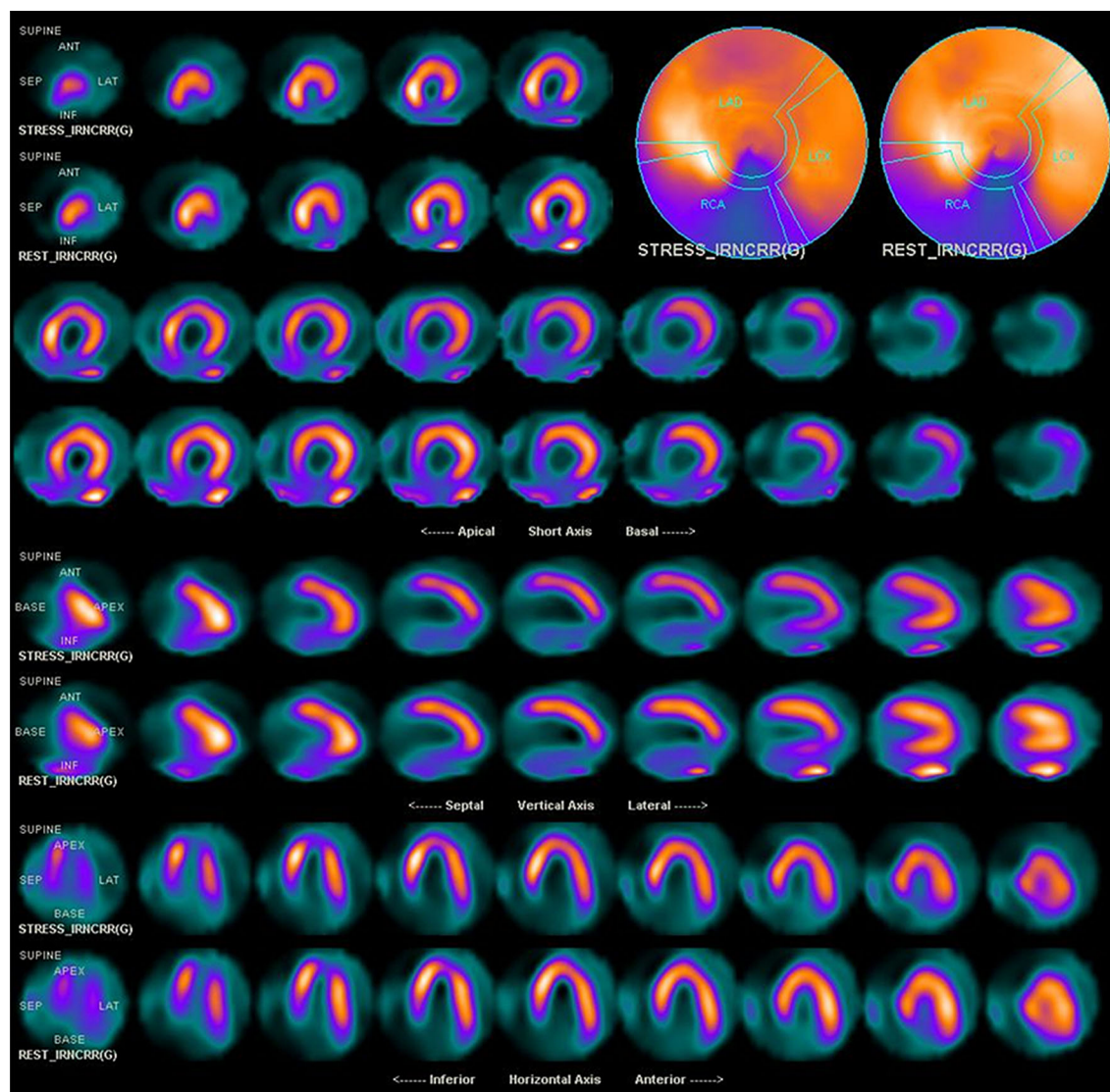
patent left internal mammary artery (LIMA) graft to the mid-LAD with a poor filling of the native LAD due to atherosclerosis progression in the native vessel

## CLINICAL CASE #2: A MIDDLE-AGED WOMAN WITH PREVIOUS PCIS COMPLAINING OF RECURRENT ANGINA UNRESPONSIVE TO $\beta$ -BLOCKERS

Mrs. P. is a 53-year-old woman referred to our hospital after a long history of CCS and multiple procedures. In 2010 she started complaining of oppressive chest pain, lasting more than 10 min, sometimes evoked by exercise, but most often occurring at rest or with mental stress. She sought medical attention and was diagnosed

with stable angina, hypertension, and mixed anxiety–depressive disorder. She had smoked 20 cigarettes/day since the age of 18 years.  $\beta$ -blockers and fluoxetine were prescribed without any improvement in her symptoms. She was sent for a CA, which showed no significant coronary stenoses.

Two years later, she was still having occasional chest pain, mainly evoked by mental stress. Although a stress myocardial perfusion scan showed normal distribution of the radioisotope and normal LVEF, a second CA was performed because of persistent symptoms (Fig. 5). Nonsignificant atherosclerosis of the RCA and the LAD was found. An antiplatelet



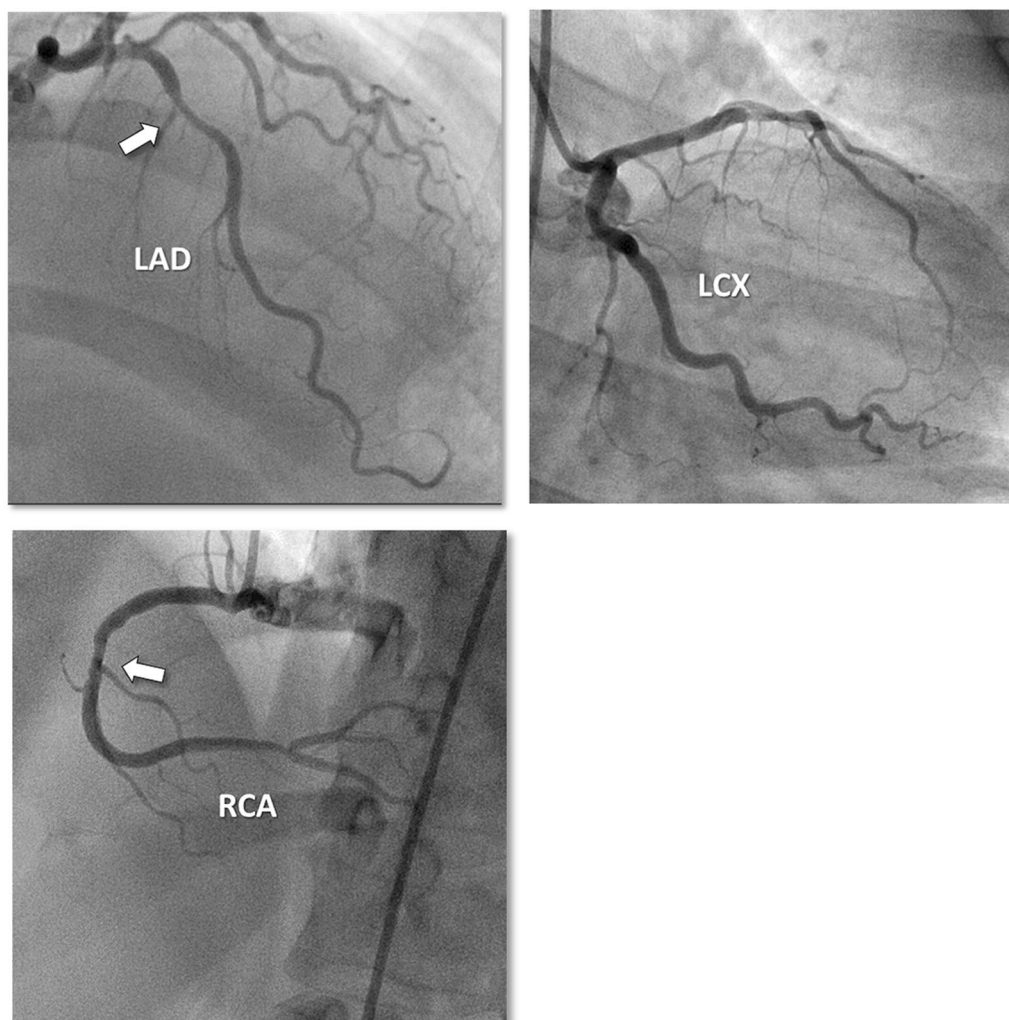
**Fig. 4** Myocardial perfusion scan by SPECT (sestamibi) with dipyridamole performed in 2020 revealed mild stress-induced myocardial perfusion abnormality in the anterior and lateral segments (reversible defect) and inferior

segments (fixed defect). The extension of myocardial ischemia was reduced from 21 to 6% of the LV. The resting LVEF increased from 36 to 51%

agent and a high-intensity statin were prescribed, and the patient was strongly advised to quit smoking.

Between 2012 and 2017, she had several admissions to the emergency department (ED) for recurring chest pain. In 2017, she underwent a third CA for prolonged chest pain, and a drug-eluting stent (DES) was placed in a proximal LAD lesion with 70% stenosis.

In March 2020, she again attended the ED for prolonged acute chest pain accompanied by nausea and profuse sweating. ECG was normal (Fig. 6), but high-sensitivity (hs)-troponin was elevated. The patient was treated for high-risk unstable angina and underwent a fourth CA (Fig. 7). PCI to the RCA with implantation of two DES was performed (Fig. 8). An echocardiogram revealed normal LV function with no structural abnormalities. She was kept on



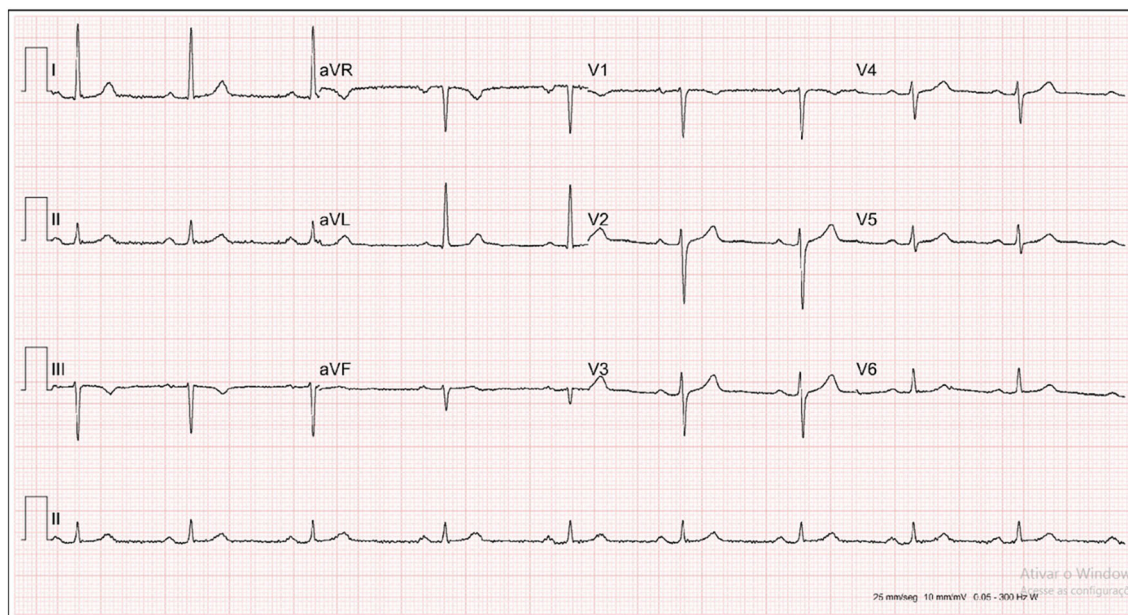
**Fig. 5** Coronary angiography performed in 2012 showed non-obstructive lesions in the left anterior descending coronary artery (LAD) and right coronary artery (RCA) (arrows). *LCX* left circumflex coronary artery

atenolol 25 mg/d, atorvastatin 80 mg/d, enalapril 20 mg/d, and dual antiplatelet therapy (aspirin 100 mg + clopidogrel 75 mg/d).

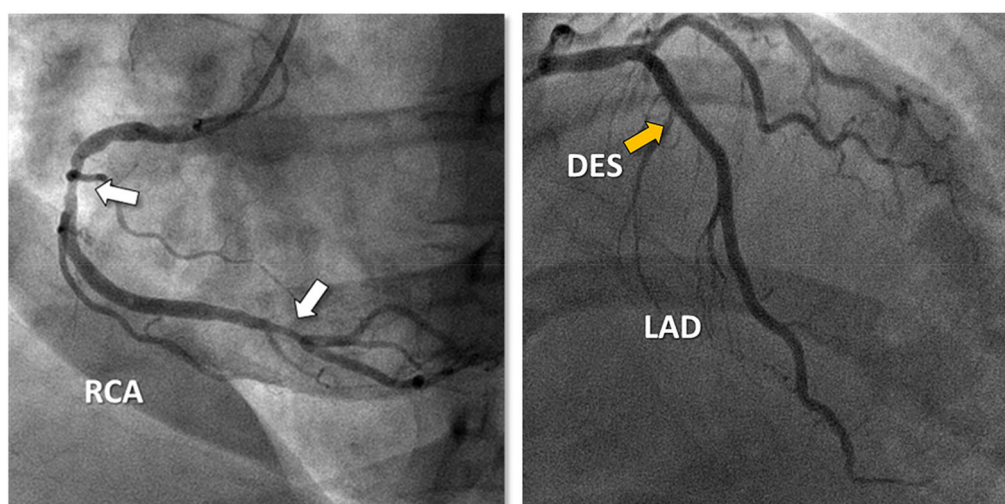
One month after the procedure, episodes of chest pain recurred at rest, predominantly late at night or early in the morning, with variable location (middle of the chest, neck, upper abdomen). Due to the COVID-19 pandemic, her scheduled appointment was canceled, but during a teleconsultation, she was asked to check her vitals with an automatic BP monitor: HR = 82 bpm and BP = 118/66 mmHg. She was advised to increase the dosage of atenolol to 50 mg/d. At her next teleconsultation, 1 month

later, her chest pain was worse. Her new readings were: HR = 74 bpm and BP = 106/64 mmHg. She was once again instructed to increase the dose of atenolol to 100 mg/d and resume fluoxetine.

For the next 3 weeks, she felt rather well until she received a call from her daughter, who was being admitted for treatment of COVID-19. Afterward, she developed a sharp, severe pain in the middle of the chest associated with nausea, vomiting, and pallor, and she was brought to the ED. The ECG obtained during the episode of pain is shown in Fig. 9. The patient was medically treated for ST-elevation myocardial



**Fig. 6** Normal resting ECG was obtained after the resolution of the chest pain before reaching the emergency department



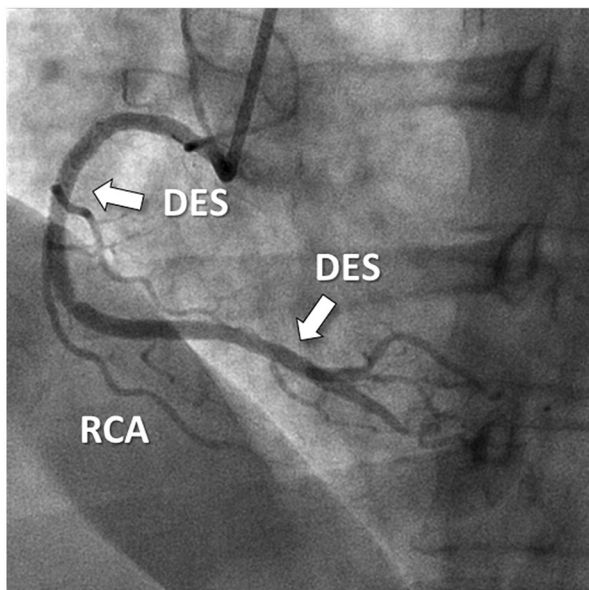
**Fig. 7** Coronary angiography was performed in March 2020, showing mild progression of previously known atherosclerotic lesions in the right coronary artery (RCA)

and a patent drug-eluting stent (DES) (arrow) in the proximal left anterior descending (LAD) coronary artery

infarction (STEMI) and immediately transferred to the catheterization laboratory. An extensive and severe narrowing of the RCA was found (Fig. 10, left), except where the two stents had been placed. Administration of nitrates relieved the spasm, and the RCA was found to be free of any significant disease (Fig. 10, right).

The patient was admitted, atenolol was suspended, and she had an uneventful recovery. Before discharge, her vitals were: HR = 72 bpm and BP = 138/82 mmHg. LV function was normal. Besides medical therapy for secondary prevention, she was given amlodipine 5 mg od + ivabradine 5 mg bid. Four weeks later, she





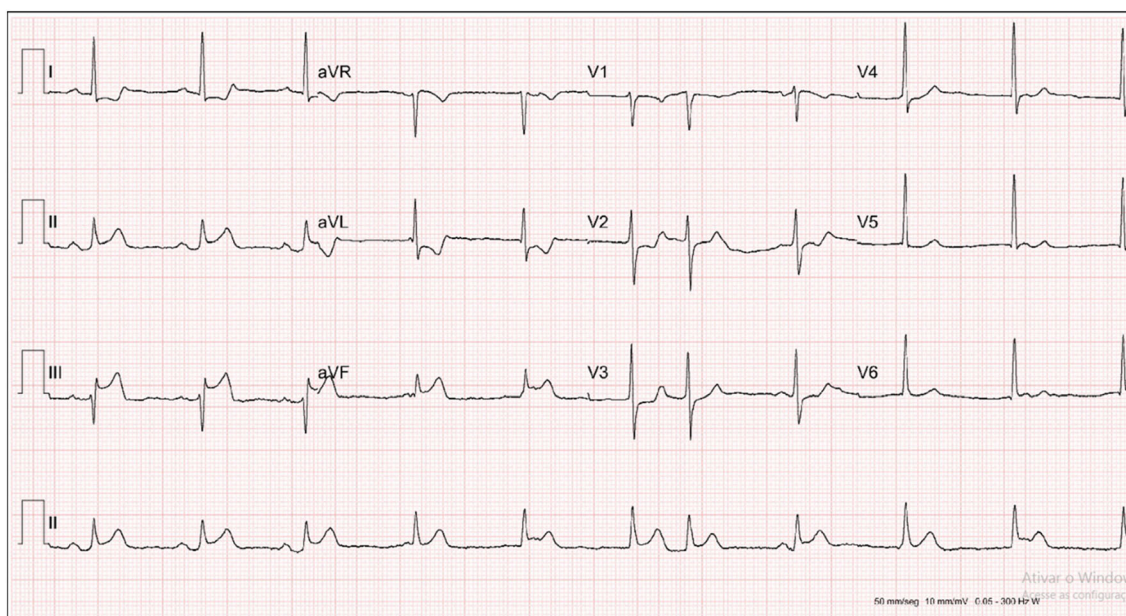
**Fig. 8** The final result after two drug-eluting stents (DES) have been placed in the proximal and distal portion of the right coronary artery (RCA)

was feeling much better, with no recurrence of symptoms. HR was 60 bpm and BP 124/76 mmHg. When last seen in March 2021, the patient had experienced no recurrence of

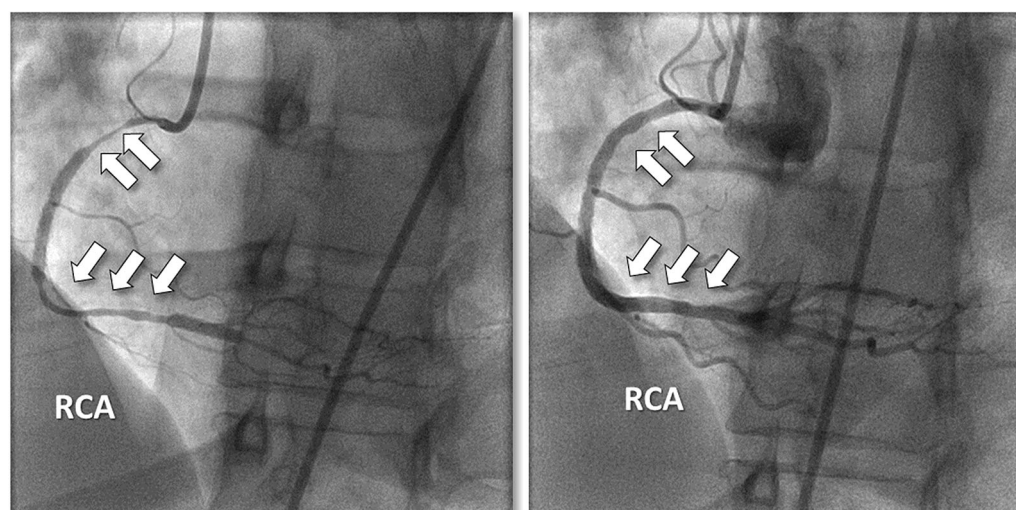
angina; she had resumed her daily life without any discomfort, and her quality of life had greatly improved. She finally quit smoking and started walking 60 min/day. Physical examination revealed a HR of 58 bpm and BP 118/72 mmHg.

## DISCUSSION

Traditionally,  $\beta$ -blockers have been considered a key player in managing patients with angina and elevated HR, adjusted to limit it to 55 to 60 bpm. However, this strategy is frequently hampered by the low tolerability of increasing doses of  $\beta$ -blockers with nonsignificant additional benefits [9]. In clinical practice, the actual dosage of any  $\beta$ -blocker varies between 50 and 75% of the recommended maximal dosage for patients with stable angina or heart failure [10]. In a very extensive registry, including more than 33,000 patients with diagnosed stable coronary artery disease (CAD), nearly half of the patients treated with  $\beta$ -blockers had resting HR above 70 bpm. Amongst the symptomatic patients in the same registry, only



**Fig. 9** Resting ECG obtained during an episode of acute chest pain showing ST-T segment elevation in inferior leads (D2, D3, and aVF) and polarization abnormalities in lateral leads (D1 and aVL)



**Fig. 10** Extensive narrowing of the right coronary artery (RCA) relieved by nitrates during STEMI

22.1% achieved HR equal to or lower than 60 bpm [11].

On the other hand, hypotension caused by increasing doses of  $\beta$ -blockers (or any BP-lowering antianginal agent) carries a high risk of worsening angina [12] and cardiovascular events [13]. The strategy of combining  $\beta$ -blockers with verapamil or diltiazem should be cautiously exercised due to the potential for developing worsening of heart failure, excessive bradycardia, or atrioventricular block.

In patients with angina and elevated HR, the addition of ivabradine was more effective than the up-titration of  $\beta$ -blockers in reducing symptoms [14] and improving physical capacity [15]. The BEAUTIFUL trial showed that in patients with CCS and LVEF < 40% with a HR above 70 bpm, ivabradine on top of optimal medical therapy led to a 36% reduction in the risk of admission for fatal and nonfatal myocardial infarction and a 30% reduction of coronary revascularization [16].

The clinical benefits and the safety profile of ivabradine may be explained by the unique mode of action of the drug. By precisely inhibiting the  $I_f$  current on the sinus node, the magnitude of the HR reduction by ivabradine is proportional to the initial HR, which decreases the risk of significant bradycardia [17]. In the SHIFT trial, bradycardia leading to the

permanent withdrawal from the study occurred in only 1% of patients on ivabradine [18].

Of particular interest in patients with angina, ivabradine increases the diastolic time, improves coronary blood flow both at rest [19] and during exercise [20], and improves the coronary flow reserve to a greater extent than  $\beta$ -blockers [21]. It also favors collateralization [22], improving the regional blood flow [23]. Finally, ivabradine may prevent deterioration of endothelial dysfunction and reduce the formation of reactive oxygen species and the atherosclerotic plaque area, as shown in experimental [24] and clinical studies [25]. All these processes elicited by ivabradine may contribute to the clinical benefits seen in patients with angina or myocardial ischemia.

We have presented two real clinical cases in patients with symptomatic CCS in whom HR control with ivabradine was fundamental for symptom control and improvement in LV function. The case studies are commonly observed in clinical practice yet pose a challenge for the attending physician to define the best medical therapy for symptom control. The patients differed in the primary mechanisms responsible for angina, but the addition of ivabradine to guideline-recommended first-line therapies for angina patients with elevated HR was well tolerated and provided both patients with rapid symptom relief. Ivabradine, due to

its effects beyond HR reduction and good tolerability, should be considered as an early ally in managing patients with angina and an elevated HR with or without LV dysfunction, as proposed by the latest European Society of Cardiology (ESC) Guidelines [6].

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**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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