Stable angina pectoris: evolving considerations for symptomatic management of patients

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There is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length and of which I do not recollect any mention among medical authors. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris.1

Since the publication of William Heberden’s brilliant paper entitled “Some Account of the Disorder of the Breast”1—which he presented in the Royal College of Physicians in London—and Edward Jenner’s subsequent theory on “the importance of the coronary arteries” at the end of the 18th century, the link between obstructive coronary artery disease and angina has been widely accepted.2 This concept, which linked angina with obstructive coronary artery stenosis caused by atherosclerosis, remained in force for a long time and was supported by the exponential growth of coronary angiography in the 20th century, which highlighted the relief of angina symptoms that follows revascularization of flow-limiting stenosis.

In 1967, however, Linkoff et al first introduced the “paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease.”3 Since then, several studies have described patients that exhibit angina-like symptoms even though their coronary angiograms do not show significant flow obstruction in the epicardial coronary arteries.4 As a consequence, considerable efforts have recently been directed toward identifying an alternative etiological theory for those patients who experience chest pain but have normal coronary angiograms and structurally normal hearts.

Why should we care?

Although mortality from cardiovascular disease in developed countries has declined slightly in recent years due to advances in both pharmacological and interventional therapies, cardiovascular disease remains a leading cause of death in these countries. Moreover, they are one of the main sources of health care expenditure and one of the principal determinants of disability. According to recent data from the United States, direct and indirect costs associated with cardiovascular disease are estimated at over $312 billion per year. While the real prevalence of stable angina pectoris is unknown and differs widely among major population studies, angina remains highly prevalent and is the most common initial symptomatic presentation of cardiovascular disease.5,6
In the past decades, research into the mechanisms underlying angina has gained interest, and a considerable number of studies have suggested that angina may be the consequence of various clinical conditions, which include not only obstructive atherosclerosis of the epicardial coronary arteries, but also functional and structural abnormalities of the coronary microcirculation.

**Are we doing enough?**

It is relatively common in daily practice to see patients who suffer from chest pain in the absence of obstructive coronary artery disease and of any other clinical condition that might either limit myocardial oxygen delivery or increase myocardial metabolic demand, such as severe aortic stenosis, anemia, or hypertrophic cardiomyopathy. Furthermore, it has been reported that in up to half of patients presenting with signs and symptoms of angina pectoris, coronary angiography does not show any obstructive coronary artery disease.

Interestingly, many features of this patient population are consistent among various studies: onset of symptoms in middle age, a markedly higher prevalence in women, severe and disabling chest pain, and inconsistent responses to conventional anti-ischemic therapy.

These patients were often disregarded as their prognosis was perceived to be benign and their long-term cardiovascular risk was thought to be low, and as a result no specific treatment beyond reassurance was offered to them. This was wrong, and it should be noted that several recent large studies with a long-term follow-up have shown that, compared with an asymptomatic reference population, these patients have a higher mortality and a greater risk of cardiovascular events. Therefore, these patients need answers, and these answers should be given by clinicians and investigators.

Until recently, the management of angina pectoris was based on a combination of lifestyle changes—especially dietary changes, weight loss in overweight or obese patients, and smoking cessation—and pharmacological and/or interventional therapies. Increased scientific awareness about this pathological entity has led to considerable efforts being made in order to improve diagnostic accuracy and develop effective therapies beyond the standard antianginal therapies based on beta-blockers, calcium channel blockers, and long-acting nitrates. As a result, alternative antianginal therapies have rapidly emerged in clinical practice as promising complementary therapies that may be used when symptoms are insufficiently controlled.

These emerging therapies include ranolazine, a metabolic antianginal agent, and ivabradine, a selective heart-rate–lowering agent whose use is supported by preliminary outcomes from registries and randomized clinical trials.8-11 There is a lot of evidence showing the benefit of ivabradine in patients with chronic angina; furthermore, the CLARIFY multinational registry (prospective observational Longitudinal Registry of patients with stable coronary artery disease) has demonstrated the importance of heart rate as a risk marker in these patients.

Despite the efforts of many over the past decades, the pathogenesis of angina and the mechanisms that contribute to its development in patients without flow-limiting stenosis remain undefined, and it can often be difficult to establish an accurate diagnosis. Basically, the most widely recognized etiological mechanisms include a functional disorder of the epicardial coronary arteries, with either endothelial dysfunction or reduced nitric oxide bioavailability, and a microcirculatory abnormality in endothelium-independent vasodilation in the absence of structural or functional epicardial coronary artery disease.

The diagnosis and management of chronic stable angina is complex, and this complexity is illustrated by the fact that the European Society of Cardiology (ESC) Guideline on the Management of Stable Coronary Artery Disease and the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease differ in several ways, despite sharing many common approaches.12,13

**Is there anything on the horizon?**

Although the development of novel therapeutic strategies in the field of cardiology has led to a decline in the incidence of some pathologies, the prevalence of angina continues to be high. More than two hundred years after its elegant description and its inherent association with flow-limiting stenosis of the epicardial coronary arteries, critically important aspects of angina pectoris remain unclear, and as a result, its diagnosis and management are challenging. It is clear, however, that the coronary microcirculation and the endothelium are involved and play an essential role.

We are convinced that in the next few years our understanding of the etiology of angina pectoris will have improved and that we will then be in a position to give answers to the non-negligible proportion of patients who have ongoing symptoms and a long-term adverse prognosis despite adequate full classic anti-ischemic therapy. Renewed efforts should be made to identify the underlying pathophysiological mechanisms by delving into the idea that stable angina can occur in the absence of flow-limiting stenosis in the coronary arteries and, likewise, that severe stenosis does not necessarily cause angina.

This issue of Medicographia aims to review all the scientific aspects of the management of angina pectoris, focusing on novel therapies and alternative etiological mechanisms beyond the “classic” etiology described several years ago.
The continuing dilemma of angina pectoris – del Val and Zamorano

References


Keywords: angina pectoris; coronary artery disease; etiology
Recent registries have provided an opportunity to analyze the clinical profiles of contemporary patients with stable coronary artery disease (SCAD). SCAD patients enrolled in randomized clinical trials tend to have similar characteristics than those included in registries. Patients with SCAD enrolled in recent studies are older, and have a higher prevalence of past myocardial infarction, heart failure, diabetes, and other comorbidities than those enrolled in earlier studies. These findings suggest that the management of outpatients with SCAD is now more complex. Although there have been improvements in the use of therapies advocated by international guidelines, many SCAD patients are still receiving suboptimal treatment. The prevalence of symptoms and major cardiovascular risk factors and their control vary markedly worldwide, reflecting the different clinical profiles of SCAD patients and the varying levels of availability of diagnostic procedures and treatments. The aim of this review is to discuss the clinical characteristics of contemporary patients with SCAD, analyze the factors influencing prognosis, and assess the changes in patient characteristics that occurred over the last decades.
ent significant coronary vessel lesions on coronary angiography. All these factors contribute to making it difficult to accurately define the population of patients with SCAD.

Data from randomized controlled trials (RCTs) are generally regarded as being of limited value here, since RCTs usually have extensive lists of exclusion criteria that may eliminate patients with comorbidities, often seen in everyday practice. For this reason, registries are considered to best reflect the demographics, treatment patterns, and outcomes of patient populations. It must be emphasized, however, that the recent SIGNIFY study (Study Assessing the Morbidity-Mortality Benefits of the I<sub>i</sub> inhibitor Ivabradine in Patients with Coronary Artery Disease) included patients with a higher prevalence of risk factors and more comorbidities than any of the global surveys conducted so far. Therefore, in SCAD, the differences in patient populations, treatment patterns, and outcomes between RCTs and surveys may not be pronounced.

Over the last 15 years several registries of SCAD patients differing in terms of geographical coverage, inclusion criteria, environment (in- or out-patients; specialist vs nonspecialist care), and outcomes measured have provided a comprehensive description of the real-life SCAD patient population. The aim of this paper is to review the clinical profiles of patients with SCAD, together with treatment patterns and outcomes, and to analyze the changes that have occurred over time.

Clinical profiles of contemporary SCAD patients

Two recent large surveys, the CLARIFY registry (prospective observational Longitudinal Registry of patients with stable coronary artery disease) and the REACH registry (Reduction of Atherothrombosis for Continued Health), have provided a global overview of patients with SCAD.

CLARIFY is an ongoing, prospective, observational, longitudinal cohort study of outpatients with SCAD with a 5-year follow-up. Between November 2009 and July 2010, a total of 33,438 patients were recruited in 45 countries in Africa, Asia, Australia, Europe, the Middle East, and the Americas (excluding the United States). In order to be eligible for the study, the patients had to meet at least one of the following criteria: documented myocardial infarction (MI) >3 months ago; >50% coronary stenosis on angiography; chest pain with myocardial ischemia confirmed by a stress test, and a history of PCI or CABG >3 months ago. The mean age of patients was 64±10 years and 78% of them were male. A majority of them had a history of MI (60%) and/or myocardial revascularization (59% PCI, 23% CABG). Only 16% of all patients had CCS class II, III, or IV angina. Comorbid conditions were frequent; hypertension was present in 71% of patients, lipid abnormalities in 75%, heart failure in 15%, diabetes in 29%, peripheral artery disease in 10%, asthma/chronic obstructive pulmonary disease (COPD) in 7%, and chronic renal disease in 22%. There were significant geographical variations in the prevalence of cardiovascular risk factors. Clinical presentation also differed between the regions. The prevalence of MI ranged from 50% in East Asia to 79% in Eastern Europe; while angina was present in 10% of patients from the Middle East or Central/South America and in 78% of those from Eastern Europe. While the use of guideline-advocated medication was generally good, risk factors were not adequately controlled. There were also sex- and age-related differences in terms of clinical presentation and management. Female patients were older than male patients, and were more likely to have diabetes and hypertension. Smoking and a history of MI were more common in men. Women were more likely to have angina, but underwent fewer revascularizations. Patients aged >75 years were less likely to be treated with aspirin, -blockers, and angiotensin-converting enzyme (ACE) inhibitors.

The worldwide REACH registry, which recruited a total of 68,236 outpatients from 29 countries between December 2003 and June 2004, comprised patients with a wider spectrum of atherothrombotic conditions: coronary artery disease, cerebrovascular disease, peripheral artery disease, or multiple risk factors for atherosclerosis. More than 45,000 patients were included in the 4-year follow-up analysis, of whom over 37,000 had either a history of MI or documented CAD. Within the CAD group, males were more prevalent (70% vs 65%) and heart failure more frequent (18% vs 12%) among patients with a history of MI than in patients with no prior acute event. The mean age was similar (68 years vs 69 years), and so was the prevalence of hypertension (79% vs 80%), hypercholesterolemia (67% vs 70%), diabetes (36% vs 37%), and current smoking (14% vs 15%). Within the entire spectrum of patients, those with a prior ischemic event at baseline had a more aggressive treatment approach.
higher risk of having a new atherothrombotic event than those with stable coronary, cerebrovascular, or peripheral artery disease (18.3 vs 12.2%; P < 0.001). Like CLARIFY, the REACH registry showed that risk factor control remains suboptimal. In the randomized, placebo-controlled SIGNIFY study—which was conducted in 51 countries worldwide and enrolled 19,102 patients between October 2009 and April 2012—the age and sex distribution (mean age 65 years, 73% males) was similar to that of recent surveys, with a very high prevalence of hypertension (86%), dyslipidemia (72%), current smoking (24%), angina (75%), diabetes (43%), and peripheral artery disease (21%) (see Table I for comparative data). Patients enrolled in SIGNIFY received excellent background drug therapy (98% of them were on antiplatelet or anticoagulant therapy, 79% took a β-blocker, and 84% were treated with an ACE inhibitor or an ARB; see Table II, page 8).

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At the European level, two studies were carried out by the European Society of Cardiology (ESC): the EuroHeart Survey, which recruited SCAD patients in 2002, and the EURObservational Research Programme, which recruited a pilot cohort of SCAD patients in 2013-2014. The recent pilot chronic ischemic cardiovascular disease registry (CICD-PILOT [Chronic Ischaemic Cardiovascular Disease Registry: Pilot phase]; part of the EURObservational Research Program) recruited 2,420 subjects scheduled for elective PCI or medical treatment, including 1,464 with SCAD, while the earlier EuroHeart Survey enrolled 3,779 patients with SCAD (for the characteristics of both cohorts see Table I). The prevalence of co-morbid conditions was much higher in CICD-PILOT, except for peripheral artery disease (PAD) and asthma/COPD. There was a noticeable improvement in secondary prevention in CICD-PILOT compared with the EuroHeart Survey (Table II).

Increased attention has recently been given to patients who have angina but do not have any visible obstructive changes on coronary arteriography. Many of these patients have occult functional or anatomical abnormalities that may be identified by additional testing. This subpopulation cannot be neglected because symptoms of angina pectoris increase the probability of disability and premature exit from the workforce even in the absence of obstructive coronary artery disease. However, since the population of patients with angina without obstructive coronary stenosis is rather poorly defined, it will not be further discussed in this paper.

Table I. Characteristics of patients in major SCAD registries.

<table>
<thead>
<tr>
<th>Recruitment period (years)</th>
<th>Patients (N)</th>
<th>Age (years; mean±SD)</th>
<th>Males (%)</th>
<th>Angina (%)</th>
<th>Current smokers (%)</th>
<th>Hypertension (%)</th>
<th>Hyperlipidemia (%)</th>
<th>Diabetes (%)</th>
<th>Renal failure (%)</th>
<th>Heart failure (%)</th>
<th>Previous MI (%)</th>
<th>Previous PCI (%)</th>
<th>Previous CABG (%)</th>
<th>PAD (%)</th>
<th>Asthma/COPD (%)</th>
</tr>
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<tr>
<td>CASS Registry²</td>
<td>1975-1979</td>
<td>24,959</td>
<td>55+9</td>
<td>79</td>
<td>27</td>
<td>36</td>
<td>-</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mayo 1⁴</td>
<td>1979-1989</td>
<td>1,928</td>
<td>62+11</td>
<td>72</td>
<td>34</td>
<td>46</td>
<td>42</td>
<td>14</td>
<td>10</td>
<td>-</td>
<td>7</td>
<td>5</td>
<td>0</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Duke⁷</td>
<td>1985-1989</td>
<td>1,471</td>
<td>61+10</td>
<td>72</td>
<td>23</td>
<td>56</td>
<td>56</td>
<td>18</td>
<td>14</td>
<td>-</td>
<td>7</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>EHS³</td>
<td>2002-2004</td>
<td>3,779</td>
<td>61+11</td>
<td>58</td>
<td>23</td>
<td>56</td>
<td>58</td>
<td>18</td>
<td>18</td>
<td>-</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>REACH Post MI²</td>
<td>2003-2004</td>
<td>21,890</td>
<td>68+10</td>
<td>70</td>
<td>14</td>
<td>79</td>
<td>66</td>
<td>12</td>
<td>14</td>
<td>-</td>
<td>7</td>
<td>0</td>
<td>5</td>
<td>8</td>
<td>-</td>
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<tr>
<td>REACH SCAD⁴</td>
<td>2003-2006</td>
<td>15,264</td>
<td>69+10</td>
<td>65</td>
<td>12</td>
<td>79</td>
<td>67</td>
<td>15</td>
<td>12</td>
<td>-</td>
<td>7</td>
<td>0</td>
<td>16</td>
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<td>7</td>
</tr>
<tr>
<td>Mayo 4⁴</td>
<td>2009-2010</td>
<td>1,463</td>
<td>67+12</td>
<td>71</td>
<td>12</td>
<td>78</td>
<td>70</td>
<td>12</td>
<td>12</td>
<td>-</td>
<td>7</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>CLARIFY⁴,⁵</td>
<td>2010-2012</td>
<td>33,285</td>
<td>64+10</td>
<td>78</td>
<td>12</td>
<td>79</td>
<td>70</td>
<td>15</td>
<td>12</td>
<td>-</td>
<td>7</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>EurObs PCI⁶</td>
<td>2013-2014</td>
<td>933</td>
<td>66+10</td>
<td>72</td>
<td>12</td>
<td>85</td>
<td>70</td>
<td>15</td>
<td>12</td>
<td>-</td>
<td>7</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>EurObs No PCI⁷</td>
<td>2013-2014</td>
<td>531</td>
<td>67+11</td>
<td>66</td>
<td>12</td>
<td>82</td>
<td>70</td>
<td>15</td>
<td>12</td>
<td>-</td>
<td>7</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

* past and current smokers; ** severe renal failure; § any revascularization; # PAD requiring revascularization. (-) denotes no data. Values are rounded to the nearest integer.

Table I. Characteristics of patients in major SCAD registries. Abbreviations: CABG, coronary artery bypass grafting; CASS, Coronary Artery Surgery Study; CLARIFY, Prospective observational Longitudinal Registry of patients with stable coronary artery disease; COPD, chronic obstructive pulmonary disease; EHS, EuroHeart Survey; EurObs, EURObservational Research Programme; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; REACH, Reduction of Atherothrombosis for Continued Health; SD, standard deviation.
Clinical outcomes

Data from RCTs and surveys indicate that the annual mortality rate in patients with SCAD ranges from 1.2% to 2.4%, with an annual incidence of cardiac death between 0.6% and 1.4%, and an annual incidence of nonfatal MI between 0.6% and 2.7%. The incidence of cardiovascular or cardiac deaths differs between studies, depending on patient characteristics.

For example, in the COURAGE trial27 (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation) and in the CORONOR registry (Suivi d’une cohorte de patients COROnariens stables en région NORd-pas-de-Calais [cohort study of coronary artery disease patients from Nord-Pas-de-Calais, France])21 most deaths were noncardiovascular, 73%, and 55%, respectively, while in the SIGNIFY trial,9 67% of patients had neither angina nor ischemia. The results of the SIGNIFY study indicate that in patients who had SCAD without heart failure, heart rate is not a modifiable determinant of outcome.1 However, improving heart rate control is likely to improve the symptoms, but not the outcome.

Increased heart rate is a major factor associated with ischemia and angina, and an important marker of risk. At the same time, there is a large body of evidence showing that heart rate control is inadequate in a high proportion of patients despite the widespread use of -blockers.9,32 The results of the SIGNIFY study indicate that in patients who had SCAD without heart failure, heart rate is not a modifiable determinant of outcome. Thus, improving heart rate control is likely to improve the symptoms, but not the outcome.

Statin and antiplatelet agents improve the prognosis of patients with SCAD.4 Their use has universally increased over the years (Table II),11,13,16,21,25 but in many geographical areas their use is still suboptimal. Surgical revascularization has the potential to decrease cardiac mortality in SCAD patients with extensive ischemia, but so far there is no evidence that the same is true for PCI.27 The ongoing ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; NCT01471522) is likely to provide definitive information.

Table II.

<table>
<thead>
<tr>
<th>Abbreviations: ACEi, angiotensin convertase enzyme inhibitor; ARB, angiotensin receptor blocker; CADENCE, Coronary Artery Disease in eGeneral practice; CASS, Coronary Artery Surgery Study; CLARIFY, Prospective observational Longitudinal Registry of patients with stable coronary artery disease; CORONOR, Suivi d’une cohorte de patients COROnariens stables en région NORd-pas-de-Calais [cohort study of coronary artery disease patients from Nord-Pas-de-Calais, France]; EHS, EuroHeart Survey; EurObs, EURObservational Research Programme; INDYCE, Insuffisance coronaire stable, Dysfonction ventriculaire gauche et fréquence cardiaque (left ventricular dysfunction and heart rate in stable coronary artery disease patients [registry]); MI, myocardial infarction; SCAD, stable coronary artery disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
</tr>
<tr>
<td>Statin (%)</td>
</tr>
<tr>
<td>Antiplatelet (%)</td>
</tr>
<tr>
<td>-Blocker (%)</td>
</tr>
<tr>
<td>ACEi or ARB (%)</td>
</tr>
<tr>
<td>PCI (%)</td>
</tr>
<tr>
<td>EurObs No PCI (%)</td>
</tr>
</tbody>
</table>

* lipid-lowering drug; # aspirin; ## other antiplatelet drug; ** any anti thrombotic drug. (-) denotes no data. Values are rounded to the nearest integer.
Changing characteristics of patients with SCAD over time

The first registries of patients with SCAD date back to the 1970s.1,2,3 Data from the CASS registry—which comprised almost 25,000 patients referred for coronary angiography who did not qualify for the CASS study (Coronary Artery Surgery Study)—was collected between 1975 and 1979.4 The Mayo Clinic Registry included over 8,900 patients who underwent PCI at the Mayo Clinic in the years 1979-2006.5 The majority of later registries, run on a global, European, or single-country scale, focused on ambulatory patients with SCAD managed by cardiologists or primary care physicians.6,7,8,9,10-16 Despite their differences, these registries seem to accurately depict the changes in patient characteristics and treatment over time (see Table I).

Over time the mean age of patients has increased by more than 10 years and the proportion of female patients has increased. The initial studies included almost exclusively symptomatic patients with angina, while in the subsequent ones there was considerable variability in the proportion of symptomatic patients, which ranged from 16% to 85%. There has been a steady increase in the prevalence of comorbidities, including hypertension, lipid abnormalities, diabetes, history of MI, heart failure, and renal failure. The same seems to be true for peripheral artery disease and asthma/COPD, although the data from older studies tend to be incomplete. While these changes can be in part attributed to the ageing of the SCAD population and to changes in diagnostic criteria, they appear to be representative of the true differences between patient cohorts. Obviously, contemporary patients are more likely to have a history of coronary revascularization (PCI, CABG, or both).

Of interest, the longitudinal, single-center registry of consecutive patients undergoing PCI for SCAD at the Mayo Clinic—which took place over 27 years and was divided into four time periods—provided a good reflection of secular trends. It showed that age and the prevalence of diabetes, hypertension, and hyperlipidemia had all increased over each time period.15 Pharmacotherapy has also evolved over the years (Table II). When the early registries were set up, secondary prevention in its present form did not exist, and in a number of papers there was no mention of drug therapy. At the beginning of the 21st century, only a minority of patients in Europe were treated with a statin, -blocker, and antiplatelet agent.12 Later registries showed a significant positive change in this respect, but there is still room for improvement.14-16-21

Summary

The populations of patients with SCAD included in observational registries and randomized clinical trials differ in terms of age, proportion of male to female patients, medical history, presence and characteristics of symptoms, and comorbidities. Generally, their prognosis is good, and in some studies it is not much different from the general age- and sex-matched population. However, patients of advanced age, with heart failure, renal dysfunction, diabetes, COPD, and PAD, as well as those with angina and ischemia or a previous ischemic event are at increased risk of an incident cardiovascular event.

Over the last decades, there has been a clear change in the characteristics of patients with SCAD. Compared with patients enrolled at the end of the 20th century, contemporary patients with SCAD are older and are more likely to have a history of MI and coronary revascularization (PCI, CABG, or both). The prevalence of heart failure, diabetes, chronic renal and pulmonary disease, and peripheral artery disease has increased substantially. Thus, today’s patients represent a higher-risk group and are more difficult to manage due to the increased complexity of their medical problems.

There is considerable geographical variation in the clinical presentation and management of patients with SCAD. Although preventive pharmacotherapy has improved, it is still inadequate in many areas; as a result, risk factor control remains suboptimal overall.
STABLE ANGINA PECTORIS: EVOLVING CONSIDERATIONS
FOR SYMPTOMATIC MANAGEMENT OF PATIENTS


Keywords: clinical trial; coronary artery disease; patient profile; prognosis; registry; stable angina; secular trends
Impact of chronic stable angina on health status – Beltrame

Angina is associated with reduced physical limitations and a poorer quality of life. The more frequent the angina, the greater the impairment in physical limitation and quality of life. While enquiring about the frequency of angina provides some insights into the disability associated with the disorder, it is important to understand the full impact of the condition on the patient's life. Unfortunately, clinicians may not be completely aware of the angina burden experienced by their patients, as alluded to in the CADENCE study (Coronary Artery Disease in gENeral practice). The objective of this review is to discuss the impact of stable angina on the health status of patients, with a focus on the existing gap between the patient's experience and the clinician's perception of the disability associated with angina and how this gap could potentially be bridged.

Stable angina – a different emphasis in the CAD spectrum

Coronary artery disease (CAD) may clinically manifest as an acute or chronic coronary syndrome, with the latter more often referred to as “chronic stable angina” or simply “stable angina.” Whereas acute coronary syndromes constitute a significant proportion of in-hospital clinical activity and therefore attract considerable medical attention, stable angina is disseminated within the community and comes to medical attention in the general practitioner's or specialist's clinic. Indeed, in developed countries the estimated prevalence of stable angina is 5% in the male population and 4% in the female population. Furthermore, the incidence of newly diagnosed cases in these developed communities is 49/100 000 males and 28/100 000 females. Hence stable angina is a significant medical problem within the community, although it receives less attention than the more acute state. The principal objectives in the management of CAD, which are applicable to both acute and chronic forms of the disease, include prevention of cardiac events (death and myocardial infarction) and improvement of health status (Figure 1, page 12).

Health status is the impact of the CAD process on the patient's lifestyle and includes the associated symptoms, functional limitations, and impairment on quality of life (Figure 2, page 12). Since coronary atherosclerosis is the most common underlying pathophysiological process for both the acute and chronic forms of CAD, the available therapies are similar. As shown in Figure 1, these include (i) revascularization therapies—coronary artery bypass grafting and percutaneous coronary interventions, (ii) cardioprotective therapies—such as anti-platelet agents, statins,
Table Angina Pectoris: Evolving Considerations for Symptomatic Management of Patients

In contemporary clinical practice, but postinfarct angina that is not amenable to revascularization therapies is often managed with conventional antianginal therapies (nitrates, β-blockers, and calcium channel blockers).

Although the treatment goals and available therapies in the acute and chronic forms of CAD are similar, the difference in prognosis between these clinical manifestations influences the emphasis placed on their respective clinical management. In acute coronary syndromes, there is a high risk of death within the first 30 days of presentation (between 2% and 10% at 30 days), primarily due to platelet activation/thrombus generation as a result of plaque disruption. In this context, antiplatelet agents, statins, and ACE inhibitors have been shown to be effective in reducing cardiac events. Similarly, early revascularization strategies have been shown not only to reduce cardiac events, but also to have an impact on health status, often improving symptoms. The use of anti-ischemic agents in acute coronary syndrome (ACS) has received less attention in contrast to ACS, where the 1-year mortality rate ranges between 8% and 10%; patients with stable angina have an annual mortality risk of 1.2% to 2.4% per year, and the condition has a chronic course so the treatment goals are focused toward improving health status. This does not diminish the essential role of cardioprotective agents, which should be utilized in all patients with stable angina. However, the role of revascularization therapies is less imperative in patients with stable angina since their impact in the prevention of cardiac events in these patients is limited. Furthermore, revascularization therapy provides only a small incremental benefit over optimal medical therapy (cardioprotective and anti-ischemic therapies) in controlling angina symptoms in patients with stable angina.

In summary, acute and chronic CAD syndromes have a common therapeutic armamentarium to target the underlying CAD; however, the relatively lower risk of cardiac events in stable angina results in some of these therapies being less effective and therefore having a less central focus in the management of these patients. Moreover, due to the chronic nature of stable angina, improving patient health status should be a central focus.

The importance of health status in stable angina

The consideration of health status in stable angina provides a more global and patient-orientated focus in clinical man-

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CADENCE</td>
<td>Coronary Artery Disease in gENeral practICE [study]</td>
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<tr>
<td>CLARIFY</td>
<td>Prospective observational LongitudinAl Registry of patients with stable coronary artery disease</td>
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<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<tr>
<td>SAQ</td>
<td>Seattle Angina Questionnaire</td>
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Angina is the hallmark symptom of stable angina and the clinical manifestation of myocardial ischemia. The American College of Physicians’ criteria for angina include (i) substernal chest discomfort with a characteristic quality and duration, (ii) provoked by exertion or emotional stress, and (iii) promptly relieved by rest or short-acting nitrates. If all three criteria are met, the symptom is considered as “definite angina,” whereas with only two criteria it is labeled as “probable angina.” If only one criterion is met, then it is considered as “noncardiac chest pain.”

In addition to confirming the presence of angina symptoms, clinical assessment should focus on quantitating the extent of the symptoms, in particular angina frequency (number of episodes over time) and the frequency of short-acting nitrate consumption to alleviate the chest pain. This latter measure provides a robust method of assessing the number of angina episodes that sufficiently concern the patient to seek treatment. Together these measures provide insights into the extent of the symptoms experienced by a patient with stable angina.

Physical limitation due to angina has been shown to be an independent determinant of all-cause mortality among patients with stable angina. In a study of over 8000 outpatients with stable angina followed for an average of 2 years, the extent of physical limitation was found to be related to all-cause mortality when compared with patients who had no limitations; ie, a hazard ratio of 1.27 (95% confidence interval [CI], 0.98-1.64) with mild limitation, of 1.61 (95% CI, 1.27-2.05) with moderate limitation, and of 2.55 (95% CI, 1.97-3.30) with severe limitation. This again reflects the clinical importance of health status in stable angina.

In addition to physical limitations, patients with stable angina may be emotionally or socially limited by their condition. Emotional limitations may manifest as anxiety disorders, with excessive worry relating to the CAD diagnosis. Social limitations may also occur with patients avoiding activities such as shopping or visiting friends since it precipitates angina. Hence the functional limitations resulting from stable angina are multi-dimensional and should be considered in the clinical assessment of patients.

In health status assessment, quality of life needs to be specifically evaluated in relation to the impact of stable angina; hence health-related quality of life (HRQoL) is a better outcome measure. Importantly, HRQoL is the “patients’ perception” of how the disease process impacts on their lifestyle and not the “clinician’s perception.” For example, a patient who experiences angina when walking 100 meters may be perceived by a clinician as having a significant impairment in his/her quality of life, yet the patient may perceive this as no significant impairment since he/she is content with being angina-free in undertaking the gardening. In contrast, an elderly patient experiencing angina only when playing competition table tennis may be perceived as only a mild impairment by a clinician, but this may be devastating for the patient. As with the other components of health status, HRQoL is associated with all-cause mortality. In a methodical review of the impact of health status domains on all-cause mortality in stable angina patients, Spertus et al demonstrated that physical limitation was the strongest determinant, followed by angina frequency, with HRQoL having a smaller impact.

The key determinants of global HRQoL include depression and anxiety. Depression in patients with stable angina has been strongly associated with an impaired HRQoL, as demonstrated in multiple studies. Women are more often affected by depression, and studies have demonstrated that women with stable angina have a poorer HRQoL than their male counterparts. However, Norris et al demonstrated that women with stable angina still have a poorer HRQoL, even following adjustment for depression, which suggests that there is an inherent sex difference in HRQoL among patients with stable angina.
Assessment of health status in stable angina

With an understanding that health status has three key components (angina symptoms, functional limitations, and HRQoL) and that these components are each related to mortality in patients with stable angina, the importance of evaluating health status in patients is clear, especially considering the chronic nature of the disorder. The assessment of health status is best achieved by utilizing established health status assessment instruments that are typically completed by the patient. However, lessons learned from the application of these questionnaires should also be translated into routine clinical assessment.

◆ Health status instruments

These questionnaires can be either generic or disease-specific. Generic health status instruments allow comparison across disease states since the questions are not specific for any one condition. Commonly utilized generic instruments include the Medical Outcomes Short Form-36 (SF-36 or its shorter version the SF-12), EuroQoL (EQ-5D), World Health Organization Quality of Life assessment (WHOQOL), Nottingham Health Profile, and McMaster Health Index Questionnaire. In contrast, disease-specific instruments for coronary artery disease have been developed and provide a more specific assessment in relation to stable angina. The McNew Scale is an example of a disease-specific coronary artery disease questionnaire, but the most commonly used instrument is the Seattle Angina Questionnaire (SAQ), which has been well validated and is available in multiple languages.

Considering that depression is a major determinant of HRQoL and may impact on the components of health status, it would be prudent to specifically assess depression in patients with stable angina. Multiple instruments for the assessment of depression have been used in patients with stable angina. These include the Patient Health Questionnaire (PHQ-9), the Center for Epidemiologic Studies Depression Scale (CES-D), the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), and the Cardiac Depression Scale (CDS).

Many of these instruments involve extensive questioning and are thus of limited benefit as screening tools in clinical practice; consequently, there is no consensus as to which one of them is the optimal instrument for depression screening of CAD patients. However, shorter versions of these questionnaires (especially the PHQ-2 and the CDS) have been recommended as routine screening tools in cardiac patients.

◆ Clinical assessment

The traditional clinical measure of health status in patients with stable angina is the Canadian Cardiovascular Society Classification (CCSC). This simple, 4-scale grading system, classifies angina on the basis of its impact on physical activity. This includes Class I – only strenuous effort precipitates angina, Class II – ordinary activities only slightly limited by angina, Class III – ordinary activities markedly limited by angina, Class IV – unable to perform any physical activity because of angina. Although easily administered, it has a number of limitations including (i) the physician’s interpretation of the patient’s symptoms, (ii) it is unclear, and thus variable, how angina-free patients are classified, (iii) it does not record many components of health status including angina frequency, emotional impairments, social impairments, and quality of life. Hence there is a need for improved clinical assessment of health status.

An important lesson from previous health status studies of stable angina is directly questioning and documenting the patient’s symptoms and functional limitations. The CADENCE study (Coronary Artery Disease in General practice) recruited 207 primary care practitioners, who each assessed between 10 and 15 consecutive stable angina patients (n=2031) in relation to their clinical status and also asked them to complete an SAQ. Although the clinicians perceived that 80% of their patients had “optimally controlled” angina, only 52% of patients reported being “angina-free” and only 47% claimed their “enjoyment in life” was not limited by their angina. These clinician-patient discrepancies in health status assessment are not limited to primary care practitioners, since similar discrepancies were observed in cardiology outpatients.

These discrepancies underscore the need for patient-related outcome measures in clinical practice. Ultimately, no matter how astute clinicians are, only the patients themselves can detail the frequency of their angina attacks and their impact on their functioning and lifestyle. Even when the clinician attempts to closely detail these health status attributes, discrepancies may occur either as a result of clinician misperception or patient anxiety and recall. Thus the routine use of abridged versions of the disease-specific instruments, such as the SAQ-7, may be the most effective approach to assess patient health status. This approach of incorporating health status assessment into clinical evaluation of CAD patients has been adopted by ICHOM (International Consortium for Health Outcome Measurement), as reflected in their CAD Standards.

An observation evident from patient assessment of health status that has clinical utility is the relationship between angina frequency and functional status/quality of life. As summarized in Figure 3, the CADENCE study demonstrated that there was a linear relationship between angina frequency and physical limitation as assessed by the SAQ. Moreover, this linear relationship was also evident between angina frequency and quality of life. Thus, as would be intuitively expected, the more angina symptoms a patient experiences, the more physical limitations he/she incurs and the greater the impact on quality of life. Thus, quantifying the frequency of angina at each clinical visit may provide the clinician with insights into other aspects of the patient’s health status.
Impact of chronic stable angina on health status – Beltrame

**Stable angina pectoris: evolving considerations**

**For symptomatic management of patients**

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**Implications in stable angina management**

In the preceding sections discussions have focused upon (i) the differences between ACS and stable angina despite their sharing a common underlying atherosclerotic process, and the need to especially focus on health status in stable angina given the low risk of cardiac events; (ii) the key components of health status including angina symptoms, functional limitations, and quality of life; and (iii) the assessment of health status in stable angina utilizing both clinical approaches and disease-specific instruments such as the SAQ. The question that now arises is how we utilize this knowledge in the management of our stable angina patients and whether we can improve their health status?

**Impact of CAD therapies on health status**

Available conventional therapies for stable angina include cardioprotective, antianginal, and revascularization therapies (Figure 1). The cardioprotective therapies are essential to reduce cardiovascular events but also, surprisingly, have an impact on health status. For example, statins have been shown to improve depression in patients with CAD, and thus improve health status. By design, antianginal therapies improve symptoms and are therefore expected to have flow-on benefits for functional capacity, quality of life, and thus health status. Indeed, health status is now routinely assessed in the development of new antianginal agents. For example, ranolazine has been shown to reduce angina frequency and improve physical functioning in patients with stable angina.

Revascularization therapies improve health status in patients with stable angina, but their incremental benefit over optimal medical (cardioprotective and antianginal) therapy is limited. This is exemplified by the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) where the benefits in health status of percutaneous coronary intervention (PCI) disappeared within 36 months; an effect that has also been observed in “real life” registry data.

**Therapeutic appropriateness**

Considering the limited impact of revascularization on cardiac events and health status, the appropriateness of these procedures needs to be carefully considered in patients with stable angina. This is reflected in the appropriate use criteria for revascularization, where the procedure has limited justification in patients who have few symptoms, or when noninvasive investigations suggest a low cardiac risk and minimal medical therapy has been prescribed. Future iterations of these criteria may incorporate baseline health status assessment, considering this is the primary goal of therapy.

**Precision medicine**

Stable angina is potentially a prime example of implementing precision medicine, where health care is customized to the individual patient. This should involve both a holistic approach and the patient’s involvement in shared decision making. Treatment should not be disease-focused, but should consider the whole patient. Hence the treatment of depression should be considered equally as important as the treatment of the anginal symptoms, since both have a significant impact on health status. Shared decision making is especially important in deciding when to embark upon revascularization therapy. For example, should PCI be considered for uncomplicated single-vessel disease when two antianginal medications have failed or should it only be considered when triple therapy + ranolazine has failed? Involving patients in these relatively arbitrary decisions will provide the opinion of the key person in the therapeutic paradigm since patients are best placed to balance the decision in relation to their overall health status.

**Concluding remarks**

Stable angina is a chronic disease that impacts on health status, and thus its management should particularly focus on improving health status in addition to minimizing the risk of cardiac events. The assessment of health status needs to be routine in clinical practice, and therapies that improve symptoms, functional limitations, and quality of life should be utilized. This will be optimized with a precision medicine approach involving shared decision making with the patient.

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Impact of chronic stable angina on health status – Beltrame
References


Keywords: angina pectoris; coronary artery disease; health status; quality of life; stable angina
ATHEROSCLEROTIC disease of the epicardial coronary arteries has been accepted as the cause of angina pectoris for more than two centuries. Subsequently, spasm of the epicardial coronary arteries was recognized as an adjunctive functional mechanism of myocardial ischemia and angina. However, the epicardial arteries, often referred to as the conductance vessels, are only one segment of the arterial coronary circulation. These vessels give rise to smaller arteries and arterioles, which in turn feed the capillaries and constitute the coronary microcirculation, the main site of myocardial blood flow regulation. The term “coronary microvascular dysfunction” was coined to provide an overarching definition that would encompass a large number of clinical scenarios characterized by evidence of a reduced coronary flow reserve and evidence of ischemia that could not be explained by an epicardial stenosis. It was also realized that coronary microvascular dysfunction could coexist with coronary artery disease, providing added prognostic value. In conclusion, angina is the main symptom of myocardial ischemia, which, for several decades, was thought to be only caused by either structural or functional disease of the epicardial coronary arteries. However, it has recently become apparent that dysfunction of the coronary microcirculation, alone or in combination with epicardial disease, is another mechanism of myocardial ischemia and angina.

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Over 200 years ago, Heberden described a relationship between anginal pain and the heart.1 The role of sympathetic afferents in cardiac nociception was recognized a century later, and the causal contribution of reversible myocardial ischemia was suggested by Keefer and Resnik in 1928.1 The anatomical pathways for the transmission of peripheral painful stimuli were established mostly on the basis of invasive experiments in animals. However, beyond the thalamic level, the central connections mediating visceral pain perception and the affective response to it have remained unclear for many years. Positron emission tomography (PET) is a powerful technique for assessing regional brain function. PET quantifies regional cerebral blood flow, a highly reliable index of cerebral glucose consumption, which increases regionally when a given cerebral territory is activated.2 Rosen et al have applied this technique to define the functional central nervous pathways activated during angina pectoris in patients with coronary artery disease (CAD).3 They found that, in addition to the hypothalamus and thalamus, several cortical structures were activated bilaterally during an episode of angina. The same

Myocardial ischemia and angina

Patients with chronic angina have an increased risk of major cardiovascular events. Factors associated with an increased risk of myocardial infarction or death in angina patients include advanced age, severe angina, coexisting chronic kidney disease and diabetes, abnormal myocardial function, and the inability to perform a stress test. These patients also have substantial rates of complications, leading to increased health care expenditures. Furthermore, anginal symptoms can seriously restrict their everyday activities and quality of life, and often lead to premature retirement in patients of working age.

Angina caused by obstructive CAD

Angina pectoris is caused by myocardial ischemia, and atherosclerotic disease of the epicardial coronary arteries has been accepted as the cause of angina pectoris for more than two centuries. The clinical manifestations of chronic CAD are related to the progressive impairment of tissue perfusion due to the growth of plaque inside the vessel lumen, which leads to a progressive reduction in the coronary flow reserve (CFR)—ie, the ratio of coronary blood flow during near-maximal coronary vasodilatation to baseline flow (Figure 2). The clinical counterpart of the reduction in CFR is demand ischemia and effort angina. Generally, these patients have risk factors for CAD and the diagnosis of typical, stable angina includes predictable and reproducible chest pain or discomfort induced by physical activity or by emotional stress. The symptoms can get worse in cold weather or after a meal and are relieved by rest or sublingual nitroglycerin. Stress testing using noninvasive techniques, such as nuclear perfusion imaging or echocardiography, can provide evidence of regional reversible per-
fusion abnormalities or regional contractile abnormalities generally associated with ST-segment depression on an electrocardiogram (ECG). Coronary angiography typically demonstrates the presence of one or more stenosis in the epicardial coronary arteries, usually reducing the lumen by more than 70%.

**Angina caused by coronary spasm**

Clinically, not all patients present with the classic (typical) anginal symptoms described above. Symptoms may occur at rest, rather than on exertion. Attacks may occur at night, generally in clusters, and patients may have a negative treadmill stress test. During an attack the ECG shows ST-segment elevation. Symptoms and ECG changes generally subside promptly after administration of nitrates. Many of these patients may have concurrent atherosclerosis of a major coronary artery, but this is often mild or not in proportion to the severity of symptoms. This condition was first described as “a variant form of angina pectoris” in 1959 by the American cardiologist Dr Myron Prinzmetal. Prinzmetal angina—also known as variant angina—is a syndrome that typically consists of angina at rest occurring in cycles. It is caused by coronary vasospasm, which is brought about by contraction of the smooth muscles in the vessel wall.

Specific provocative testing, normally carried out during coronary angiography has been used for more than 40 years to provoke an attack when Prinzmetal angina is suspected. At present, intracoronary injection of acetylcholine is used during monitoring of patient symptoms, ECG, and angiographic documentation of coronary artery spasm. Alternatively, the alkaloid ergonovine can be administered by intravenous or intracoronary injection. A positive test must induce all of the complications were observed, and only 1% of the patients had minor complications such as transient arrhythmias.

**Angina caused by coronary microvascular dysfunction**

A sizeable proportion of patients undergoing coronary angiography for anginal symptoms are found to have normal coronary arteries or nonobstructive CAD (stenosis <50%). For many years there was uncertainty regarding the real significance of anginal symptoms that are accompanied by electrocardiographic evidence of ischemia during stress. A study published by Cannon and Epstein in 1988 demonstrated that, compared with a group of asymptomatic controls, in patients with chest pain and angiographically normal coronary arteries, the coronary microcirculation has a heightened sensitivity to vasoconstrictor stimuli and a limited microvascular vasodilator capacity during atrial pacing. This condition was termed “microvascular angina.”

It is worth noting that the epicardial coronary arteries—often referred to as the conductance vessels—are only one segment of the arterial coronary circulation. These vessels give rise to smaller arteries and arterioles, which in turn feed the capillaries and constitute the coronary microcirculation, the main site of myocardial blood flow regulation. The coronary arterial system is composed of three compartments that have different functions, although the borders of each compartment cannot be clearly defined anatomically. The large epicardial coronary arteries, which have a diameter ranging from approximately 500 mm to 2 to 5 mm, constitute the proximal compartment. They have a capacitance function and offer little resistance to coronary blood flow. During systole, they accumulate elastic energy as they increase their blood content by up to about 25%. This elastic energy is converted into blood kinetic energy at the beginning of diastole and contributes to the prompt reopening of the intramyocardial vessels that are squeezed closed during systole. The prearterioles, which have a diameter ranging from approximately 100 mm to 500 mm, and are characterized by a measurable pressure drop along their length, constitute the intermediate compartment. These vessels are not under direct vasomotor control by diffusible myocardial metabolites because of their extramyocardial position and wall thickness. Their specific function is to main-

### Selected Abbreviations and Acronyms

<table>
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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CFR</td>
<td>coronary flow reserve</td>
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<tr>
<td>CMD</td>
<td>coronary microvascular dysfunction</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<tr>
<td>PET</td>
<td>positron emission tomography</td>
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Stable angina pectoris: evolving considerations
for symptomatic management of patients

Acetylcholine i.c.

Nitroglycerine i.c.

Figure 3. Epicardial and microvascular spasm.
A and B. Left coronary artery angiograms and ECGs of a patient with epicardial spasm. Note the diffuse, but distal accentuated narrowing of the left anterior descending artery during acetylcholine (ACH) infusion (arrows) together with ischemic ECG shifts (A) and the resolution of both findings after intracoronary nitroglycerine (B). C and D. Example of a patient with microvascular spasm. During ACH infusion the patient experienced angina pain (angina reproduction), and there were ischemic ECG changes, but no epicardial constriction (C). After intracoronary nitroglycerine infusion, the chest pain and ECG changes resolved (D).


Figure 4. Mechanisms of myocardial ischemia.
In addition to the “classic” mechanisms (ie, atherosclerotic disease and vasospastic disease) that lead to myocardial ischemia, coronary microvascular dysfunction has recently emerged as a “third” potential mechanism of myocardial ischemia. As with the other two mechanisms, coronary microvascular dysfunction (alone or in combination with the other two) can lead to transient myocardial ischemia in patients with coronary artery disease.
Abbreviations: CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction.


The not-so-short list of reasons for angina – Camici

Maintain pressure at the origin of the arterioles within a narrow range when coronary perfusion pressure or flow changes. Proximal prearterioles are more responsive to changes in flow, whereas distal prearterioles are more responsive to changes in pressure. Finally, the intramural arterioles form the more distal compartment; they have diameters of less than 100 μm and are characterized by a considerable drop in pressure along their path. Under resting conditions, the tone of the coronary microvasculature is high. This intrinsically high resting tone allows the coronary circulation to increase flow when myocardial oxygen consumption increases through rapid changes in small vessel diameter, a mechanism known as functional hyperemia. The fall in arteriolar resistance drives a number of subsequent vascular adaptations that involve both prearterioles and arteries. The initial arteriolar response is due to the strict cross-talk that exists between these vessels and contracting cardiomyocytes, which is the basis of metabolic vasodilatation.

Stable plaque

Reduction in CFR

Demand ischemia ± angina

Plaque rupture

Acute coronary syndromes/infarction

Microvascular dysfunction

Impairs coronary physiology and myocardial blood flow in subjects with risk factors

Contributes to myocardial ischemia in CAD and CMP

Induces severe acute ischemia ‘Takotsubo’

Vulnerable plaque

Focal/transient vasospasm

Prinzmetal angina

Myocardial infarction

Persistent vasospasm

These three mechanisms can overlap

Atherosclerotic disease

Vasospastic disease
There is no technique at present that allows the direct visualization of the coronary microcirculation in vivo. Coronary microvascular dysfunction can be indirectly assessed using several invasive and noninvasive techniques that enable the measurement of parameters such as myocardial blood flow and CFR, which, under normal circumstances, are strongly dependent on the functional integrity of the coronary microcirculation.

The development and refinement of noninvasive cardiac imaging over the past two decades has provided new tools for the identification of preclinical disease. A bulk of studies, mainly using PET for the noninvasive quantification of regional myocardial blood flow, have demonstrated that dysfunction of the coronary microcirculation occurs in many clinical conditions in the absence of demonstrable stenoses in the large epicardial arteries. Studies in asymptomatic subjects, but with risk factors for CAD such as hypercholesterolemia, essential hypertension, diabetes mellitus, and smoking, have provided evidence of how these risk factors translate into measurable damage to the coronary microcirculation.20

The term “coronary microvascular dysfunction” (CMD) was coined to provide an overarching definition that would encompass a large number of clinical scenarios characterized by evidence of a reduced CFR and evidence of ischemia that could not be explained by an epicardial stenosis.21 It was also realized that CMD could coexist with CAD, thereby providing added prognostic value (Figure 4).22 Coronary microvascular dysfunction can result from functional and/or structural alterations. The importance of these mechanisms seems to vary across clinical settings, but several of them may coexist in the same condition (Table I).22 Clinically, CMD can be severe enough to cause myocardial ischemia in isolation or in conjunction with the traditional “epicardial” mechanisms.

Camici and Crea20 have proposed a clinical classification of CMD into four main types on the basis of the clinical setting in which it occurs: type 1 CMD occurs in the absence of CAD and myocardial diseases; type 2 CMD occurs in patients with evidence of myocardial disease; type 3 CMD occurs in patients with obstructive CAD; and type 4 CMD—also known as iatrogenic CMD—occurs after interventions such as bypass surgery, percutaneous revascularization, etc.... Discussing type 2 CMD is beyond the scope of this article so it will not be described below.

### Type 1 CMD
Type 1 CMD is the functional counterpart of traditional coronary risk factors and is the cause of microvascular angina. Microvascular angina is the prototypical clinical manifestation of type 1 CMD. Primary stable microvascular angina is defined as the occurrence of anginal attacks in relation to effort, in the absence of obstructive CAD, myocardial disease, and any other significant cardiovascular disease. In these patients CMD is the cause of myocardial ischemia and chest pain. Microvascular angina is caused by a variable combination of: (i) structural abnormalities; (ii) alterations in endothelium-dependent vasodilatation; (iii) alterations in endothelium-independent vasodilatation; (iv) enhanced pain perception.21

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Main pathogenetic mechanisms</th>
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<tr>
<td>Type 1: in the absence of myocardial diseases and obstructive CAD</td>
<td>Risk factors  Microvascular angina</td>
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<tr>
<td>Type 2: in myocardial diseases</td>
<td>Hyperrophic cardiomyopathy  Dilated cardiomyopathy  Anderson-Fabry’s disease  Amyloidosis  Myocarditis  Aortic stenosis</td>
</tr>
<tr>
<td>Type 3: in obstructive CAD</td>
<td>Stable angina  Acute coronary syndrome</td>
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<tr>
<td>Type 4: iatrogenic</td>
<td>PCI  Coronary artery grafting</td>
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### Type 3 CMD
In patients with obstructive CAD, the development of myocardial ischemia during increased oxygen demand is generally attributed to an inadequate increase in flow due to exhaustion of the CFR. However, it is worth noting that there is only a weak correlation between stenosis severity and CFR in vivo, which suggests that other factors might contribute to the development of myocardial ischemia. For instance, there is evidence that, on a background of optimal medical therapy, revascularization by percutaneous coronary interventions (PCIs) can improve anginal symptoms compared with medical therapy alone.

However, in a substantial proportion of patients, the prevalence of angina at follow-up remains high despite successful revascularization. For instance, in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive druG
Evaluation) more than 30% of patients were still experiencing angina 1 year after PCI, and at the 5-year follow-up the incidence of angina was not significantly different from that in patients who did not undergo a revascularization procedure.

These findings suggest that, although revascularization is effective in removing coronary stenosis and its hemodynamic consequences, other mechanisms, including CMD, contribute to the pathogenesis of ischemia and angina in these patients.20-23

Another proof of the importance of CMD in patients with CAD comes from PET studies showing that the inclusion of CFR in risk prediction models resulted in the correct reclassification of risk in a substantial proportion of patients, including a sizeable proportion of those at intermediate risk. CFR is an integrated measurement of the function of both the macro- and microcirculation. An abnormal CFR gives incremental risk stratification over and above that obtained by the conventional semi-quantitative evaluation of myocardial perfusion studies (ie, summed rest and stress scores).20-23

In summary, in patients with obstructive CAD, angina can be suspected to have a microvascular origin in those who have prolonged angina or angina that is poorly responsive to sublingual nitrates. Similarly, a microvascular origin can be suspected in patients in whom angina is more severe than predicted by the severity of coronary stenoses. Finally, it may be suspected in patients in whom the angina threshold is remarkably variable, although this variability can also be accounted for by the presence of “dynamic” stenoses.

**Type 4 CMD**

Coronary revascularization by PCI or bypass surgery can induce a transient impairment of CFR in the territory subtended by a successfully recanalized artery. This is most likely triggered by an intracoronary reflex resulting in a reversible - adrenergic receptor–mediated constriction of coronary microvessels limiting hyperemic blood flow, which can be prevented by giving - adrenergic receptor antagonists before the procedure. This phenomenon may contribute to the delayed improvement in exercise-induced myocardial ischemia that can be observed after successful PCIs.20

**Conclusion**

Angina is a symptomatic manifestation of myocardial ischemia. Structural (CAD) and functional (spasm) disease of the epicardial coronary arteries were thought to be the only mechanisms of myocardial ischemia for several decades. However, it has recently become apparent that dysfunction of the coronary microcirculation, alone or in combination with CAD, is another mechanism of myocardial ischemia and angina. ■

References


Keywords: angina pectoris; coronary anatomy; coronary artery disease; coronary microvascular dysfunction; coronary spasm; myocardial ischemia
Despite the technical progress in coronary angioplasty leading to the treatment of more complex and extensive atherosclerotic lesions, the prevalence of anginal pain after successful percutaneous coronary revascularization (PCI) remains high. Recurrent angina, defined as the persistence of chest pain due to myocardial ischemia after revascularization, may be triggered by several causes not necessarily related to revascularization failure. Chest pain of coronary origin may recur after PCI due to both structural and functional causes, many of which have a common pathophysiological background, such as endothelial dysfunction. Appropriate diagnostic tools, including intracoronary physiological assessment, should be used for the correct identification of the conditions provoking recurrent angina. In light of the complex pathogenesis of this disorder, treatment strategies should be tailored to the clinical characteristics of each patient. In addition to mechanical therapies for the treatment of structural disorders, pharmacological therapy should be optimized with the use antianginal drugs and other compounds that may help treat the pathological conditions behind recurrent angina to maximize the benefit for patients. This article will analyze the most common causes of recurrent angina after PCI and focus on possible diagnostic and therapeutic approaches.

Percutaneous coronary intervention (PCI) is a cornerstone in the treatment of coronary artery disease (CAD). Through the restoration of epicardial coronary flow, PCI procedures aim to abolish myocardial ischemia. Timely revascularization is a life-saving procedure in acute coronary syndromes, whereas in the context of stable CAD, the main goal of PCI is to improve the quality of life by relieving the principal clinical manifestation of myocardial ischemia, ie, angina pectoris. However, despite technical progress, the prevalence of anginal pain after successful revascularization remains high. Recurrent angina, defined as the persistence of chest pain due to myocardial ischemia after revascularization, represents a clinical challenge for cardiologists for both diagnosis and treatment.

Several causes may be responsible for recurrent angina after PCI, and recurrent angina does not necessarily derive from revascularization failure. It is important to highlight that recurrent angina is distinct from refractory angina, which is defined as a chronic condition caused by clinically established reversible myocardial ischemia in the presence of CAD that cannot be controlled adequately with a combination of medical therapy, angioplasty, or coronary artery bypass grafting. The aim of this ar-
article is to analyze the most common causes of recurrent angina after PCI and to focus on possible diagnostic and therapeutic approaches.

**Magnitude of the problem**

Recurrent angina remains a highly prevalent condition, occurring in 20% to 60% of patients within 1-year post-PCI. In a recent study that analyzed 9081 patients treated with PCI in two hospitals, 9.8% were readmitted within 30 days after the procedure. The main cause for early readmission was chest pain or other symptoms concerning for angina (38.1% of cases). In the large randomized RITA-2 trial (second Randomized Intervention Treatment of Angina), which compared medical therapy alone with PCI in patients with chronic stable angina, the percentage of symptomatic subjects (Canadian Cardiovascular Society score ≥2) was reduced from 60% to 20% within 1 year post-PCI, while the percentage remained unchanged in the medical arm. However, after a long-term follow-up, no difference was found in the incidence of angina between the interventional and medical groups.

In the more recent COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), 2287 patients with stable CAD were randomized to PCI plus medical therapy or medical therapy alone. At baseline, 22% of patients were angina-free. PCI was superior to medical therapy in reducing anginal symptoms at both the 12- and 24-month follow-up, whereas no significant difference was found at the 36-month follow-up. Moreover, in the PCI group, the percentage of angina-free patients was 57% at 12 months and 59% at 24 and 36 months, which means that nearly 40% of patients still experienced chest pain after coronary revascularization.

Of note, most of the patients enrolled in the studies mentioned above received bare-metal stents (BMS) and, in some cases, the recurrence of angina may be related to in-stent restenosis, a complication that has drastically decreased with the advent of drug-eluting stents (DES). However, in a prospective study of 200 patients treated with DES, at 4 weeks post-PCI, 21% still experienced angina. More recently, in the SYNTAX trial (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery), the reported rate of freedom from angina in patients undergoing PCI for left-main or three-vessel disease was just 71.6% at 12 months.

**Potential causes of recurrent angina**

Recurrent angina may be due to structural or functional causes.

**Structural causes of recurrent angina**

- **Stretch pain**
  
  Stretch pain is a precordial pain that develops in the immediate phase after stent implantation, and it is not associated with myocardial ischemia. Stretch pain may occur after PCI due to overexpansion of the treated vessel segment, which is “stretched” by the stent, with a resulting stimulation of the sensory nerves located in the adventitia. Stretch pain is a common condition after PCI (36% to 41% of the cases) with a generally benign prognosis, although it may be associated with a higher risk of stent restenosis.

- **In-stent restenosis**
  
  In-stent restenosis (ISR) is a condition characterized by a reduction in lumen diameter following stent implantation due to arterial damage resulting in neointimal proliferation. Binary angiographic restenosis is defined as a ≥50% luminal narrowing at the follow-up angiography. Clinically relevant ISR is defined as a binary angiographic restenosis with symptoms or signs of myocardial ischemia or as a ≥70% luminal narrowing. Neointimal proliferation occurs gradually, usually 5 to 12 months after PCI (earlier for BMS than for DES), and unstable angina represents the most common clinical presentation, followed by myocardial infarction. BMS are associated with a 20% to 30% rate of ISR 6 to 9 months after implantation. The incidence of ISR has dramatically dropped after the advent of DES, although it is still encountered in 5% to 10% of patients with second-generation DES. A study with angiographic follow-up, which was conducted in 10,004 patients 6 to 8 months after PCI, reported an ISR incidence of 30.1% with BMS, 14.6% with first-generation DES, and 12.2% with second-generation DES. Moreover, in the recent RESOLUTE All-comers trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention), which compared zotarolimus-eluting stents with everolimus-eluting stents, the rates of target lesion failure and clinically indicated target lesion revascularization were 15% and 7%, respectively. In conclusion, despite technical innovation, ISR remains one of the leading cause of recurrent angina.

- **Stent thrombosis**
  
  Stent thrombosis is the most detrimental manifestation of stent failure and often presents as an acute myocardial infarction or sudden cardiac death. The global incidence of stent throm-
bosis is roughly 1% per year, and it is more frequent after a PCI that is performed in the context of acute coronary syndrome. A recent network meta-analysis has shown that all contemporary DES (with the exception of paclitaxel-eluting stents and bioresorbable vascular scaffolds) were superior to BMS in terms of stent thrombosis occurrence.26

**Incomplete revascularization**

When coronary revascularization is not able to remove myocardial ischemia completely, chest pain recurs early after PCI,17 which has important prognostic implications. In the SYNTAX trial, the residual atherosclerotic burden was strongly associated with the 5-year mortality rate.28 Moreover, in a meta-analysis including 89,883 patients with multivessel CAD, revascularization was incomplete in 56% of those treated with PCI, which was associated with a significant increase in total mortality, myocardial infarction, and repeat revascularization as compared with complete revascularization.13 Similar results were recently obtained in a subanalysis of the SCAAR registry (Swedish Coronary Angiography and Angioplasty Registry).22

In addition to the technical aspects of PCI that prevent the treatment of all coronary lesions—which are related to anatomic complexity and atherosclerotic burden—diagnostic issues may also be responsible for incomplete revascularization. In fact, angiography alone is not always able to identify functionally significant coronary stenoses, and a significant proportion of angiographically intermediate lesions are not correctly classified and, consequently, not appropriately treated.27 In other words, even when angiographically complete revascularization is achieved, other lesions are considered insignificant, and therefore, left untreated. These untreated lesions may induce ischemia and thus recurrent angina. Therefore, regular physiological assessment of coronary stenoses using fractional flow reserve (FFR) and FFR-guided PCI may help optimize treatment strategies and achieve functionally complete coronary revascularization.22,23

**CAD progression**

The development of significant disease in previously untreated coronary segments is common, especially in high-risk patients, such as those with diabetes mellitus. Symptomatic progression of coronary disease after PCI accounts for up to 50% of repeat revascularizations in diabetic patients, which has a significant impact on clinical outcomes.24 In a prospective study that evaluated 428 patients treated with PCI, after 5 years, 110 patients (25.7%) had a new clinical event (i.e., myocardial infarction or repeat revascularization), and 37.1% of the repeat revascularization cases were due to disease progression in previously untreated coronary segments.25

**Myocardial bridging**

Myocardial bridging is a coronary anomaly that may be associated with exertional angina, acute coronary syndromes, cardiac arrhythmias, syncope, or even sudden cardiac death.26 In a recent study of 139 patients with angina in the absence of obstructive CAD, the prevalence of myocardial bridging identified using intravascular ultrasound (IVUS) was as high as 57.9%, and this condition was often associated with endothelial dysfunction.27

**Functional causes of recurrent angina**

Up to one-third of patients with recurrent chest pain after PCI do not have evidence of obstructive CAD.26,29 In this setting, functional causes of recurrent angina, which include epicardial coronary spasm (often at the stent edge) and microvascular dysfunction, should be considered. Both of these conditions may occur in the presence of endothelial dysfunction. The vascular endothelium is a multifunctional organ whose integrity is essential to normal vascular physiology, and whose dysfunction may be crucial in the pathogenesis of vascular disease. In fact, endothelial dysfunction is considered the primary mover of atherosclerosis; therefore, it may predispose patients treated with PCI to ISR26 and CAD progression.23

**Epicardial coronary spasm**

The acetylcholine provocation test (ACH test) may be used to assess coronary endothelial function because, when the endothelium is functioning normally, ACH causes vasodilation by stimulating the release of endothelium-derived relaxing factor; whereas, when the endothelium is removed or damaged, ACH causes vasospasm. In a series of 104 patients with a previous PCI, recurrent angina, and angiographic evidence of a nonobstructive ISR, the intracoronary ACH test was normal in only 34% of patients, while it elicited enhanced epicardial vasoconstriction (evidence of a >75% reduction in vessel diameter and symptoms) or microvascular vasoconstriction (only symptoms and ECG changes) in the others.32 Of note, in patients previously treated with PCI, epicardial vasoconstriction was most often localized to distal segments,32 and stent length seemed to be linked to a positive ACH test at angiographic follow-up after DES implantation (vasoconstriction is more common with increasing stent length).33 Versaci et al also reported a high percentage of ergonovine-induced coronary spasm in patients with recurrent angina.29

**Microvascular dysfunction**

Microvascular dysfunction due to endothelial impairment is another potential cause of recurrent angina despite angiographically unobstructed epicardial coronary arteries. In a recent study, Li et al have shown for the first time that PCI patients experiencing recurrent angina in the absence of structural causes had a significantly higher index of microvascular resistance (IMR) and lower coronary flow reserve (CFR) than a control group.34 Exercise-induced ischemia late after successful PCI also seems to be related to distal coronary endothelial dysfunction,35 and peripheral endothelial dysfunction can predict recurrent angina after PCI30 and worse outcomes in patients with CAD.36,37

### Stable angina pectoris: evolving considerations

**FOR SYMPTOMATIC MANAGEMENT OF PATIENTS**

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<th>TABLE ANGINA PECTORIS: EVOLVING CONSIDERATIONS</th>
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<td><strong>Objective of PCI</strong></td>
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| - To optimize 
| - To achieve functional complete revascularization |

**CAD progression**

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Diagnostic approach

The first step in the diagnostic approach to recurrent angina should be an accurate evaluation of symptoms to assess the probability of facing true angina versus chest pain deriving from other causes not related to myocardial ischemia. It is important to ascertain whether the chest pain characteristics are similar to those reported before the revascularization procedure and to quantify the time between the procedure and the new onset of symptoms. The longer this interval is, the higher the probability that symptoms are due to CAD progression, rather than other causes. Physicians should also interrogate the patients carefully regarding compliance to dual antiplatelet therapy because premature discontinuation is one of the most common causes of stent thrombosis.

In symptomatic patients after PCI, an imaging stress test (stress echocardiography, magnetic resonance imaging, or myocardial perfusion scintigraphy [MPI]) is recommended by the European Society of Cardiology (ESC) guidelines.1 For patients with low-risk findings (ie, ischemia <5% of the myocardium), the suggested strategy is to reinforce medical therapy and promote lifestyle changes. A coronary angiogram is recommended for patients with intermediate- to high-risk findings (ischemia at low workload, early onset ischemia, multiple zones of high-grade wall motion abnormality, or reversible perfusion defect). However, for patients with typical symptoms suggesting an ischemic origin and/or in the presence of high-risk features for PCI failure (eg, diabetes mellitus, diffuse CAD, poor compliance to treatment), physicians may decide to perform a cardiac catheterization directly, without prior noninvasive tests.1 In the absence of angiographic evidence of stent failure or CAD progression, functional causes of recurrent angina could be investigated in the catheterization laboratory through a comprehensive invasive assessment, including an ACH test for endothelial dysfunction,27 IMR and CFR measurement for coronary microvascular dysfunction,28-30 and FFR measurement for occult or diffuse epicardial coronary disease.31-36 Intracoronary imaging with IVUS or optical coherence tomography may also be used to search for anatomical abnormalities (eg, myocardial bridging) that are not apparent on coronary angiography, but may be responsible for inducible ischemia.26

Treatment strategies

In patients with evidence of stent failure or functionally significant atherosclerotic lesions (residual or novel), repeat PCI is the treatment of choice. However, optimizing medical therapy is crucial for these patients and those with functional causes of recurrent angina.

According to the most recent ESC guidelines, the first-line therapy for angina relief should include short-acting nitrates plus -blockers or non-dihydropyridine calcium channel blockers (CCBs).3 Dihydropyridine-CCBs may be an alternative for patients with low heart rate or intolerance/contraindications to -blockers and non-dihydropyridine CCBs. Furthermore, dihydropyridine-CCBs can be used in association with -blockers for patients with persistent angina and a Canadian Cardiovascular Society (CCS) score >2. As a second-line therapy, it is recommended to add either a long-acting nitrate or one of three options—ivabradine, nicorandil, or ranolazine; trimetazidine may also be considered. A second-line treatment may be used as first-line treatment in selected patients. However, in all cases, medical therapy should be tailored to each patient according to the underlying cause of recurrent angina, heart rate, blood pressure, tolerance, comorbidities, etc. As an example, in the case of angina with a microvascular origin, -blockers remain the first-line treatment, while chronic preventive treatment of vasospastic angina is mainly based on the use of CCBs.

- Ivabradine

Ivabradine, a direct inhibitor of the sinus node, current, reduces heart rate, which results in the prolongation of diastole and a reduction in myocardial oxygen demand, without affecting inotropism or blood pressure. It is approved in Europe (at a dose of up to 7.5 mg twice daily) for the treatment of chronic stable angina in patients who have a heart rate >70 bpm (in sinus rhythm) and who are intolerant to or inadequately controlled by -blockers. Ivabradine was as effective as atenolol in terms of antianginal and anti-ischemic events in a double-blinded trial that enrolled 939 patients with stable angina.37 Moreover, in patients with chronic stable angina pectoris treated with atenolol and with a heart rate >60 bpm, the addition of ivabradine improved exercise tolerance, without affecting safety or tolerability.38

The SIGNIFY trial (Study assessInG the morbidity-mortality benefits of the If inhibitor ivabradine in patients with coronary artery disease)39 failed to demonstrate a reduction in the composite end point of death from cardiovascular causes or non-fatal myocardial infarction in patients with stable CAD, but no clinical heart failure, who were treated with ivabradine at a dose of up to 10 mg twice daily, in addition to standard medical therapy. However, in the SIGNIFY trial, ivabradine produced consistent improvements in self-reported quality of life parameters related to angina pectoris, particularly in terms of angina frequency and disease perception.40

In the recent RIVENDEL study (heart Rate reduction by IVa-Bradine for improvement of ENDothELial function in patients with coronary artery disease),41 the hypothesis tested was that, through a reduction in heart rate and consequent reductions in oxidative stress, vasoconstriction, smooth muscle cell migration and proliferation, inflammation, and extracellular matrix degradation at the level of the arterial wall, ivabradine could exert a beneficial effect on vascular endothelial function. Patients with CAD who underwent complete revascularization by PCI were randomized to receive ivabradine or to continue with standard medical therapy, and endothelial function was assessed by flow-mediated dilatation (FMD) of the brachial...
artery up to 8 weeks after enrollment. The addition of ivabradine to standard medical therapy significantly improved endothelial function proportionally to the reduction in heart rate. Ivabradine treatment also resulted in a significant reduction in the proportion of patients with endothelial dysfunction, defined as FMD <7%. Based on these results and in light of the potential effects of endothelial dysfunction on the genesis of recurrent angina, ivabradine may play a central role in the pharmacological armamentarium for the treatment of patients with CAD undergoing PCI.

◆ Ranolazine

Ranolazine acts as a late sodium current blocker that reduces intracellular calcium overload during ischemia, without negative inotropic, chronotropic, or dromotropic effects. Its efficacy in patients with chronic stable angina has been assessed in several randomized trials. Ranolazine reduces the frequency of angina, increases pain-free exercise duration and time to ST-segment depression, improves exercise performance, and reduces the use of sublingual nitroglycerin. The antianginal efficacy of ranolazine has also been proven in diabetic patients with CAD. In the MERLIN-TIMI 36 trial (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 36), which evaluated patients with a history of acute coronary syndrome, ranolazine did not reduce the incidence of myocardial infarction or death, but in the subgroup of patients with prior chronic angina, it significantly reduced recurrent ischemia, and it also modestly improved angina frequency and quality of life compared with placebo. The recent RIVER-PCI trial (Ranolazine for Incomplete Vessel Revascularization) failed to demonstrate any benefit of ranolazine in terms of a reduction in ischemia-driven revascularization or hospitalization without revascularization in patients with a history of chronic angina who had incomplete revascularization after a PCI. In this population, ranolazine also had a neutral effect on angina frequency and quality of life at the 1-year follow-up.

◆ Nicorandil

Nicorandil is a nitrate derivative of nicotinamide. It activates adenosine triphosphate-sensitive potassium channels and promotes systemic venous and coronary vasodilatation through a nitrate effect. This drug was evaluated in the IONA trial (Impact Of Nicorandil in Angina), which enrolled 5126 patients with chronic stable angina. The addition of nicorandil to standard therapy reduced the composite primary end point (coronary death, nonfatal myocardial infarction, or unplanned hospitalization for angina). However, symptom relief was not reported in this trial. Older studies have shown that the antianginal properties of nicorandil are similar to those of oral nitrates, β-blockers, and calcium channel blockers.

◆ Trimetazidine

Trimetazidine inhibits fatty acid oxidation, resulting in a shift to glucose metabolism, which is more efficient, and a reduction in myocardial oxygen demand. In the TRIMPOIL II trial (TRIMetazidine in POLand), the addition of trimetazidine to standard therapy reduced angina episodes and improved exercise tolerance. A recent meta-analysis confirmed the efficacy of trimetazidine in the treatment of stable angina pectoris versus conventional antianginal agents. However, large outcome trials evaluating the role of trimetazidine in stable CAD patients are still needed.

◆ Other compounds

In addition to pure antianginal drugs, other compounds may be useful in the treatment of patients with recurrent angina. Allopurinol, an inhibitor of xanthine oxidase used in the prevention of gout, seems to have an antianginal effect, probably by improving endothelium-dependent vasodilatation and abolishing oxidative stress. In a randomized crossover study of 65 patients with CAD, allopurinol 600 mg/day increased the time to both ST-segment depression and chest pain, compared with placebo. Larger trials are necessary to confirm these interesting results. High-dose statin therapy is well known to improve endothelial function and clinical outcomes in patients with CAD, and there is also evidence for a reduction in angina and ischemic episodes.

Conclusions

Recurrent angina is a common event after PCI that may have several causes which often share a common pathophysiological background. The diagnosis and treatment of recurrent angina represent a clinical challenge, and an accurate identification of the underlying causes is crucial to select the right treatment strategy.

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**Stable Angina Pectoris: Evolving Considerations for Symptomatic Management of Patients**

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### Stable Angina Pectoris: Evolving Considerations for Symptomatic Management of Patients

**Keywords:** antianginal drug; coronary atherosclerosis; myocardial ischemia; percutaneous coronary intervention; recurrent angina

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**Recurrent Angina after Percutaneous coronary interventions – Mangiacapra and others**
Evidence has accumulated that ischemia contributes to myocardial remodeling and the subsequent development of heart failure. In 60% of patients with heart failure, coronary artery disease and ischemia contribute to the development and progression of the heart failure syndrome. Remodeling of the heart extends beyond myocardial remodeling and involves vascular effects, which are mechanically driven by neuroendocrine activation and heart rate elevation.

Angina in patients with left ventricular dysfunction or heart failure

Myocardial ischemia and its symptom angina pectoris contribute to left ventricular dysfunction and the progression of remodeling. Remodeling after myocardial infarction is induced by a loss of functional myocytes and by neuroendocrine activation, and eventually leads to left ventricular dilatation and fibrosis. Vascular mechanisms like endothelial dysfunction and remodeling of atherosclerotic plaques also contribute to the progression of asymptomatic left ventricular dysfunction to heart failure. After a myocardial infarction, patients often have residual angina. β-Adrenergic blockade and heart rate reduction are valuable strategies to reduce angina, in particular in heart failure. Furthermore, β-blockers and heart rate–lowering drugs have been found to have beneficial effects on morbidity and mortality in heart failure. These findings reinforce the importance of optimal therapy in patients with impaired left ventricular function and anginal symptoms to slow the progression of left ventricular dysfunction, and eventually the development of heart failure.

Coronary artery disease—whose most common symptom is angina—is one of the most important comorbidities of heart failure, and is prevalent in approximately 60% of patients.1,2 In the United States, coronary artery disease affects 15.54 million patients and accounts for 538,000 deaths yearly, not including its consequences like acute myocardial infarction, left ventricular dysfunction, and heart failure, which are predicted to affect 8 million patients by 2030.3

Myocardial remodeling

When different loading conditions are imposed on the myocardium, the left ventricle adapts to pressure and volume overload and undergoes structural changes. A loss of myocardial mass after myocardial infarction due to coronary artery disease can alter chamber geometry and wall stress in the left ventricle. Left ventricular hypertrophy and dilatation are two distinct types of cardiac remodeling that occur subsequently in the infarcted and noninfarcted ventricular myocardium, and which were first described following experimental coronary artery ligation in the rat.4 Loss of contractility of the left ventricle in infarcted areas increases wall stress and then causes hypertrophy in remote areas, with secondary global dilatation (Figure 1). Residual ischemia and loss of myocardial tissue can pave the way for global remodeling, and subsequently, for overt chronic heart failure.5 The late Janice Pfeffer showed that ventricular remodeling is sensitive to the application of angiotensin-converting en-
and provided a treatment target to prevent heart failure. This evidence for the role of neuroendocrine activation in the heart, sure overload, and then myocardial infarction.

Neuroendocrine activation is important to maintain the presence of increased left ventricular mass. The ejection fraction is preserved and volumes are normal or reduced in ventricular dilatation with impaired ejection fraction.

In atherosclerotic disease, heart rate is associated with a variety of cardiovascular end points like heart failure, cardiovascular death, stroke, but not myocardial infarction. Therefore, vascular remodeling may contribute to the progression of coronary disease and the development of angina in the absence or presence of heart failure. Vascular remodeling, microvascular function, ventricular remodeling, and ischemia accentuate the development of clinical vascular events and heart failure complications (Figure 2).

### Endothelial and vascular remodeling

Other remodeling processes beyond myocardial remodeling have recently attracted attention, such as those involving vascular and endothelial mechanisms. Risk factors—ie, low-density lipoprotein (LDL)-cholesterol and stress—reduce endothelial function and accelerate atherosclerosis. High heart rate can further exacerbate atherosclerosis, and this process is sensitive to heart rate reduction with ivabradine.

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Figure 2. Pathophysiology of cardiac events and progression to heart failure.

Following a vascular event, ischemia and contractile dysfunction induce neuroendocrine activation in the heart, and the sympathetic nervous system leads to relatively high resting heart rates. The direct effects of neurohormones and high heart rate induce myocardial, vascular, and interstitial remodeling, and this leads to cardiomyopathy and progression of atherosclerosis. In addition, by increasing peripheral resistance, high heart rate and neuroendocrine activation increase oxygen demand, and reduce the duration of diastole, which reduces oxygen supply, thereby promoting ischemia. This process is accentuated by the progression of atherosclerosis and endothelial dysfunction. Eventually, heart failure and major cardiovascular events occur and are promoted by myocardial ischemia.

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Outcomes of heart failure in the presence of angina

Angina and coronary artery disease are present as comorbidities in 60% of heart failure patients and significantly contribute to poor prognosis. Between 16.4% and 21% of patients remain symptomatic and use antianginal drugs 1 to 12 months after a coronary revascularization, coronary intervention, or coronary bypass operation. This was confirmed by the Euro Heart Survey of the European Society of Cardiology, which showed that in Europe the majority of patients take at least one antianginal drug, and sometimes more than two, even after revascularization. Nevertheless, coronary artery bypass surgery in heart failure patients with ischemic heart disease reduces cardiovascular outcomes, and in particular sudden death and fatal pump failure events.

Angina treatment in heart failure

While there is no doubt that revascularization is a necessity, antianginal treatment represents the mainstay in the presence of anginal symptoms. Heart rate reduction favorably influences the relation between myocardial oxygen supply and myocardial oxygen consumption. -Blockers are the mainstay in the guidelines for the treatment of angina, besides calcium antagonists. However, the use of -blockers and calcium antagonists is often limited by adverse effects. Therefore, maximum doses can often not be tolerated. High heart rates increase oxygen consumption and are often a trigger for myocardial infarction and angina pectoris. Heart rate reduction with ivabradine in the absence of -blockers reduces anginal symptoms and improves exercise tolerance. In patients with treatment-resistant anginal symptoms, ivabradine reduces angina and improves exercise tolerance in patients already treated with -blockers or amiodipine. Even in the presence of -blockers, ivabradine strongly reduces heart rate (Figure 3).

Anginal symptoms and their adverse effects on morbidity and mortality have not been evaluated in patients with impaired left ventricular function. Recently, a study in more than 19,000 patients investigated whether ivabradine improves outcomes in patients with stable coronary artery disease without heart failure or left ventricular dysfunction. There was no change in cardiovascular death, myocardial infarction, or stroke. In patients with impaired left ventricular function and angina pectoris, ivabradine was associated with a 24% reduction in the primary end point (cardiovascular mortality, hospitalization for fatal and nonfatal myocardial infarction or heart failure). Interestingly, outcomes were worse in the presence of angina compared with patients with left ventricular dysfunction with and without angina symptoms. In turn, in patients with impaired left ventricular function and symptomatic chronic heart failure, a subanalysis of the SHIFT trial (Systolic Heart Failure treatment with the I, inhibitor ivabradine Trial) showed that in patients with concomitant angina pectoris, ivabradine was associated with a significant reduction in cardiovascular death and myocardial infarction that was comparable to that seen in the whole heart failure population of the trial.

Keywords: angina; heart failure; heart rate; left ventricular dysfunction; neuroendocrine activation; remodeling

Figure 3. Heart rate reduction following ivabradine treatment in patients with stable angina treated with atenolol.

A further heart rate reduction of approximately 6 beats per minute can be brought about by adding ivabradine (7.5 mg bid) to a preexisting treatment with a -blocker. Heart rate was measured at baseline, after 2 months (M2), and after 4 months (M4 = end of study). Based on data from reference 40: Tardif et al. Eur Heart J. 2009;30:540-548.

Conclusions

Evidence has accumulated that ischemia contributes to myocardial remodeling and the subsequent development of heart failure. In 60% of patients with heart failure, coronary artery disease and ischemia contribute to the development and progression of the heart failure syndrome. Remodeling of the heart extends beyond myocardial remodeling and involves vascular effects, which are mechanistically driven by neuroendocrine activation and heart rate elevation. Neuroendocrine antagonists and heart rate reduction are treatment options for heart failure and left ventricular dysfunction. Anginal symptoms can be treated by heart rate reduction either with ivabradine, -blockers, or both types of drugs combined. The pathophysiological concept described above and the data available reinforce the importance of using optimal antianginal and anti-ischemic therapy in patients with impaired left ventricular function or heart failure in order to slow the progress of left ventricular remodeling and heart failure and to control symptoms.
References
Cardiac rehabilitation programs present an opportunity to improve the functional status of patients and help them to reach and maintain optimal physical, psychological, and social functional levels. Optimal pharmacological therapy, which improves coronary perfusion, symptoms, exercise capacity, and quality of life, is not only an essential part of patient management, but also acts in synergy with cardiac rehabilitation to achieve the goals of patient management. Heart rate is not just a physical sign; it is a biomarker and a therapeutic target in patients with cardiovascular disease. It regulates myocardial oxygen consumption and coronary flow, and plays a central role in adapting the cardiac output to the metabolic needs of the whole body. In many cardiac diseases, an increase in heart rate is associated with a higher mortality. Ivabradine is a pure heart rate–reducing agent with anti-ischemic and anti-anginal effects but without any influence on blood pressure and contractility, and it is therefore well tolerated. Since heart rate determines oxygen consumption and delivery, its modulation by ivabradine strongly influences cardiac performance and exercise tolerance and leads to functional status improvement in all patients taking part in cardiac rehabilitation programs.
fects of rehabilitation and exercise training. Rate-adaptive cardiac pacing was developed to optimize exercise tolerance in patients with chronotropic incompetence, structural heart disease, or both acting in concert. A sustained increase in heart rate by atrial or ventricular pacing in animal models induces left ventricular dysfunction along with symptoms of heart failure (dyspnea, cachexia, congestion, and exercise intolerance).4-12

Although cardiac rehabilitation programs are of great importance for all patients with heart disease, research in this area has mainly focused on patients with recent myocardial infarction or undergoing myocardial revascularization. In recent years, however, a growing number of studies have been conducted in other groups of patients, especially older patients, women, and patients at higher risk of heart failure or angina. In this paper we analyze the effect of heart rate in patients undergoing cardiac rehabilitation and the role of ivabradine in this setting.

Patients with stable coronary artery disease

Improved survival, coupled with a decline in the incidence of acute myocardial infarctions, has dramatically changed the pattern of health care use over recent years. Patients with stable CAD have somehow “fallen off the radar” of clinical interest: no longer in cardiac rehabilitation (which is mainly offered immediately after acute myocardial infarction or CABG), discharged from ongoing specialist care, and with suboptimal patterns of health care use over recent years. Patients with stable CAD have somehow “fallen off the radar” of clinical interest: no longer in cardiac rehabilitation (which is mainly offered immediately after acute myocardial infarction or CABG), discharged from ongoing specialist care, and with suboptimal drug compliance, adherence, and persistence. These patients, however, vary widely in their risk of subsequent acute myocardial infarction or coronary death—there is approximate-ly a 10-fold difference between the top and bottom deciles of risk—and this clearly has different resource implications.

Increased heart rate results in increased myocardial oxygen consumption,13-15 and reduced diastolic function.16 When the coronary circulation is free from occlusion, metabolic vasodilation can compensate for decreased diastolic duration and adjust to the increased oxygen demand with increased oxygen supply.16,17 However, in the presence of atherosclerotic narrowing/stenosis of an epicardial coronary artery and coronary microvascular dysfunction, the scenario is very different. Increased heart rate can exacerbate hemodynamic impairment caused by coronary stenosis. In such cases, vasodilation can maintain normal coronary blood flow at rest; but it is unable to respond to further increases in heart rate during stress.17 The decrease in diastolic duration now even reduces coronary blood flow, which particularly affects the more vulnerable subendocardial layers of the myocardium.18,19 In this scenario, collateral blood flow from the adjacent myocardium is also reduced with increased heart rate because the driving pressure gradient for collateral blood flow is reduced. Pressure at the orifice of collaterals into the post-stenotic coronary circulation is increased since the post-stenotic coronary vascular bed is already maximally dilated to compensate for the stenosis, and decreased diastolic duration then reduces coronary blood flow or, conversely, increases coronary resistance.20

Ivabradine-mediated heart rate reduction reverses the unfavorable blood flow to the ischemic myocardium.21 In contrast to β-blockade, which also reduces heart rate and improves blood flow to the ischemic myocardium,22 ivabradine has no negative inotropic effect and does not unmask coronary vasosconstriction23-26 during sympathetic activation, eg, by exercise.22 There is an ongoing debate regarding the effects of β-blockade and the unmasking of coronary vasosconstriction. -Blockade reduces oxygen consumption in non-ischemic myocardium more than ivabradine for an equivalent reduction in heart rate.23 As long as heart rate is reduced, β-blockade also induces a favorable redistribution of blood flow toward the ischemic myocardium during sympathetic activation27 but, in the absence of heart rate reduction, β-blockade reduces regional myocardial blood flow and contractile function in exercise-induced myocardial ischemia.28 Adrenergic coronary vasoconstriction during sympathetic activation has been proposed to maintain a uniform transmural blood flow distribution,29,30 or to cause a more favorable blood flow distribution toward the ischemic myocardium;31 but both these hypotheses are contentious.32 All available clinical studies suggest a deleterious role for adrenergic coronary vasoconstriction in myocardial ischemia32-35; therefore, the fact that ivabradine is not associated with adrenergic coronary vasoconstriction is an advantage.

Several small proof-of-concept trials have demonstrated the symptomatic efficacy of ivabradine in reducing anginal pain and improving exercise tolerance.36-44 In the large BEAUTIFUL trial (morBidity-mortality EvaLuation of the Ii inhibitor ivabra-dine in patients with coronary disease and left ventricular dysfunction) in patients with stable CAD and left ventricular systolic dysfunction, ivabradine reduced hospitalization for myocardial infarction and coronary revascularization, particularly in patients with angina and a resting heart rate >70 bpm at baseline.46 The reductions in these endpoints (75% reduction in hospitalization for myocardial infarction and 59% reduction in coronary revascularizations) appeared largely out of proportion with the small (7 bpm) placebo-corrected heart rate reduction.46 More recently, in the large SIGNIFY study (Study assessing the morbidity-mortality BeNefits of the Ii inhibitor ivabradine in patients with coronary artery disease) in patients with stable CAD with preserved ejection fraction, ivabradine

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>LV</td>
<td>left ventricular</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
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did not reduce the primary composite end point of death from cardiovascular causes or nonfatal myocardial infarction.\textsuperscript{47} Heart rate reduction with ivabradine improves symptoms, but not clinical outcome in patients with stable CAD and preserved ejection fraction; this is also true for all other antianginal drugs on the market and for \textit{-}blockers too.

**Patients after myocardial infarction**

During ischemia—and in particular if the heart rate is elevated—the ventricular muscle develops diastolic dysfunction. The resulting rise in filling pressure impairs exercise tolerance and increases pulmonary wedge pressure, causing shortness of breath. Ivabradine has previously been shown to reduce heart rate after myocardial stunning, and also after PCI for ST-segment elevation myocardial infarction (STEMI).\textsuperscript{48} In the VIVIFY study (\textit{eValuation of the IntraVenous \textit{I} inhibitor ivabradine after ST-segment elevation myocardial infarction}), the use of intravenous ivabradine in STEMI patients produced a rapid and sustained reduction in heart rate, which was safe and well tolerated and did not affect blood pressure or hemodynamic parameters.\textsuperscript{48} Furthermore, in STEMI patients treated with primary PCI, heart rate at discharge correlates with mortality.\textsuperscript{49} In the failing heart, the Bowditch effect is impaired, resulting in a negative force-frequency relationship in vitro and in vivo. Initial evidence to this effect came from isolated cardiac preparations and patients undergoing heart transplantation.\textsuperscript{50} Failing heart preparations also develop a relaxation deficit at higher heart rates.\textsuperscript{50} In patients after a Q-wave myocardial infarction with early left ventricular ejection fraction (LVEF) <45%, combining ivabradine to low-dose metoprolol tartrate was associated with improved systolic and diastolic left ventricular function, decreased serum NT-pro-ANP by day 25,\textsuperscript{51} and increased exercise tolerance at the 6-month follow-up, compared with up titrating the metoprolol dose.\textsuperscript{52}

Ivabradine is a pure heart rate-reducing agent that has no effect on blood pressure and contractility and can reverse left ventricular (LV) remodeling in patients with heart failure.\textsuperscript{53} Since heart rate determines oxygen consumption and delivery, its modulation by ivabradine strongly influences exercise tolerance, in particular during ischemia. This property makes ivabradine a valuable component in the armamentarium of coronary therapy even in the early phase of myocardial infarction, with long-term benefits in terms of cardiac performance and functional capacity.

The stepwise process of rehabilitation begins immediately after a cardiac event and continues throughout life, with different interventions introduced at appropriate stages. Standard drug therapy for post-infarct patients is usually instituted while patients are still in hospital. After being able to sit up, patients may walk in the corridors for 2 to 5 minutes, 4 times daily. Their heart rate should not exceed 120 bpm, and in patients with resting tachycardia it should not be greater than 20 bpm above the resting heart rate.

Exercise stress testing and ECG is required in high-risk patients to assess ventricular function and residual ischemia and for those who wish to participate in high-intensity exercise. High-risk patients (patients with residual ischemia or significant left ventricular dysfunction) require constant monitoring and their heart rate should not be allowed to exceed 10 bpm below the rate at which ischemia was provoked on stress testing. Impaired chronotropic response (failure to reach 80% of maximum heart rate) is associated with increased mortality post–myocardial infarction, especially with heart failure, and may be improved by \textit{-}blockade and ivabradine. The combination of ivabradine with low-dose bisoprolol in stable angina patients produces more antianginal and anti-ischemic benefits than twice the dose of the \textit{-}blocker alone and also improves chronotropic reserve.\textsuperscript{54}

\begin{figure}
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\includegraphics[width=\textwidth]{figure1.png}
\caption{Diastolic function at admission, discharge, and at the 3-month follow-up of coronary artery bypass graft (CABG) patients randomized to either standard medical therapy including bisoprolol 2.5 mg to 3.75 mg once daily (BB) or ivabradine 5 mg twice a day + standard medical therapy including bisoprolol 1.25 mg once daily (I-BB). Based on data from reference 57: Marazia et al. J Cardiovasc Pharmacol Ther. 2015;20:547-553.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Systolic function at admission, discharge, and at the 3-month follow-up of coronary artery bypass graft (CABG) patients randomized to either standard medical therapy including bisoprolol 2.5 mg to 3.75 mg once daily (BB group, blue line) or ivabradine 5 mg twice a day + standard medical therapy including bisoprolol 1.25 mg once daily (I-BB). Based on data from reference 57: Marazia et al. J Cardiovasc Pharmacol Ther. 2015;20:547-553.}
\end{figure}
Patients with recent coronary artery bypass graft or percutaneous transluminal coronary angioplasty

The European Society of Cardiology (ESC) guidelines for myocardial revascularization recommend adequate medical therapy, other secondary prevention strategies for risk factor modification, and permanent lifestyle changes as goals to achieve after myocardial revascularization. Cardiac rehabilitation is an integral part of the management strategy after revascularization, because such measures reduce future morbidity and mortality in a cost-effective way and can further ameliorate symptoms. In this sense, even though not clearly specified in the guidelines, heart rate control might have an added value in revascularized patients, even in the presence of normal ejection fraction. β-Blockers are especially useful in patients with previous acute myocardial infarction or heart failure. Although the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines for CABG recommend that β-blockers should be prescribed to all CABG patients without contraindications at the time of hospital discharge, the number of CABG patients discharged from heart surgery with β-blockers ranges between 67.4% and 83%.56

Adding ivabradine to low-dose bisoprolol (1.25 mg once daily) in patients undergoing cardiac rehabilitation after recent CABG surgery has been shown to provide further benefits compared with standard medical therapy (including bisoprolol 2.5 mg to 3.75 mg once daily). Taking the ivabradine/bisoprolol regimen shortly after CABG was associated with improved functional status, enhanced diastolic function (Figure 1), and increased LVEF (Figure 2), with no negative cardiovascular effects. In addition, adding ivabradine to standard therapy including bisoprolol can improve exercise capacity (Figures 3 and 4).57

Cardiac surgery and cardiopulmonary bypass trigger inflammation and apoptosis. Transient myocardial ischemia and the ischemia-reperfusion phenomenon lead to myocardial stunning. There are two main determinants of this phenomenon: local production of free oxygen radicals and altered myocyte calcium homeostasis. Inflammatory response, operative trauma, myocardioilegia and priming volume, and nonpulsatile flow during cardiopulmonary bypass may impair systemic and diastolic function in the postoperative period. Optimization of hemodynamic parameters (ie, heart rate, ventricular filling pressure, and mean arterial pressure) is crucial in the postoperative phase. β-Blockers have well-documented direct effects on cardiovascular and pulmonary function, causing symptoms such as fatigue and dizziness.58 Because of these effects and other adverse effects—hypotension, dyspnea, cardiac decompensation, and excessive bradycardia—target doses of β-blockers may be difficult to achieve. Adverse effects like fatigue and dyspnea may also explain why β-blockers have been shown to limit exercise capacity in healthy individuals.59 Ivabradine could play a crucial role in the setting of hemodynamic parameters (ie, heart rate, ventricular filling pressure, and mean arterial pressure) is crucial in the postoperative phase. β-Blockers have well-documented direct effects on cardiovascular and pulmonary function, causing symptoms such as fatigue and dizziness. Because of these effects and other adverse effects—hypotension, dyspnea, cardiac decompensation, and excessive bradycardia—target doses of β-blockers may be difficult to achieve. Adverse effects like fatigue and dyspnea may also explain why β-blockers have been shown to limit exercise capacity in healthy individuals. Ivabradine could play a crucial role in the setting of hemodynamic parameters (ie, heart rate, ventricular filling pressure, and mean arterial pressure) is crucial in the postoperative phase. β-Blockers have well-documented direct effects on cardiovascular and pulmonary function, causing symptoms such as fatigue and dizziness. Because of these effects and other adverse effects—hypotension, dyspnea, cardiac decompensation, and excessive bradycardia—target doses of β-blockers may be difficult to achieve. Adverse effects like fatigue and dyspnea may also explain why β-blockers have been shown to limit exercise capacity in healthy individuals. Ivabradine could play a crucial role in the setting of hemodynamic parameters (ie, heart rate, ventricular filling pressure, and mean arterial pressure) is crucial in the postoperative phase. β-Blockers have well-documented direct effects on cardiovascular and pulmonary function, causing symptoms such as fatigue and dizziness. Because of these effects and other adverse effects—hypotension, dyspnea, cardiac decompensation, and excessive bradycardia—target doses of β-blockers may be difficult to achieve. Adverse effects like fatigue and dyspnea may also explain why β-blockers have been shown to limit exercise capacity in healthy individuals.
of cardiac rehabilitation, as it is devoid of inotropic, lusitropic, or vasoactive effects. Since ivabradine and \(-\)blockers use distinct mechanisms of action to reduce heart rate, the combination of ivabradine with low-dose bisoprolol appears to be a valuable option in patients with CABG undergoing cardiac rehabilitation.60

In a recent multicenter survey, cardiac rehabilitation was found to increase patient adherence to \(-\)blockers from 67.4% to 88.8% at discharge.51 In patients admitted for cardiac rehabilitation after myocardial revascularization, heart rate lowering is a useful objective, even if in most cases the target dose of \(-\)blocker is not easily achievable because these patients are highly susceptible to hypotension, mainly because of unstable hemodynamic conditions and the use of diuretic therapy to reduce fluid retention following cardiopulmonary bypass. Moreover, in the months following the procedure, heart rate variability increases due to a transient loss of autonomic control, so these patients tend to alternate between tachycardia and bradycardia. Here, the use of a higher dose of \(-\)blocker may be dangerous, whereas ivabradine, whose effect on \(i_f\) channels is frequency-dependent, carries a lower risk of bradycardia.

The results of the SHIMT trial (Systolic Heart Failure treatment with the \(i_f\) inhibitor ivabradine Trial) showed that a decrease in heart rate with ivabradine reversed LV remodeling in patients with heart failure. Similarly, ivabradine improved the LV pressure-volume relationship, decreased interstitial collagen content, and increased capillary density in young adult rats with acute myocardial infarction and congestive heart failure.62 Only one trial investigated the effects of ivabradine versus \(-\)blockers using echocardiography in patients with anterior STEMI and impaired LV function treated with primary PCI.55 In this study, at the 2-month follow-up, patients treated with ivabradine had a significant increase in LVEF, with a concomitant reduction in LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) compared with the metoprolol group. However, in this randomized trial, patients in the ivabradine group were not given \(-\)blockers and ivabradine was delivered late after angioplasty (ie, 12 hours).

A pilot study has evaluated the additional value of ivabradine in STEMI patients treated with successful primary PCI (TIMI 3 reperfused STEMI) and optimal medical therapy. Early administration of ivabradine was shown to improve LV remodeling when added to current guideline-based therapy, including \(-\)blockers (Figure 1). Clinical and experimental studies have revealed several mechanisms that may explain the beneficial effects of ivabradine on cardiac remodeling. First, ivabradine does not have negative inotropic or lusitropic effects; so hemodynamic and myocardial contractility are not impaired.64,65 Ivabradine leads to a decrease in heart rate, which reduces myocardial oxygen demand and simultaneously improves oxygen supply by prolonging diastole, which allows increased coronary flow and myocardial oxygenation. Second, Mulder et al showed that ivabradine improves the LV pressure-volume relationship, prevents LV systolic dysfunction, and increases capillary density in a rat model of congestive heart failure.66 Similarly, Dedkov et al have documented several effects of ivabradine in middle-aged rats with acute myocardial infarction, including reduction of periartrial and interstitial collagen content, attenuation of the increase in end-diastolic pressure, and attenuation of the decrease in LVEF.67 These beneficial effects of ivabradine after acute myocardial infarction were investigated in models of permanent coronary ligation. Third, in a rabbit model of ischemia reperfusion, Couvreur et al observed that ivabradine reduces myocardial stunning in rats with acute myocardial infarction and congestive heart failure.68

Elderly patients

Following hospitalization for a coronary event such as an acute coronary syndrome or heart failure, all patients—and in particular the elderly—are at increased risk of disability, including a repeat cardiovascular event. Nowadays, patients with stable CAD, including patients with stable angina and those who have become stable after an acute coronary syndrome, are older and living longer, and so make greater use of health care resources. Despite their poor prognosis and high hospital admission rate, the management of this population is often suboptimal. Effective drugs are underprescribed and interventions that improve patient outcomes such as education, psychosocial counseling, and lifestyle modification, are not widely available yet. Despite the increasing prevalence of CAD among older patients, there seems to be a strong age bias in the treatment of cardiovascular diseases, including preventive strategies.

Although elderly patients are often underrepresented in clinical trials, they are perhaps most likely to benefit from a multidisciplinary approach because of polypharmacy, comorbidity, and poor health-related quality of life. Therefore, cardiac rehabilitation is an effective model of care for older patients.69 Cardiac rehabilitation programs are designed to enhance recovery from acute cardiovascular events and to improve both quality of life and survival. In addition, patients with stable coronary heart disease treated medically or those who have undergone myocardial revascularization with PCI or CABG surgery derive benefit. The indications for cardiac rehabilitation in the elderly are the same as for the general population.69 Cardiac rehabilitation also results in statistically significant improvements in behavioral characteristics such as scores of anxiety, somatization, depression, and hostility in very elderly patients. The altered functional status of elderly cardiac patients reflects both the anatomical and physiological cardiovascular changes that occur with aging and the dysfunction that results from specific cardiovascular disorders. The changes of aging decrease the reserve capacity of the heart; problems become evident at times of cardiovascular stress, as occurs with disease. Furthermore, cardiac disease in the elderly rarely occurs
in isolation; there are typically additive impairments of multiple systemic illnesses that may directly or indirectly impair cardiovascular performance.

The decreases in maximal oxygen consumption, maximal exercise heart rate, exercise stroke volume, and cardiac output that are associated with aging reduce the capacity to exercise, to work, and to tolerate a variety of stresses. Recent studies suggest that cardiac output can be preserved thanks to an increase in stroke volume enabled by an increase in end-diastolic volume. In elderly patients with CAD and other comorbidities, addition of ivabradine reduces heart rate, increases end-diastolic volume, and improves symptoms without modifying the main hemodynamic (noninvasively measured cardiac output, stroke volume, and cardiac index) and echocardiographic (left ventricular ejection fraction and aortic transvalvular gradients) parameters.70

References


Conclusion

In recent years, there has been impressive progress in pharmacological therapies and sophisticated, technology-based diagnostic and therapeutic procedures in cardiovascular diseases. As a consequence, a greater number of men and women now survive acute events, but with a heavier subsequent burden of chronic conditions and clinical need. Cardiac rehabilitation has been shown to accelerate physical and psychological recovery and reduce mortality after acute cardiac events. Heart rate control improves symptoms, exercise capacity, and quality of life in patients undergoing cardiac rehabilitation programs and provides long-term benefits. In the hospital phase, optimizing -blocker treatment may not be easy, as hemodynamic conditions are usually unstable. Adding ivabradine early in this context is a possible and promising therapeutic strategy that will need to be validated by specific studies.


Coumeur N, Tissier P, Fons E, et al. Chronic heart rate reduction with ivabradine improves systolic function of the repurposed heart through a dual mechanism involving a direct mechanical effect and a long-term increase in FKBP12/12.6 expression. Eur Heart J. 2010;31:1529-1537.


Keywords: cardiac rehabilitation; coronary artery disease; functional status; myocardial revascularization
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The Question

Despite the widespread use of β-blockers, many patients with stable CAD continue to experience angina symptoms and/or limitations in exercise capacity. What is your strategy for optimizing antianginal therapy in patients who remain symptomatic despite therapy with β-blockers? Do you usually uptitrate β-blockers, add another antianginal agent, or do both, i.e., uptitrate β-blockers in combination with adding another antianginal agent or using another strategy?

Symptomatic patients treated with β-blockers: what is your strategy for further optimizing therapy in these stable CAD patients?

1. M. Grabowski, Poland
2. S. M. S. Hiremath, India
3. E. López de Sá, Spain
4. L. A. Machado César, Brazil
5. Q. N. Nguyen, Vietnam
6. D. Pop, Romania
7. Z. Raissouni, Morocco
8. E. J. F. Ramos, Philippines
9. I. Simova, Bulgaria
10. E. Tagliamonte, Italy
11. K. Toth, Hungary
Controversial question

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Stable angina is a global health care burden. In many patients, symptoms seriously restrict everyday activities, reduce quality of life (QoL), and lead to premature retirement. In fact, patients who have refractory angina without the possibility of revascularization represent one of the most challenging clinical situations. In clinical practice, symptomatic angina in treated stable patients is not a rare problem despite the widespread use of β-blockers. Due to tolerability issues, the efficacy of first-line therapy might be decreased by using doses of β-blockers that are too low. Common comorbidities—such as chronic obstructive disease and peripheral artery disease—also limit the use of effective doses of β-blockers, and this may lead to a suboptimal effect. Last, but not least, the reason for uncontrolled angina might be a high heart rate, which increases myocardial oxygen demand and limits oxygen supply. In those patients, heart rate reduction is a recognized strategy to improve oxygen balance and alleviate symptoms.

Ivabradine is a selective inhibitor of the I1-pacemaker current, and as such it decreases heart rate. It exerts its antianginal efficacy by increasing myocardial diastolic perfusion time, enhancing coronary flow reserve, and improving endothelial function without reducing myocardial contractility. The proven clinical benefits of ivabradine for stable angina include symptom relief, increased exercise capacity, and improved QoL. Moreover, in a subgroup analysis of the BEAUTIFUL trial, treatment with ivabradine in patients with left ventricular systolic dysfunction, limiting angina, and a heart rate ≥70 bpm reduced hospitalizations for fatal and nonfatal myocardial infarctions (73% relative risk reduction). It is important to note that randomized clinical trials have showed that ivabradine has an anti-ischemic effect not only when used as monotherapy, but also when used in combination with a β-blocker.

A recent pooled analysis of three studies (ADDITIONS, REDUCTION, and RESPONSIVE), which included a total of 8555 patients, showed that treatment with ivabradine was associated with a reduction in the mean number of angina attacks and the use of short-acting nitrates, and an improvement in clinical status and QoL. After 4 months of treatment with ivabradine, 85% of patients achieved a heart rate of less than 70 bpm or a reduction in heart rate of at least 10 bpm. In patients with an elevated heart rate despite the use of a β-blocker, ivabradine significantly reduced the number of angina attacks and the use of short-acting nitrates.

A post hoc analysis from the ADDITIONS trial focused only on patients taking metoprolol (mean dose, 109 mg/day). At the end of the study, of the patients treated with metoprolol plus ivabradine for 4 months, 80% were receiving a daily dose of metoprolol of at least 95 mg, and 55% were treated with the maximum dose of ivabradine (15 mg/day). Another post hoc analysis from the ADDITIONS database, which investigated the effectiveness and tolerability of ivabradine in combination with a β-blocker, confirmed that this treatment is an effective and well-tolerated antianginal treatment in patients with stable angina after a percutaneous coronary intervention. This treatment reduces the frequency of weekly angina attacks (84% reduction) and nitrate consumption, leading to an improvement in the Canadian Cardiovascular Society (CCS) class and a substantial improvement in QoL.

Recently, a form of angina occurring in the absence of obstructive disease has been described. It is known as “microvascular angina” and is thought to be caused by structural alterations in the coronary microvasculature. New anti-ischemic drugs, including ivabradine, have been shown to be effective in some patients with microvascular angina.

Treatment strategies have a fundamental role in improving angina. To reduce the heart rate and control angina, ivabradine may be considered in all eligible patients with a heart rate ≥70 bpm, including those with a concomitant β-blocker treatment. The possible clinical outcomes include symptom relief, increased exercise capacity, and improved QoL, and thus it may actually provide complete management of stable angina pectoris. Treatment with ivabradine is usually well-tolerated with a low risk of side effects, contraindications, drug-drug interactions, and precautions.

References
2. S. Hiremath, *India*

Among people 60 to 79 years old, approximately 25% of men and 16% of women have coronary heart disease, and these figures rise to 37% and 23% among men and women >80 years old, respectively. The principal goals of management in patients with stable coronary artery disease (CAD) are to decrease mortality and myocardial infarction, to ensure symptom-free long-term survival, and to improve overall quality of life. Compared with medical therapy, coronary revascularization reduces mortality or myocardial infarction rates in patients with ST-segment elevation myocardial infarction and in high-risk patients with acute coronary syndromes. However, in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI 2D (Bypass Angioplasty Revascularization Investigation 2–Diabetes) trials, an initial management strategy of revascularization plus optimal medical therapy for patients with stable CAD did not reduce the long-term rates of death, myocardial infarction, or other cardiovascular events compared with the optimal medical therapy alone.1,2 About 30% of the patients enrolled in the BARI trial never returned to work after a coronary revascularization, and 15% to 20% of patients rated their own health as “fair” or “poor” despite revascularization.3

An estimated 50% of the reduction in cardiovascular mortality in the past few decades is attributed to aggressive lifestyle and risk-factor modification, together with the use of recommended dosages of antiplatelet agents and statins.1,4 β-blockers reduce myocardial oxygen consumption by reducing heart rate, myocardial contractility, and afterload, and attenuate cardiovascular remodeling with long-term use by decreasing left ventricular wall tension. Long-term β-blocker treatment is well tolerated, has proven benefits in stable ischemic heart disease—as it reduces the ischemic burden and increases the ischemic threshold—and improves survival in patients with left ventricular dysfunction or a history of myocardial infarction. However, optimization of the β-blocker dose is limited by the occurrence of adverse effects, such as hypotension, bronchospasm, fatigue, lethargy, sexual dysfunction, and sleep disturbances, and it has the potential to worsen symptoms in patients with significant depressive illness or peripheral artery disease. Calcium channel blockers or long-acting nitrates should be prescribed in combination with a β-blocker to provide symptom relief when the initial β-blocker monotherapy is unsuccessful in patients with stable ischemic heart disease.

Ivabradine is a specific inhibitor of the I_Na current of pacemaker cells in the sinoatrial node. This action results in a reduction in heart rate, prolonging diastole and thereby improving myocardial oxygen balance. Ivabradine has no effect on blood pressure, myocardial contractility, or intracardiac conduction parameters. It improves exercise capacity and reduces angina frequency by effectively controlling heart rate. In the BEAUTIFUL trial (morBidity-mortality EvAlUaTion of the I_Na inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), ivabradine reduced the composite primary end point (ie, cardiovascular death, hospitalization for an acute myocardial infarction, and hospitalization for new-onset or worsening heart failure) and the hospitalizations for myocardial infarction.4 The effect was predominant in patients with a heart rate ≥70 bpm. Ivabradine is thus an effective antianginal agent, alone or in combination with β-blockers. Due to its focused action on the sinoatrial node, it is safer in terms of adverse effects and drug interactions.

References

3. E. López de Sá, Spain

-Blockers are the first drugs with demonstrated efficacy in relieving the symptoms of stable angina. The -blocker dose is generally uptitrated to reduce the patient’s heart rate at rest and, during exercise, to a frequency below the level that triggers angina or leads to harmful side effects. Checking whether these objectives have been met is probably the most reasonable initial strategy for optimizing antianginal therapy in those patients who remain symptomatic despite therapy with -blockers. Unfortunately, this approach fails to alleviate symptoms in a significant number of patients. Since the main objective of the management of stable angina is to control symptoms, it makes no sense to continue increasing the -blocker dose, especially if the -blocker produces uncomfortable symptoms due to side effects. In this case, a combination with another antianginal drug would be recommended.

However, for stable angina, the hypothesis that low doses of multiple drugs could offer better control of symptoms with fewer adverse effects, as is the case when treating hypertension, remains controversial. The TIBET trial (Total Ischaemic Burden European Trial), which was designed to determine the impact of a moderate dose of atenolol vs nifedipine or an atenolol/nifedipine combination in patients with mild chronic stable angina, demonstrated that, when compared with placebo, each medication alone, and in combination, significantly reduced symptoms. However, the trial did not reveal any significant advantage of the combination over the single-drug treatments, although combination therapy led to a larger reduction in baseline blood pressure than either treatment alone. In contrast, a small trial that evaluated the antianginal efficacy of combining ivabradine (7.5 mg twice a day) with bisoprolol (5 mg/day) vs uptitrating bisoprolol to a target dose of 10 mg/day in patients with stable angina and left ventricular dysfunction suggested that the addition of ivabradine might be superior to increasing the -blocker dose for symptom control.

In order to assess potential new treatments for stable angina patients, a distinction should be made between those treatments that improve the prognosis and those that only improve symptoms. With regard to improving the prognosis, only -blockers and ivabradine have been shown to improve outcomes in patients with heart failure or left ventricular dysfunction over other antianginal drugs. Therefore, the most reasonable second step is to assess whether the patient is a good candidate for this therapy based on the ejection fraction, presence of sinus rhythm, and heart rate. Outside of this setting, the choice of one antianginal drug over another should be based on the clinical profile of the patient because there is no study that demonstrates that one has an advantage over another. However, since antianginal drugs differ in their mechanisms of action, the treatment can be tailored to suit the patient’s needs. For example, the most appropriate strategy for a patient with high blood pressure and a slow heart rate is a dihydropyridine calcium channel blocker or nitrates, and for a patient with a slow heart rate and low blood pressure, the choice must be ranolazine or trimetazidine. Ivabradine should be used in those with sinus rhythm and a resting heart rate >70 bpm because the ESC guidelines state that combining -blockers with non-dihydropyridine calcium channel blockers should be avoided due to the risk of bradycardia or atrioventricular block. Therefore, I usually increase the dose of -blockers in combination with the addition of another antianginal agent.

References
When treating patients with coronary artery disease (CAD), persistence of angina symptoms despite -blocker therapy is a frequent scenario. This situation happens because, until now, we have considered -blockers as the best first-line antianginal drugs, even in the absence of studies showing a reduction in events in patients with stable CAD. The only exceptions are for patients after an acute coronary syndrome when -blocker treatment confers protection over a period of months. In fact, there has only been one study with a long follow-up—the Norwegian Multicentre Study. In this study, patients were followed-up after an acute coronary event for a mean of 2.5 years. This trial took place in the 1980s when other therapies such as primary angioplasty, thrombolytic therapy, anti-platelets, anti-coagulants, and statins were not available or routinely used. Other post-myocardial infarction trials followed-up patients for no more than 3 months, but -blockers are now the first-line treatment of choice for angina based on these post-myocardial infarction studies.

Until recently, we up-titrated the -blocker dose and added a long-acting nitrate to treat angina. However, this will usually eliminate angina in only a few patients, especially if the heart rate is already below 70 bpm. At least 20% of patients cannot take nitrates due to headaches, and, even with nitrates, many continue to have angina. Another strategy is to add a dihydropyridine calcium channel blocker to the -blocker, but this strategy results in angina control in only a few more patients. Some studies have showed that adding nifedipine or amiodipine to a -blocker does not reduce angina episodes substantially, and the same is observed when a long-acting nitrate is added to -blockers. For a while there was a lack of new strategies to treat angina other than interventions such as coronary artery bypass grafting (CABG) and angioplasty. However, many patients treated with CABG and angioplasty continue to have angina symptoms.

New agents were developed in order to achieve a better control of angina symptoms in most patients. Some studies show that trimetazidine has a substantial antianginal effect when added to any previous antianginal therapy, such as -blocker monotherapy, -blockers combined with nitrates, or -blockers combined with calcium channel blockers.

The effect is similar regarding the percent reduction in angina, regardless of the previous treatment. Ivabradine, a drug that reduces heart rate, is another drug that can be used to control angina episodes. It was tested against atenolol, amiodipine, and combined with a -blocker as a baseline therapy. All studies confirmed the benefits of ivabradine as an effective antianginal drug. There are also others drugs, such as nicorandil and ranolazine, but I have no experience with them.

At the moment, my strategy for treating angina is as follows: (i) if the patient is on an average dose of a -blocker, exceptionally I consider up titration; (ii) I add ivabradine first if the heart rate is above 70 bpm; (iii) if angina persists, I up titrate ivabradine to 7.5 mg twice a day; and (iv) if necessary, I add trimetazidine next. The heart rate of patients taking -blockers and ivabradine together usually goes down to almost 60 bpm. With a heart rate of <70 bpm at the beginning, I add trimetazidine first, and, if the ejection fraction is <40%, I use both ivabradine (for heart rates >70 bpm) and trimetazidine. Long-acting nitrates remain the third option. This is what the stable coronary disease guidelines from the Brazilian Society of Cardiology suggest, and reflects my current practice.

References
5. Q. N. Nguyen, Vietnam

Stable coronary artery disease (CAD) can easily progress into an acute coronary syndrome, which might lead to fatal outcomes, especially in patients with a heavy atherosclerotic burden. Both the severity of lumen stenosis and the atheroma burden are predictors of plaque rupture and future major adverse cardiac events. For CAD patients, symptoms (typical angina or limitation in exercise capacity) are warning signs to reconsider the stability state of the entire coronary artery tree.

Initially, I determine: (i) if there is any existing lesion that needs to be revascularized; (ii) if there is any relevant plaque rupture to fix; and (iii) if there is any significant emerging stenosis to treat. While the second point should be ruled out by serial testing of cardiac troponin, the first and third points usually take time and resources and involve the use of noninvasive or invasive cardiac imaging procedures and anatomical or functional approaches. Aggressive approaches should be reserved only for high-risk groups, such as patients with a previous stent or bypass, suggestive ischemic changes on a resting electrocardiography, and new abnormal wall motion or mitral valve dysfunction evidenced by echocardiography.

Second, for newly symptomatic stable patients, I determine if there are comorbidities that may result in similar signs/symptoms. The most common causes are uncontrolled hypertension, atrial fibrillation with rapid ventricular response, frequent ventricular premature beats (especially in patients with scars from a previous myocardial infarction), and the less common cause is uncompensated heart failure. Ambulatory blood pressure and heart rate monitoring could easily exclude these issues, and reflect the patient’s blood pressure and heart rate variability, which recently emerged as a new risk factor for future cardiovascular adverse events and as a marker of efficacy or treatment adherence.

Finally, for newly symptomatic stable patients, I determine whether patients are adherent to their treatment or if their treatment regimen is suboptimal. In daily practice, patients receiving long-term treatment usually tend to cut their treatment short due to financial cost, medication side effects, or psychological reasons. It is critical to reeducate this kind of patient on the importance of secondary prevention against the progression of atherosclerosis and the occurrence of unpredictable major adverse cardiac events, and to discuss the balance between potential side effects and future benefits.

For patients receiving a suboptimal treatment regimen, I would add another kind of anti-ischemic drug rather than uptitrate the β-blocker, to minimize the adverse effects and maximize the antianginal effect, an approach that is similar to that of the evidence-based blood pressure-lowering or cholesterol-lowering strategies. Adding one more drug to either lower heart rate continuously (such as ivabradine or a calcium channel blocker) or optimize cellular energy metabolism (such as trimetazidine or ranolazine) is a matter of choice. Ivabradine appears to affect coronary collateral function positively in chronic stable CAD patients, which could benefit patients who are not amenable to further coronary revascularization. In addition to the standard existing β-blocker treatment in stable CAD patients, adding ivabradine significantly improves the symptoms and quality of life, which further supports using a multiple anti-ischemic drug combination strategy.

In heart failure patients ivabradine should also be a first-line treatment due to its additional prognostic benefit. Ivabradine also has a demonstrated efficacy in particular subpopulations where β-blocker use is limited, such as patients with asthma, chronic obstructive pulmonary disease, peripheral vascular disease, diabetes, or elderly patients (older than 80). However, in stable CAD patients without left ventricular dysfunction, β-blockers and ivabradine have symptomatic benefits but lack prognostic benefits. A recent analysis has raised some concerns about increased central systolic pressure, which can abolish the potential benefits of heart rate–lowering therapy with β-blockers or ivabradine, especially in patients with hypertension and CAD. In such patients, a vasodilating β-blocker or calcium channel blocker, or metabolic anti-ischemic agent should be the first-line treatment.

References

Mortality due to ischemic heart disease (including stable angina) continues to be very high in Europe: 40% in men and 49% in women, despite the complex methods of treatment currently available. The ESC guidelines on the management of stable coronary artery disease recommend -blockers and/or calcium channel blockers as first-line antianginal medications, along with short-acting nitrates. If symptoms persist, ivabradine, long-acting nitrates, nicorandil, ranolazine, or trimetazidine should be added. Obviously, we must not forget cardioprotective medications (statins, antiplatelet agents, angiotensin-converting enzyme inhibitors). The guidelines also recommend using optimal drug therapy in all patients, even those with an indication for revascularization. However, there are many patients who continue to have effort angina and/or decreased exercise capacity despite an appropriate first-line treatment including maximal tolerated doses of -blockers. On the other hand, while -blockers are the most frequently prescribed drug class in patients with stable coronary artery disease, data from registries and studies show that they are used at low doses. This low dosing could be explained by limitations for -blocker uptitration due to tolerability issues. These limitations raise questions about how we can optimize medical therapy in these patients.

In this context, we must remember that in a healthy person adaptation to exercise involves both peripheral (eg, arteriolar vasodilatation in striated muscle, vasoconstriction in other territories, such as venous territories, and increased \(O_2\) factor extraction) and central mechanisms (eg, increased preload, heart rate, ejection fraction, and contractility). All of these changes lead to an increase in \(O_2\) intake in the muscles during exercise. In effort angina, there is an imbalance between oxygen requirements and intake due to the presence of coronary stenoses. Myocardial ischemia (clinically manifested by angina attacks) is significantly influenced by a number of other factors that need to be treated. Collateral circulation plays an important role in preserving coronary flow reserve. Bradycardia also favors the development of collateral circulation, facilitating angiogenesis and arteriogenesis. Ivabradine 7.5 mg twice daily stimulates collateral blood vessel growth in the ischemic myocardium, and the induced reduction in heart rate is accompanied by a significant increase in myocardial perfusion through collateral vessels. Coronary reserve has a primary role in adaptation to exercise, and heart rate reduction is associated with improved myocardial coronary perfusion. Recent experimental studies have demonstrated that ivabradine may increase coronary reserve up to 26%, helping to ensure an optimal supply of oxygen under myocardial ischemia conditions. Increasing diastolic perfusion time is another important mechanism (myocardial perfusion occurs predominantly in diastole). Ivabradine has proven its effectiveness in this respect, as it has been shown to trigger an increase of 41% in diastolic perfusion time. Finally, ensuring that coronary flow is optimal may help to relieve ischemia in stable angina. Although atenolol and ivabradine cause a similar improvement in coronary flow at rest, during physical effort the improvement in coronary flow is significantly higher in patients treated with ivabradine. The mechanisms described above, which improve myocardial perfusion, may explain the well-known effects of ivabradine (reduced number of angina attacks, increased exercise capacity, improved quality of life). Ivabradine represents a viable therapeutic alternative for patients with stable angina who remain symptomatic despite being treated with a -blocker at the maximum tolerated dose.

**References**

Coronary artery disease is the most frequent type of heart disease, and stable angina pectoris (SAP) is one of its more common presentations. SAP is the clinical expression of myocardial ischemia secondary to an imbalance in myocardial oxygen supply and demand. The goals of treatment include relief of symptoms and inhibition of disease progression. Here we focus on the role of medical therapy in the management of SAP. Two major classes of drugs are essential for SAP therapy and are prescribed as first-line treatment: anti-ischemic drugs and drugs that prevent myocardial infarction (MI) and death.1

Anti-ischemic drugs include \( \beta \)-blockers, calcium channel inhibitors, and nitrates (short- and long-acting). The mechanisms of action of most of these drugs involve a reduction in systemic vascular resistance, coronary vasodilatation, or negative inotropism, which improves the imbalance between myocardial oxygen supply and requirement.

Numerous drugs are available to improve prognosis by preventing MI and death. Aspirin at a dose of 75 mg per day reduces cardiovascular morbidity and mortality by 33% in patients with coronary artery disease.2 Clopidogrel combined with aspirin is not significantly more effective than aspirin alone in reducing the rate of MI, stroke, or death. Statins lower the incidence, as it offers clear therapeutic benefits for a whole range of patients with SAP in sinus rhythm.

Ivabradine is a heart rate-lowering agent that selectively blocks the sinus node \( f \) current, decreasing the myocardial oxygen demand without any negative inotropic effects. The European Medicines Agency (EMA) approved it for the treatment of SAP in patients intolerant to—or inadequately controlled by—\( \beta \)-blockers and with a heart rate >60 bpm.3,4 Ivabradine is also recommended by the ESC guidelines with a level of evidence, as it offers clear therapeutic benefits for a whole range of patients with SAP in sinus rhythm.

Trimetazidine is a metabolic agent that acts at the cellular level to improve myocardial metabolism during ischemia. By increasing glucose utilization it increases the production of adenosine triphosphate (ATP) per unit of oxygen consumed. Added to \( \beta \)-blockers, trimetazidine (35 mg twice daily) improves effort-induced myocardial ischemia, as reviewed by the EMA in June 2012.3 These data indicate that trimetazidine is safe and effective for the treatment of SAP symptoms, either as monotherapy or adjunctive treatment, and that it can be considered as a second-line treatment (IIb).1

SAP symptoms can usually be managed using optimum doses of one of the available antanginal drugs, along with lifestyle modifications, and drugs such as aspirin, statins, and ACE inhibitors. Several new drugs with a different mechanism of action provide new treatment options, and have precise indications in the new European guidelines. Finally, patients who remain symptomatic despite medical treatment should be considered for revascularization.

### References

Controversial question

8. E. J. F. Ramos, Philippines

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-$blockers have been used for decades in the management of ischemic heart disease, mainly to decrease oxygen demand through heart rate reduction. In patients with stable coronary artery disease (CAD), angina pectoris occurs at certain thresholds of physical activity, triggered by an increase in heart rate and relieved by rest and the corresponding heart rate normalization. Patients oftentimes learn to anticipate the onset of angina pectoris at specific physical exertion levels. Other than the avoidance of physical exertion, optimal use of -$blockers and anticipatory use of nitrates—orally or sublingually—minimize the occurrence of angina. When angina occurs in spite of such measures, or at lower physical exertion levels, coronary angiography is warranted. In the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), however, a significant percentage of post-percutaneous coronary intervention (PCI) patients continued to have angina at 1 year post-intervention, implying that mechanisms other than stenosis of the epicardial arteries are involved.

In places where access to a cardiac catheterization laboratory is limited, or when coronary intervention is not feasible, optimizing medical therapy on top of -$blockers, antiplatelets, nitrates, and statins requires more aggressive reduction of cardiovascular risks and the use of newer drugs. The challenge increases when the patient is hypertensive or diabetic, or both, with evidence of ventricular hypertrophy and diastolic dysfunction, and peripheral and microvascular circulatory disorder. It gets worse when the patient has contraindications to the use of -$blockers, or when increasing the dose of the -$blocker is not medically feasible.

At the cellular level, optimal therapy in stable CAD requires efficient production of mitochondrial ATP to meet the metabolic demands of the cardiac myocytes in times of stress. Oxidative stress and the production of oxygen free radicals contribute significantly to angina pectoris. Coronary flow occurs during diastole; therefore, increasing diastolic duration by decreasing the heart rate improves coronary flow in addition to decreasing the demand for oxygen. -$blockers decrease heart rate but negatively affect myocardial contractility at high doses. Their -agonist effect also promotes vasoconstriction. The non-dihydropyridine calcium channel blockers diltiazem and verapamil reduce heart rate and cause coronary vasodilatation, but have negative inotropic effects at higher doses.

Ivabradine, with its neutral impact on myocardial contractility or blood pressure, has made optimal therapy in stable CAD patients with concomitant disorders much easier to achieve. These patients are likely to be already on many other drugs like aspirin, -$blockers, nitrates, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, all of which have unique properties in restoring or preserving myocardial function. Drug-drug interaction is a real risk in this situation, however, but interactions between these drugs and ivabradine have been shown to be safe. A study has shown that ivabradine prolongs diastolic duration more than -$blockers even at a similar level of heart rate reduction. Ivabradine alleviates myocardial ischemia and reduces angina pectoris not only by reducing oxygen demand but also by improving oxygen supply through coronary vasodilation at the microvascular level. Moreover, a study showing a favorable effect of ivabradine in endothelial function points to an improvement in the efficiency of energy production at the intracellular level.

Optimal therapy of stable CAD patients treated with -$blockers who are still symptomatic requires a combination of drugs that promote myocardial perfusion, maintain coronary reserve, and improve cellular function, given at dosages that do not cause side effects or increase the risk of drug-drug interactions. Ivabradine has been shown not only to decrease oxygen demand through heart rate reduction, but also to increase coronary flow and improve cellular function.

References

CONTROVERSIAL QUESTION

9. I. Simova, Bulgaria

-Blockers are the most frequently prescribed drug class in patients with stable coronary artery disease (SCAD). Dosing regimens, however, are often suboptimal due to problems of tolerability. This is probably the reason why many patients with SCAD still continue to experience angina symptoms and/or limitation in exercise capacity, despite β-blocker therapy. Presented here is a personal perspective and a step-by-step management strategy for patients who remain symptomatic despite therapy with β-blockers.

Step 1: control risk factors
Risk factors—which include hypertension, hypercholesterolemia, diabetes, a sedentary lifestyle, obesity, and smoking—should be addressed and properly controlled. The patient’s blood pressure should be measured at every visit, while lipid status, serum glucose, and glycated hemoglobin should be assessed periodically.

In addition, the importance of maintaining a healthy lifestyle should be promoted and counseling on smoking cessation, diet, regular physical activity, and weight loss—if necessary—should be provided. Depression, anxiety, and distress should also be addressed.

Risk factors should be taken into account when prescribing concomitant medications. For example, if a patient has diabetes and should take a diuretic for blood pressure control, then a metabolically neutral diuretic, like indapamide, should be prescribed, instead of hydrochlorothiazide.

Step 2: address precipitating factors
Patients whose symptoms have worsened while on β-blocker therapy should be evaluated for the presence of precipitating factors, like hyperthyroidism, anemia, tachyarrhythmias, aortic stenosis, hypertrophic cardiomyopathy, fever, malignant hypertension, hypotension, etc…. If present, these conditions should be treated.

Step 3: assess β-blocker treatment
β-Blockers are clearly effective in controlling exercise-induced angina, improving exercise capacity, and limiting ischemic episodes. There is no unequivocal evidence, however, that β-blocker therapy improves prognosis in SCAD patients without myocardial infarction or heart failure. If a patient is symptomatic while on β-blocker therapy, the first thing to do is to assess treatment compliance. If poor compliance is due to forgetfulness, then the patient should be instructed on the importance of persisting with the treatment. Poor compliance, however, is often due to the adverse effects of β-blockers, which include hypotension, fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, hypoglycemia, or masked hypoglycemia. If these adverse effects are present, then the patient is intolerant to β-blockers. Depending on the findings, there are several possible scenarios:
- If the patient can tolerate β-blockers but compliance is suboptimal, then compliance should be reinforced.
- If the β-blocker dose is suboptimal, and the treatment is tolerated, then the dose should be uptitrated.
- If the patient is intolerant to β-blockers, then the dose should be downtitrated in order to find the maximal tolerated dose. There are patients, however, that do not tolerate any β-blocker dose and the therapy should be discontinued. In case of β-blocker intolerance, then a second anti-ischemic agent should be added.

Step 4: choose a second anti-ischemic agent
- If the resting heart rate (HR) is ≥70 beats per minute (bpm), then ivabradine should be added and uptitrated in order to achieve a resting HR of 50-60 bpm.
- If the resting HR is <60 bpm, then we should consider adding a dihydropyridine calcium channel blocker, and/or long-acting nitrate, and/or trimetazidine for symptomatic relief.

Step 5: consider coronary revascularization
If all of the above-mentioned measures have been addressed and the patient is still symptomatic, then the physician should consider referring the patient for coronary angiography with a view to revascularization.

Reference
10. E. Tagliamonte, Italy

Stable angina pectoris is the most common manifestation of coronary artery disease (CAD). Although the annual mortality rate is relatively low, anginal symptoms are often disabling. The aims of treatment are to relieve anginal symptoms and improve the quality of life. In patients who remain symptomatic despite optimal medical treatment, there is evidence that coronary revascularization improves anginal symptoms. However, in a substantial proportion of these patients, the prevalence of angina at follow-up remains high despite successful revascularization. These findings suggest that, although revascularization is effective in removing coronary stenosis, other mechanisms, including coronary microvascular dysfunction, contribute to the pathogenesis of ischemia and angina in these patients.

Resting heart rate (HR) is an important and independent risk factor and a predictor of cardiovascular mortality and morbidity. HR-lowering agents have been shown to improve clinical outcomes, although whether HR reduction is the only mechanism of benefit is hard to demonstrate and is perhaps too simplistic. β-blockers are used as first-line therapy to control symptoms in patients with chronic stable angina and they can significantly reduce cardiovascular events. More recently, the sinus node β1 channel inhibitor ivabradine, which reduces HR both at rest and during exercise, has been proven to have antianginal efficacy.

Because of their HR-lowering effects, ivabradine and β-blockers are often considered to be “similar” drugs. Large clinical trials have investigated the use of ivabradine as an alternative to β-blockers, when β-blockers cannot be tolerated or are contraindicated, or in addition to them, when HR is not adequately controlled. But we should ask ourselves whether their effect is really that similar. Recent experimental and clinical investigations have demonstrated that ivabradine may reduce myocardial ischemia and its consequences not only through HR lowering, but also through additional pleiotropic mechanisms that contribute to improve coronary vascular and myocardial structure and function. It is clear that diastolic perfusion time mainly affects subendocardial blood flow, since coronary blood flow is greatest during diastole. In experimental studies, ivabradine increased diastolic time both at rest and during treadmill exercise to a greater extent than atenolol, though both drugs had a similar effect on HR. These data were also confirmed in humans, as recently demonstrated in clinical studies on patients with stable CAD.

Moreover, contrary to β-blockers, ivabradine does not increase or unmask β-adrenergic coronary vasoconstriction in the epicardial coronary arteries and, more importantly, in the coronary microcirculation. This effect of ivabradine is especially important in human atherosclerotic coronary vessels, since β-adrenergic vasoconstriction is enhanced in the presence of endothelial dysfunction.

Reduced coronary flow reserve (CFR) may reflect narrowing of the epicardial coronary arteries or dysfunction of the coronary microcirculation. Ivabradine and β-blockers were found to have a different effect on CFR, with two studies showing that ivabradine has a stronger effect on CFR than β-blockers, despite both drugs achieving a similar HR reduction.

Finally, the development of collateral circulation is a natural mechanism that can compensate for the limitation of coronary flow resulting from coronary stenosis progression, and it is advantageous in protecting tissues from ischemia. In patients with stable CAD ivabradine has been shown to improve coronary collateral function.

Clinical and experimental studies show that the effect of ivabradine on the pathophysiology of the coronary circulation is different from that of β-blockers, as it has both antiischemic and anti-β-adrenergic effects. Since β-blockers and ivabradine produce a similar reduction in HR, the effect of ivabradine treatment actually appears to go beyond its HR-lowering effect. Thus, ivabradine should not be considered as an alternative to β-blockers, it should be a first-choice treatment in symptomatic patients with stable CAD, even in those already treated with β-blockers. Further studies may even suggest that ivabradine is preferable to β-blockers in these patients.

References

Optimizing therapy in symptomatic stable CAD patients treated with β-blockers
CONTROVERSIAL QUESTION

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-Blockers are the most frequently prescribed drug class in patients with stable coronary artery disease (CAD), although they are often used at low doses as -blocker up titration can be limited by problems of tolerability. Moreover, many patients with stable CAD continue to experience angina symptoms and/or limitation in exercise capacity despite the use of -blockers. Clinical trials and meta-analyses have shown that almost half of stable CAD patients experience typical angina symptoms that impact their daily activities and lifestyle. The main purpose of treatment, besides improving the prognosis, is to reduce the frequency and severity of angina so that quality of life improves.

It is well known that a high resting heart rate worsens cardiovascular outcomes.1 It increases the myocardial oxygen demand and decreases diastolic time, and as a result myocardial perfusion is altered, leading to ischemia and anginal symptoms.2 In CAD the recommended target resting heart rate is 55-60 bpm, although in refractory angina it can even be lowered to < 50 bpm in case of asymptomatic bradycardia. -Blockers, which are the first-line treatment, should be uptitrated and when symptoms are not relieved, they can be combined with dihydropyridine calcium antagonists. Although the efficacy of -blockers is proven, difficulties often arise regarding initiation, up titration, and maintenance of -blocker treatment because of adverse effects or because of an inadequate response due to a -receptor polymorphism. If first-line medications are not sufficient in combination, a second line treatment (long-acting nitrates, ivabradine, ranolazine, trimetazidine, or nicorandil) can be given.

Ivabradine is a specific sinus node inhibiting agent that can be used in patients with sinus rhythm whose heart rate is ≥70 bpm. It inhibits the I f current in the sinus node and—in contrast to -blockers—does not have negative inotropic effects. It decreases heart rate but has no effect on cardiac output and blood pressure. Several clinical trials have demonstrated the benefit of combining a -blocker with ivabradine. This combination improves chronotropic reserve and exercise tolerance due to an additive antianginal effect, decreases angina episodes and nitroglycerin consumption, and enhances quality of life. 3,4 This therapeutic strategy can be applied in patients with sinus rhythm when up titrated -blockers do not achieve the desired heart rate reduction and the patient remains symptomatic. Furthermore it can also facilitate the up titration of -blocker therapy.

Trimetazidine is another second-line option. It improves myocardial glucose utilization—thereby increasing coronary flow reserve, decreasing the frequency of anginal episodes and nitrate consumption, and improving exercise tolerability—but has no effect on heart rate and has no negative inotropic and vasodilatory effects.5 In clinical practice trimetazidine is a safe and effective agent that can be used as an add-on treatment in patients who are symptomatic or intolerant to first-line antianginal therapies, and also in patients with bradyarrhythmia and atrial fibrillation.

Although a number of clinical studies have demonstrated that combining ranolazine with traditional medical therapy provides sufficient angina relief,6 we have limited clinical experience with this drug since it is not currently available in several European countries. Long-acting nitrates can also be added sequentially if symptoms persist. Unfortunately, nitrate tolerance can develop with continuous exposure. Moreover, headache and hypotension can also limit its use. Nicorandil is another vasodilator, which acts both as a nitric oxide donor and an arterial K+ ATP channel opener. It is recommended as a second-line agent after -blockers and calcium channel antagonists, although there is limited clinical experience with this drug since it is not available in several European countries.

In conclusion, ivabradine is an option for symptomatic patients in sinus rhythm after -blockers and calcium channel blockers have been uptitrated. In case of bradycardia and atrial fibrillation other therapeutic options like trimetazidine, ranolazine, and vasodilatory drugs can provide alternative treatments, even though the last two drugs can often produce adverse effects owing to their hemodynamic action.

References
The success of revascularization and recent clinical trial findings may result in underestimation of the importance of angina. Yet angina has not gone away. Indeed, it remains the most common initial symptom of coronary artery disease and its severity is closely associated with every aspect of perceived health status. The aggressive treatment of angina is a cornerstone of patient management. Experimental and clinical data show that Procoralan (ivabradine) improves coronary flow reserve, coronary collateral circulation, and endothelial function in patients with angina. When added to β-blockers, Procoralan further improves exercise capacity and quality of life in angina patients. Analysis of pooled data from the Procoralan angina development program and from observational studies in daily practice provides clinical evidence that Procoralan diminishes angina in all types of patients, regardless of age, sex, angina severity, revascularization status, history of myocardial infarction, peripheral vascular disease, or diabetes. These clinical benefits show that Procoralan is an important agent for symptomatic treatment of patients with angina pectoris.
diseases that frequently and unavoidably limit the choice of therapy. These findings indicate a clear need for improved medical management of stable angina. Procoralan is an antianginal agent with specific heart rate–lowering properties that selectively modulates pacemaker activity in the sinoatrial node of the heart, resulting in improved coronary perfusion and pump efficiency. Procoralan improves exercise capacity and quality of life when used as a single agent and also in combination with -blockers. Large development programs in angina and data on antianginal efficacy from observational studies show that Procoralan diminishes angina in all types of patients, irrespective of age, sex, angina severity, revascularization status, history of myocardial infarction (MI), peripheral vascular disease, or diabetes.10,11

Improvement of coronary blood flow with Procoralan

Although the main antianginal mechanisms of Procoralan are reduction of myocardial oxygen consumption and improvement of coronary blood flow due to prolongation of diastolic perfusion time, more recent clinical investigations have demonstrated that Procoralan may reduce myocardial ischemia and its consequences through other beneficial effects that help improve coronary blood flow (Figure 1).8

◆ Effect on diastolic perfusion time and coronary blood flow

As coronary blood flow occurs mostly during diastole, diastolic time is of major importance in ensuring an adequate blood supply to the myocardium. -Blockers reduce heart rate, thereby decreasing myocardial oxygen demand, and also increase diastolic time. The effects of both Procoralan and the -blocker atenolol on diastolic time, and the resulting coronary blood flow changes, were compared in dogs. Procoralan increased diastolic time at rest and during exercise to a greater extent than atenolol, with a larger increase in coronary blood flow, despite a similar reduction in heart rate with both agents.12

In a recent randomized, double-blind, crossover study, Dillinger et al11 reported an increase in diastolic time with Procoralan in stable coronary patients receiving -blockers. Treatment with Procoralan over 3 weeks resulted in a 41% increase in diastolic time and a 39% increase in the subendocardial viability ratio, an index of myocardial oxygen supply and demand. This shows that Procoralan improves perfusion and has a positive impact on myocardial ischemia. These results are of major importance when the oxygen supply to the myocardium reaches the ischemic threshold in patients with angina pectoris.

◆ Preservation of coronary vasodilatation

-Blockers unmask -adrenergic vasoconstriction, as is apparent to physicians when patients complain about Raynaud’s syndrome or cold fingertips after -blockade. -Blockade also unmask -adrenergic vasoconstriction in coronary arteries, as demonstrated in experimental dog models15 and in humans.16 In contrast, Procoralan does not unmask -adrenergic vasoconstriction.17 Experimental data show that -blockade results in constriction of coronary arteries during exercise, while Procoralan preserves coronary vasodilatation during exercise, despite producing a similar reduction in heart rate.17 Importantly, -adrenergic vasoconstriction is enhanced in the presence of endothelial dysfunction. Therefore, the ability of Procoralan to preserve coronary dilation during exercise is of major therapeutic importance in patients with CAD.

◆ Improvement in endothelial function

Experimental data indicate that Procoralan may prevent deterioration of endothelial function in dyslipidemic mice,16 and recent clinical data suggest that Procoralan improves endothelial function in stable angina patients. Jedlickova et al used an Endo-PAT 2000 device to assess endothelial function in 30
stable angina patients treated with Procoralan for 3 months.\textsuperscript{16} They observed a significant improvement in mean reactive hyperemia index, which suggests improved endothelial function. Another recently published study—the RIVENDEL study (heart Rate reduction by IVabravine for improvement of ENDothelial function in patients with coronary artery disease)—evaluated the effect of Procoralan on endothelial function in 70 patients with CAD after complete revascularization by percutaneous coronary angioplasty. Patients were randomized to Procoralan 5 mg twice daily, subsequently uptitrated to 7.5 mg twice daily, or to continued standard medical therapy (control group).\textsuperscript{23} Procoralan significantly reduced heart rate and improved brachial artery reactivity, as witnessed by increases in flow-mediated dilation (12.2\%±6.2\% after 4 weeks, 15.0\%±7.7\% after next 4 weeks; \textit{P}<0.001) and nitroglycerin-mediated dilation (16.6\%±10.4\% after 4 weeks, 17.7\%±10.8\% after next 4 weeks; \textit{P}<0.001). No significant changes were observed in the control group.

\textbf{Improvement of coronary flow reserve}

Coronary flow reserve (CFR) reflects the functional capacity of the coronary circulation to adapt to increased blood demand during cardiac work. Abnormal CFR can be due to narrowing of the epicardial coronary arteries or, in the absence of angiographically demonstrable obstructive CAD, may reflect dysfunction of the coronary microcirculation. The latter can be caused by structural or functional changes, which may involve endothelial dysfunction. Skaliidis et al studied the effect of treatment with Procoralan on CFR in the “non-culprit vessel” in 21 patients with angina.\textsuperscript{21} Procoralan increased hyperemic coronary flow velocity in response to intracoronary adenosine and CFR (3.51±0.81 versus 2.78±0.61 at baseline, \textit{P}<0.001). CFR at a pacing heart rate similar to baseline heart rate remained significantly improved compared with baseline. Therefore, improvement of CFR even after heart rate correction may suggest that Procoralan improves the microcirculation. In a more recent randomized, controlled study, Tagliamonte et al compared the effects of bisoprolol and Procoralan on CFR in 59 patients with stable CAD.\textsuperscript{22} After one month of treatment, CFR was increased in both groups, but significantly more in the Procoralan group than the bisoprolol group (3.52±0.64 versus 3.35±0.70, respectively; \textit{P}<0.01), despite a similar reduction in heart rate.

\textbf{Improvement in coronary collateral circulation}

The development of collateral circulation is a natural mechanism that compensates for decreasing coronary flow as coronary artery stenosis progresses and protects the myocardium from ischemia. Procoralan promotes the development of coronary collaterals both in experimental models and in clinical trials. In an apolipoprotein E–deficient mouse model with hind limb ligation, Schirmer et al reported that Procoralan-induced heart rate reduction stimulated collateral artery growth.\textsuperscript{23} In a study in post-infarct remodeled hearts, reduction of heart rate with Procoralan promoted growth of coronary vessels in the surviving portion of the left ventricular myocardium.\textsuperscript{24}

These experimental data are in line with clinical findings. In a recent proof-of-concept study, Gloekler et al examined the effect of heart rate reduction by Procoralan on coronary collateral function.\textsuperscript{25} In this randomized placebo-controlled study in 46 patients with stable CAD, coronary collateral function was assessed by invasive measurement of a collateral flow index (CFI) during balloon occlusion by means of a pressure guidewire distal to the balloon-occluded artery. CFI did not differ in the placebo group, but increased from 0.107±0.077 at baseline to 0.152±0.090 in the Procoralan group (\textit{P}=0.0461). This improvement of CFI was accompanied by reduced ECG signs of ischemia.

\textbf{Antianginal efficacy of Procoralan in combination with \textit{\textsuperscript{-}} blockers in patients with angina}

Throughout its development program, Procoralan effectively reduced angina attacks and improved exercise capacity in angina patients. Procoralan substantially reduced the frequency of angina attacks and the consumption of short-acting nitrates compared with placebo,\textsuperscript{26} standard antianginal therapies such as \textit{\textsuperscript{-}} blockers or calcium channel blockers\textsuperscript{27,28} in the short term (2 to 3 months), and maintained antianginal efficacy in long-term (1 year) therapy, without development of pharmacological tolerance.\textsuperscript{29} Procoralan also showed significant anti-ischemic efficacy and improved exercise capacity, effects that are clinically important in angina. Procoralan improved time to 1-mm ST-segment depression, time to angina onset, and time to limiting angina in monotherapy,\textsuperscript{25,26} and in patients receiving \textit{\textsuperscript{-}} blocker therapy.\textsuperscript{30} In addition, the clinical benefit of Procoralan is also confirmed in day-to-day practice when added to \textit{\textsuperscript{-}} blockers, with significant reductions in angina attacks and short-acting nitrate consumption.\textsuperscript{31}

The ASSOCIATE trial (evaluation of the Antianginal efficacy and Safety of the aSSociation Of the \textit{\textsuperscript{-}} blocker with a BeTa-blockEr) examined the effects of Procoralan in patients with chronic stable angina pectoris receiving \textit{\textsuperscript{-}} blocker therapy.\textsuperscript{32} In this double-blind trial, 889 patients on 50 mg atenolol daily were randomly assigned to additional treatment with either Procoralan up to 7.5 mg twice daily or a placebo for 4 months. This study clearly demonstrates that, in patients with stable angina receiving the \textit{\textsuperscript{-}} blocker atenolol, Procoralan further improved significantly all parameters of the exercise test, at 2 and 4 months. Importantly, despite the fact that combination therapy is widely used in clinical practice to achieve adequate control of angina, clinical trials evaluating combination therapy have yielded inconsistent results. This makes Procoralan with \textit{\textsuperscript{-}} blockers the best evidence-based combination therapy for angina patients. In addition, treatment was well tolerated: less than 1% of patients stopped drug therapy because of side effects (generally bradycardia), and minor reversible visual effects were reported by 2% of the Procoralan-treated patients and 0.9% of the placebo-treated patients.
Procoralan also showed substantial antianginal efficacy in day-to-day practice in the large open-label, multicenter ADDITIONS study (PrAxical Daily efficacy and safety of Procoralan) in combination with betablocker therapy in a broad range of patients with stable angina. Procoralan added to β-blockers in 2330 patients with stable angina resulted in a significant reduction in angina attacks and short-acting nitrate consumption (from 1.7 to 0.3 and from 2.3 to 0.4 units per week, respectively).\(^3\) In addition to reducing angina attacks, Procoralan improved quality of life—assessed using the EQ-5D questionnaire (both the EQ-5D index and the EQ-5D visual analog scale)—throughout 4 months of treatment.

![Figure 2. Increase in exercise capacity by Procoralan plus β-blocker vs up titration of β-blocker in patients with stable angina.](image)


Two studies have addressed an important practical question: Is combining Procoralan and β-blocker therapy a more effective strategy for angina control than up titration of β-blockers? Amosova et al compared the efficacy of a combination of Procoralan 7.5 mg twice daily with 5 mg od bisoprolol versus a full dose of bisoprolol (10 mg once daily) in patients with stable angina.\(^3\) Two months of treatment with Procoralan substantially reduced the mean weekly number of angina attacks compared with bisoprolol alone (from 3.3 to 1.7 vs from 3.2 to 2.5, respectively; \(P\) between groups, 0.041). As a result, there were more patients with CCS class I angina in the group with Procoralan than in the group with bisoprolol alone (62% vs 67%, respectively; \(P=0.037\)). Addition of Procoralan also improved exercise capacity, as shown by the results of the 6-minute walking and exercise tolerance tests, whereas in the bisoprolol group neither parameter was significantly affected (Figure 2). These results suggest that combining Procoralan with low-dose bisoprolol provides better antianginal and anti-ischemic efficacy than up titration of bisoprolol in stable angina patients.

The above results were once again confirmed in a 16-week, multicenter, open-label comparative study (the CONTROL 2 study), which assessed the efficacy of combinations of Procoralan and β-blockers compared with up titration of β-blockers in 1104 patients with stable angina.\(^3\) Addition of Procoralan to β-blockers resulted in a significantly lower heart rate than β-blocker up titration at the end of the study (61±6 vs 63±8 bpm, \(P=0.001\)). At the end of the study more patients were free from angina (50.6% vs 34.2%, \(P<0.001\)) in the Procoralan combination group. The number of angina attacks for the last 8 treatment weeks was also significantly lower in the Procoralan group (4 [2;10] vs 6 [2;15], \(P=0.015\)). This resulted in significantly better quality of life assessed using a visual analog scale in the Procoralan group (\(P<0.001\)). Up titration of β-blockers resulted in a twofold higher rate of adverse reactions compared with addition of Procoralan (18.4% vs 9.4%, \(P<0.001\)). Dyspnea (1.3% vs 0, \(P=0.009\)), hypotension (5.7% vs 0.9%, \(P<0.001\)), and fatigue (1.3% vs 0.1%, \(P=0.03\)) were significantly more common in the up titration group than in the Procoralan group. The percentage of bradycardia—defined as heart rate <50 bpm—was equal in the Procoralan and β-blocker up titration groups (0.7% vs 0.4%, \(P=1.0\)). This study demonstrated that combination therapy with Procoralan and β-blockers significantly improved angina symptoms and quality of life, with better tolerability than for β-blocker up titration.

**Clinical benefits of Procoralan across a wide range of angina patients**

The antianginal efficacy of Procoralan in different subgroups of patients with stable angina was analyzed using pooled data from randomized clinical trials in the angina development program.\(^3\) Data on the frequency of angina attacks, short-acting nitrate consumption, and heart rate were pooled from 5 randomized trials in patients with stable angina pectoris treated with Procoralan for 3 or 4 months. A recent pooled analysis of data from observational studies provides complementary data on the effectiveness and safety of Procoralan in real-life clinical situations.\(^3\) For this analysis, data were pooled from three German observational studies in stable angina patients receiving Procoralan for 4 months. Data from these two pooled analyses show that Procoralan diminishes angina in all types of patients, regardless of age, sex, angina severity, revascularization status, history of MI, peripheral vascular disease, or diabetes (Figure 3). Such clinical benefits show that Procoralan is valuable for symptomatic treatment of patients with angina pectoris.

**Patients with a history of coronary revascularization**

As CAD is a diffuse disease process, frequently involving the entire coronary vasculature, systemic treatments such as medical therapy are essential in controlling ischemia and angina. In the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation), only 4 of 10 patients treated with percutaneous coronary intervention (PCI) on top of medical therapy did not have angina 1 month after PCI and up to 40%-50% of patients were symptomatic 6 to
36 months after PCI. A recent meta-analysis confirmed that recurrent angina in the first year after PCI is seen in one-third of patients.

The data from the two pooled analyses cited above\textsuperscript{10,11} show that Procoralan reduces angina attacks and the use of short-acting nitrates in patients with a history of revascularization. Clinical data show that, even 3 to 6 months after PCI, endothelium-dependent vasodilation was impaired not only at the site of previous maximal stenosis, but also in segments directly injured by balloon inflation.\textsuperscript{34} In the recent RIVENDEL study, Procoralan improved endothelial function in CAD patients after PCI.\textsuperscript{20} Procoralan may, therefore, help maintain coronary dilation, and thus prevent microvascular dysfunction and recurrence of angina after coronary intervention.

\textbf{Patients with a history of myocardial infarction}

Rates of coronary heart disease death have fallen since the late 1970s. Data from the MONICA study (MONItoring trends and determinants in CArdiovascular disease)\textsuperscript{35} show that this trend has in part been due to a fall in the rate of occurrence of new major coronary events. However, falling incidences of MI in many countries have been largely offset by an increase in the incidence of angina.\textsuperscript{36} One-fifth of patients report angina symptoms 1 year after acute MI.\textsuperscript{37} Furthermore, these patients have a high risk of developing left ventricular systolic dysfunction (LVSD) and heart failure (HF), which occur in approximately 40% of acute MI patients.\textsuperscript{38} A large proportion of patients (up to 50%) in the two pooled analyses cited above\textsuperscript{10,11} had a history of MI. Procoralan significantly reduced angina attacks (by 86%) and short-acting nitrate consumption (by 87%) in these patients.\textsuperscript{11}

\textbf{Patients with left ventricular systolic dysfunction or heart failure}

CAD is the major cause of chronic LVSD and HF, because of irreversible myocyte loss with scar formation and/or hibernating myocardium, ie, chronically dysfunctional but viable tissue, which improves function after revascularization.\textsuperscript{39} Furthermore, repeated episodes of myocardial ischemia followed by chronic stunning could be a potential mechanism of hibernation. A recent study demonstrated that Procoralan can limit episodes of stunning in patients with angina,\textsuperscript{40} and this cardioprotective effect, together with the anti-ischemic properties of Procoralan, could play a significant role in limiting progression to myocardial hibernation and LVSD. This mechanism could explain, at least in part, the reduction in coronary events in patients with CAD and LVSD seen in the population of the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Antianginal effectiveness after 4 months of treatment with Procoralan in different subpopulations.}
\end{figure}

\textit{Bars are relative changes from baseline (mean ± standard deviation). The values shown in the bars are absolute changes from baseline (mean ± standard deviation). P<0.0001 for all changes. From reference 11: Werdan K et al. Cardiology. 2016;135(3):141-150. © 2016 The Author(s). Published by S. Karger AG, Basel.}
Procoralan improves prognosis in patients with chronic HF, as demonstrated by SHIFT (Heart failure treatment with i, inhibitor Procoralan Trial), a randomized, placebo-controlled, clinical trial in 6558 patients with chronic HF and LVSD.43 The primary composite end point (cardiovascular death or hospital admission for worsening HF) was significantly reduced by 26% (P<0.014) and hospitalization for HF by 16% (P=0.0006). Cardiovascular death and all-cause death diminished by 9% and 10%, respectively (both not significant). In patients with a heart rate of 75 bpm or higher, there were statistically significant reductions of 17% in all-cause death (P=0.0109) and 17% in cardiovascular death (P=0.0166).44 Of 6558 patients in SHIFT, 2220 (34%) reported angina at randomization. A recently published analysis suggests that the outcome benefits of Procoralan among such patients are maintained and are similar to those seen in individuals without angina and all patients with chronic HF.45

The recent ESC Guidelines on HF acknowledge the advantages of Procoralan in this population and recommend it as the antianginal of choice together with β-blockers, ahead of other antianginal agents such as nitrates, amiodipine, nicorandil, or ranolazine.46

◆ Patients with concomitant diabetes

In two studies, nearly 19% of angina patients in a pooled population from randomized controlled trials and 46% of angina patients from daily clinical practice had diabetes.10,11 Recent trial data indicate that 82% of patients with CAD and type 2 diabetes may have angina symptoms despite the use of recommended therapies.47 The need for therapies that effectively reduce symptoms is thus essential. In addition, diabetic patients often develop cardiac autonomic neuropathy, leading to elevated sympathetic tone and resting tachycardia.48 As a result, a large proportion of angina patients who have diabetes may be eligible for Procoralan treatment. In this population, Procoralan was associated with significant reductions of 60% and 86% in angina attacks and of 61% and 85% in the use of short-acting nitrates in the pooled population from randomized controlled trials and the pooled population from observational studies, respectively.50,51 These data are consistent with the improved exercise tolerance and reduced angina symptoms observed in randomized controlled trials with Procoralan in subgroups of patients with angina and diabetes.38

Another important point to consider is that Procoralan does not alter glycosylated hemoglobin (HbA1c) and fasting glucose, whereas atenolol and amiodipine increase both.52

◆ Elderly patients with angina

Elderly patients with stable angina represent a growing population with specific characteristics. They are hard to treat because of a higher prevalence of comorbidities and more frequent side effects or intolerance to drugs.53 Procoralan significantly reduced angina attacks and consumption of short-acting nitrates in a subgroup of 91 elderly patients with stable angina in a pooled analysis of randomized controlled trials.10 Pooled analysis of observational studies confirmed the antianginal effectiveness of Procoralan in more than 1600 patients aged ≥75 years seen in real clinical practice.11 In addition to the reduction in angina attacks (by 84%) and in use of short-acting nitrates (by 82%), Procoralan significantly improved quality of life in this elderly population with impaired health status scores at baseline.11 Importantly, all these beneficial effects were accompanied by a good safety profile, as the rate of adverse events was similar to that in younger patients.11

◆ Patients undergoing cardiac rehabilitation

Cardiac rehabilitation is an integral part of the contemporary treatment of patients with multiple presentations of CAD and HF, because such measures cost-effectively reduce future morbidity and mortality, ameliorate symptoms, and increase exercise capacity. Cardiac rehabilitation is an effective and safe management strategy after MI and coronary revascularization, and in HF patients. In patients with angina who cannot be operated on or revascularized percutaneously, cardiac rehabilitation together with optimal medical therapy can increase the anginal threshold. A recent study demonstrated that the addition of Procoralan to low-dose bisoprolol (1.25 mg once daily) in patients who underwent cardiac rehabilitation after recent coronary artery bypass grafting (CABG) yielded further benefits compared with standard medical therapy including bisoprolol up titration (2.5 to 3.75 mg once daily).51

Treatment with the Procoralan/bisoprolol regimen shortly after CABG was associated with improved functional status, increased LV ejection fraction, and improved exercise capacity. -Blockers have well-documented direct effects on cardiovascular and pulmonary function, causing symptoms such as fatigue and dizziness, which limit exercise capacity. Procoralan could play a crucial role in cardiac rehabilitation, as it is devoid of inotropic, lusitropic, or vasoactive effects.52 The different mechanisms of action of Procoralan and -blockers make their combination a valuable option in patients undergoing cardiac rehabilitation.
**Patients treated with β-blockers**

In a recent pooled analysis, a combination of Procoralan and metoprolol reduced heart rate, angina attacks, and nitrate use, and improved quality of life in 1376 stable angina patients.11 The investigators considered that this combination therapy was well tolerated, as there was a low rate of reported adverse events, with 1 patient reporting phosphenes and 1 experiencing symptomatic bradycardia with palpitations, although 30.3% of previously untreated patients had a heart rate of 55-60 bpm.

The efficacy and tolerability of Procoralan in combination with metoprolol provide a rationale for a fixed-dose combination of these 2 drugs, which is now available as Implicor. Another combination, that of ivabradine and carvedilol (Carivalan), will be useful for symptomatic treatment of chronic stable angina pectoris for chronic stable angina pectoris or congestive heart failure with left ventricular systolic dysfunction. The use of fixed-dose combination treatments is well known to be associated with a significant reduction in the risk of nonadherence when compared with free combinations. Patel et al demonstrated that, after a year of taking a fixed-dose combination, adherence was significantly higher when compared with patients taking each treatment separately.25

**Good tolerability and ease of use**

Procoralan is well tolerated in patients with angina. Brady-cardia was reported in 2.2% of angina patients treated with Procoralan 7.5 mg twice daily compared with 4.4% with atenolol 100 mg once daily.22 This low percentage is explained by the direct rate-related dynamics of the heart rate-lowering effect, ensuring the greatest heart rate reduction in patients with the highest pretreatment heart rate and limiting the risk of excessive bradycardia. Importantly, abrupt discontinuation of Procoralan does not result in a rebound phenomenon.24

The absence of rebound tachycardia with Procoralan not only simplifies the management of antianginal treatment, but also reduces the risk of adverse effects following missed doses or unscheduled gaps in medication administration. These characteristics of the heart rate-lowering action of Procoralan make it suitable and simple to use in most symptomatic patients with CAD. Procoralan improves exercise capacity and quality of life in patients with angina. Pooled data from the Procoralan angina development program and from observational studies provide clinical evidence that Procoralan diminishes angina in all types of patients, regardless of age, sex, angina severity, revascularization status, history of MI, peripheral vascular disease, or diabetes. ■

**References**


Keywords: angina, heart rate reduction; I(f) current; Implicor; ivabradine; Procoralan; quality of life
Since ivabradine is a pacemaker channel inhibitor, it adds to the therapeutically wished-for negative chronotropic effect of β-blockers, thereby further reducing myocardial oxygen demand, increasing oxygen supply to the heart by prolonging diastolic perfusion, improving endothelial function, and enhancing coronary flow reserve as well as coronary collateral flow. Furthermore, ivabradine may reduce left ventricular filling pressure and improve stroke volume in response to exercise.”

Implicor: a new therapeutic solution for patients with angina

by K. Werdan, Germany

Since drug approval 10 years ago, the role of ivabradine in the treatment of stable coronary artery disease (SCAD) has changed from a rare alternative to β-blockers—in the case of contraindications or intolerance—to a partner drug. β-Blockers, the symptomatic first-line medication in SCAD, lower heart rate and thereby improve diastolic coronary perfusion and reduce myocardial oxygen demand. However, because of contraindications and intolerance, recommended target doses of β-blockers often cannot be given to the patient and therefore heart rate reduction is often lower than recommended, with more than half of β-blocker-treated SCAD patients having a resting heart rate ≥70 beats per minute (bpm). In these patients, if in sinus rhythm, adding ivabradine to concomitant β-blocker therapy can reduce resting heart rate by a further 6 to 20 bpm, and this additional heart rate reduction results in further symptomatic improvement, as shown by a reduction in angina pectoris attacks and in the use of short-acting nitrates, as well as by an improvement in health-related quality of life. Patient adherence is good with this effective combination of β-blocker and ivabradine, which is safe—the only rare, reversible side effects being bradycardia and visual disturbances (phosphenes). And if a SCAD patient in sinus rhythm ≥70-75 bpm suffers from systolic heart failure, then ivabradine will support the β-blocker as a proven heart failure agent; no alternative second-line antianginal agent can do the same. Metoprolol is one of the most often used β-blockers in the symptomatic treatment of SCAD patients. The combination of metoprolol and ivabradine in daily practice has been analyzed in more than 1300 patients from prospective observational studies, and the results were comparable to those described above for the combination of ivabradine and β-blockers as a group. Implicor, the fixed-dose combination of ivabradine and the β-blocker metoprolol (ivabradine 5 mg/7.5 mg + metoprolol tartrate 25 mg/50 mg) can therefore help those SCAD patients already taking metoprolol and ivabradine separately to simplify their medication regimen.

Unmet needs in the treatment of angina

◆ Treatment goals: reduction in mortality is not everything!

The annual rates of cardiac death and nonfatal myocardial infarction (MI) in stable coronary artery disease (SCAD) are low (0.6%-1.4% and 0.6%-2.7%, respectively); so while reduction in mortality as a treatment goal is important, it is only a poor reflection of how SCAD patients experience their situation and what impact treatment may have on a patient’s day-to-day life. Health-related quality of life (HRQoL)—as reflected by symptoms and the impact of disease...
on social, emotional, and occupational function—may be even more important than longevity. Many SCAD patients report moderate or severe problems with respect to pain/discomfort (78.5%), anxiety/depression (42.4%), mobility (35.6%), and usual activities (22.5%). Treatment goals in patients with SCAD are therefore not only to reduce the rates of cardiovascular death, nonfatal MI, and heart failure, but also to attenuate angina symptoms effectively and thereby decisively improve HRQoL.

**Angina treatment with -blockers and calcium channel blockers — many patients remain symptomatic**

For relief of angina and myocardial ischemia, the ESC guidelines on the management of SCAD recommend -blockers and/or calcium channel blockers as first-line treatment to control heart rate and symptoms. Even with this first-line medical treatment, 25% of patients with SCAD report monthly angina, and 8% report daily or weekly angina, with an inverse correlation of angina symptoms and HRQoL. One-fifth of patients who have had an acute MI have symptoms of angina one year later, and even after revascularization two-fifths of SCAD patients remain symptomatic. These data clearly indicate an unmet need for treatment options to relieve angina and improve HRQoL in patients with SCAD, beyond first-line medications, which are associated with low adherence and also have little power to improve HRQoL.

**Synergy between -blocker and ivabradine in the treatment of patients with stable coronary artery disease**

**Heart rate reduction — a general treatment goal in SCAD patients**

Elevated heart rate is independently associated with cardiovascular and all-cause mortality and morbidity in patients with established cardiovascular disease. In SCAD patients, several large series show an association of higher resting heart rate with higher all-cause mortality, cardiovascular (CV) mortality, CV morbidity, and CV rehospitalizations, as well as with the risk of developing myocardial ischemia. SCAD patients with reduced ejection fraction (<40%) and a resting sinus rhythm >70 bpm showed—in comparison with those with a sinus rhythm <70 bpm—a 34% higher risk for CV death, a 46% higher risk for MI, a 38% higher risk for coronary revascularization, and a 53% higher risk for hospital admission because of heart failure, with each 5 bpm increment in resting heart rate (RHR) being associated with approximate increases of 8% in CV death, 7% in MI, 8% in coronary revascularization, and 16% in admission with heart failure.

Also, SCAD patients in sinus rhythm without heart failure in the SIGNIFY trial (Study assessing the morbidity-mortality benefits of the if inhibitor ivabradine in patients with coronary artery disease)—with 83% being treated with a -blocker—have yielded important information: RHR was reduced by ivabradine from 77.1±6.9 bpm initially to 60.7±9.0 bpm at 3 months, while in the placebo group heart rates were 77.2±7.1 bpm initially and 70.6±10.1 bpm after 3 months. This 10 bpm lower heart rate in the ivabradine group coincided in 2084 patients with CCS ≥2 angina, with a significant reduction in angina frequency and a better disease perception, angina stability, treatment satisfaction, and health status than in the 2103 patients in the placebo group. The latter findings seem to be of special practical importance, as more than half of SCAD patients have an RHR of ≥70 bpm. Therefore, lowering heart rates from ≥70 bpm to <70 bpm is a therapeutic target in SCAD patients for symptomatic relief and improvement in HRQoL.

**Heart rate reduction by -blockers improves prognosis only during the first years after myocardial infarction, but attenuates symptoms also thereafter**

-Blockers produce their therapeutic effects mainly by heart rate reduction, which results in improved diastolic coronary perfusion and reduced myocardial oxygen consumption, thereby bringing relief in myocardial ischemia, rhythm disturbances, and anginal symptoms. Heart rate reduction is responsible for the prognostic benefit of -blockers in MI patients within the first one to three years after MI, but no longer. In MI patients more than three years after the event and in patients with SCAD without a history of MI, no prognostic benefit with respect to reduction in mortality is seen despite heart rate reduction.

However, independently of the prognostic effects, heart rate reduction by -blockers in SCAD patients is an effective way to reduce angina pectoris symptoms and consumption of short-acting nitrates, and to improve exercise tolerance.
As a consequence, suboptimal obstructive pulmonary disease and/or peripheral artery disease based on existing comorbidities of their patients, like cardiomyopathy, or because of physicians’ reservation of giving medication. Suboptimal β-blocker doses are not easy, because of side effects like dizziness, fatigue, bradycardia, and hypotension, or because of physicians’ reservation of giving medication. Suboptimal β-blocker doses are not easy, because of side effects like dizziness, fatigue, bradycardia, and hypotension, or because of physicians’ reservation of giving medication.

What should be done with SCAD patients remaining symptomatic when first-line treatment with a β-blocker—albeit accepted by the patient—is not enough? It is known from randomized controlled trials (RCTs) as well as from daily outpatient practice that achievement of β-blocker treatment at the recommended doses is—atenolol 100 mg/day, bisoprolol 10 mg/day, carvedilol 50 mg/day, metoprolol 200 mg/day—is not easy, because of side effects like dizziness, fatigue, bradycardia, and hypotension, or because of physicians’ reservation of giving medication. Suboptimal β-blocker doses are used in SCAD patients, as seen in RCTs, multicenter surveys, and registries, but also in non-interventional observational studies reflecting daily practice, with mean doses of only 40% to 70% of the recommended target doses, or even less (Table I).

Table I. Treatment of patients with stable coronary artery disease with β-blockers – mean daily doses as percentage of target doses.

<table>
<thead>
<tr>
<th>Trial/Registry</th>
<th>Atenolol</th>
<th>Bisoprolol</th>
<th>Carvedilol</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Heart Survey</td>
<td>55%</td>
<td>59%</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>SIGNIFY</td>
<td>57%</td>
<td>62%</td>
<td>50%</td>
<td>39% (metoprolol succinate)</td>
</tr>
<tr>
<td>ADDITIONS</td>
<td>67%</td>
<td>70%</td>
<td>59%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Percentage of patients treated with the following β-blocker doses

<table>
<thead>
<tr>
<th>β-blocker dose as percentage of target dose (atenolol 100 mg/day, bisoprolol 10 mg/day, carvedilol 50 mg/day, metoprolol 200 mg/day)</th>
<th>&lt;0%-12.5% of target dose</th>
<th>&lt;12.5%-25% of target dose</th>
<th>&gt;25%-60% of target dose</th>
<th>&gt;50% of target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBTAIN</td>
<td>21.7%</td>
<td>33.8%</td>
<td>23.1%</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

EUROPEAN HEART SURVEY: Prospective, observational cohort study of 3779 patients with stable angina newly presenting to cardiology departments, with 66.5% having received a β-blocker.

SIGNIFY trial (Study assessing the morbidity-mortality benefits of the β-blocker ivabradine in patients with coronary artery disease): randomized, double-blind, placebo-controlled trial in 19 102 patients with stable coronary artery disease without clinical heart failure and with sinus rhythm ≥70 bpm, with 83% having received a β-blocker (5% atenolol, 28% bisoprolol, 10% carvedilol, 17% metoprolol succinate, 13% metoprolol tartrate, 8% nebivolol).

ADDITIONS study (prActical Daily efficacy and safety of Procoralan In combination with beta blockers): noninterventional, multicenter, prospective study in 816 German centers with 2330 patients on β-blocker therapy (<1% atenolol, 37% bisoprolol, 7% carvedilol, 43% metoprolol, 13% nebivolol) for the symptomatic treatment of chronic stable angina pectoris and sinus rhythm ≥60 bpm.

OBTAIN registry (Outcomes of Beta-blocker Therapy After myocardial Infarction): multicenter registry (26 centers in US, one center in Canada) of 6882 patients with acute myocardial infarction, with 91.5% of the patients with a β-blocker at discharge—3.8% atenolol, 2.8% bisoprolol, 24.3% carvedilol, 67.7% metoprolol, 1.3% others—and follow-up (median 2.1 years).

◆ Side effects and contraindications limit achievable β-blocker dose in daily practice to 40%-70% of recommended target doses

What should be done with SCAD patients remaining symptomatic when first-line treatment with a β-blocker—albeit accepted by the patient—is not enough? It is known from randomized controlled trials (RCTs) as well as from daily outpatient practice that achievement of β-blocker treatment at the recommended doses is—atenolol 100 mg/day, bisoprolol 10 mg/day, carvedilol 50 mg/day, metoprolol 200 mg/day—is not easy, because of side effects like dizziness, fatigue, bradycardia, and hypotension, or because of physicians’ reservation of giving medication. Suboptimal β-blocker doses are used in SCAD patients, as seen in RCTs, multicenter surveys, and registries, but also in non-interventional observational studies reflecting daily practice, with mean doses of only 40% to 70% of the recommended target doses, or even less (Table I).

◆ Ivabradine – the partner drug of β-blockers in heart rate reduction

In this situation it makes sense to combine the tolerated β-blocker dose with another drug with heart rate-reducing and antianginal effects, but lacking the β-blocker–specific side effects. Therefore, combination of a β-blocker with the pacemaker channel inhibitor ivabradine is a valuable option in those patients who do not tolerate recommended doses of β-blockers or those with insufficient reduction of heart rate or persisting angina symptoms despite the tolerated β-blocker medication in use. Ivabradine given twice daily in a daily dose of 10 to 15 mg in combination with a β-blocker, or without in the case of β-blocker contraindications or intolerance, reduced mean resting sinus rhythm by 6 bpm20 and 10 bpm21 in RCTs, and by 19.4 bpm,31 12.4 bpm,32 and 15.4 bpm33 in prospective observational studies.

The combination of a β-blocker with ivabradine (Ila/B) has two advantages in comparison with a combination with another recommended second-line drug, like long-acting nitrates, nitr鹜, or ranolazine (Ila/B). First, since ivabradine is a pacemaker channel inhibitor, it adds to the therapeutically wished-for negative chronotropic effect of β-blockers, thereby further reducing myocardial oxygen demand, increasing oxygen supply to the heart by prolonging diastolic perfusion, improving endothelial function, and enhancing coronary flow reserve as well as coronary collateral flow. Furthermore, ivabradine may reduce left ventricular filling pressure and improve stroke volume in response to exercise.24 Secondly, many patients with SCAD suffer from ischemic heart failure with reduced ejection fraction (HFrEF), as in every second HFrEF patient heart failure is of ischemic origin. In this large subgroup...
of patients with SCAD, the combination of a β-blocker with ivabradine doubles the benefits to the patient as both β-blockers and ivabradine are effective antianginal drugs and additionally reduce mortality and rehospitalization because of heart failure, in patients with sinus rhythm ≥70-75 bpm in the case of ivabradine.29-33 As mentioned above, no other second-line antianginal medication can achieve this double goal like ivabradine.

◆ The “proof of concept” in daily practice

The “proof of concept” of symptomatic angina improvement with the combination of ivabradine—given twice daily—and β-blocker in patients with SCAD comes not only from large randomized controlled trials like BEAUTIFUL30 (morBidity-morBidity in patients with SCAD comes not only from large randomized controlled trials like BEAUTIFUL30 (morBidity-morBidity-blocker in patients with SCAD comes not only from large randomized controlled trials like BEAUTIFUL30 (morBidity-morBidity-blocker in patients with SCAD comes not only from large randomized controlled trials like BEAUTIFUL30 (morBidity-morBidity-blocker in patients with SCAD comes not only from large randomized controlled trials like BEAUTIFUL30 (morBidity-morBidity-blocker in patients with SCAD comes not only from large randomized controlled trials like BEAUTIFUL30 (morBidity-morBidity-blocker in patients with SCAD comes not only from large randomized controlled trials like BEAUTIFUL30 (morBidity-morBidity-blocker in patients with SCAD 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(morBidity-morBarity of other concomitantly used β-blockers (bisoprolol, carvedilol, and nebivolol) in this pooled analysis. Very similar results were found when analyzing the antianginal effects of ivabradine in the metropolol subgroup (n=877) of the ADDITIONS study, with a mean metropolol dose of 107.9±50.3 mg/day at baseline and 102.5±49.9 mg/day by month four.36 Even in those patients, in whom metropolol alone does not achieve heart

In Figure 1B, the antianginal effects of ivabradine are present in the subgroup of 1376 SCAD patients of the pooled analysis with concomitant metropolol, the β-blocker most used (40%) in this series. The mean number of angina attacks progressively decreased from 1.6±2.20 at baseline to 0.5±1.20 and 0.3±0.91 after one and four months, respectively. Use of short-acting nitrates was reduced from 2.2±3.26 at baseline to 0.7±1.43 and 0.3±1.08 after one and four months, respectively. Finally, an improvement in CCS class distribution was noted at the end of the study, with the majority of patients (64%) graded as class I at the last visit (baseline, 26%) and fewer patients as class II (32%; baseline, 51%) and III+IV (4%; baseline, 22%). The effects of ivabradine on angina attacks, nitrate use, and CCS class were comparable with those of other concomitantly used β-blockers (bisoprolol, carvedilol, and nebivolol) in this pooled analysis. Very similar results were found when analyzing the antianginal effects of ivabradine in the metropolol subgroup (n=877) of the ADDITIONS study, with a mean metropolol dose of 107.9±50.3 mg/day at baseline and 102.5±49.9 mg/day by month four.36 Even in those patients, in whom metropolol alone does not achieve heart

Figure 1. Pooled analysis of three prospective observational ivabradine studies in 8555 patients with stable coronary heart disease, sinus rhythm ≥60 bpm, and either concomitant -blocker therapy (40%) or without -blocker therapy because of -blocker contraindications/ intolerance.

A. Antianginal effectiveness of ivabradine in the overall population (n=8555). (a) Angina attacks per week; (b) Short-acting nitrate consumption per week; (c) Canadian Cardiovascular Society (CCS) angina class. Bars are means ± SD. *P<0.0001 for changes from baseline or CCS class changes.

B. Antianginal effectiveness in the subgroup with concomitant metropolol treatment (n=1376). (a) Angina attacks per week; (b) Short-acting nitrate consumption per week; (c) Canadian Cardiovascular Society (CCS) angina class. Bars are means ± SD. *P<0.0001 for changes from baseline or CCS class changes.

Recruitment was from the ADDITIONS study31 with 2330 patients in 818 centers treated with a mean dose of 12.37 mg/day in addition to -blocker. These ivabradine doses reduced the mean resting heart rate by 19.4 bpm in the ADDITIONS study, 12.4 bpm in the REDUCTION study, and 15.4 bpm in the RESPONSIVE study.

rate reduction below 70 bpm, addition of ivabradine succeeds in lowering heart rate by more than 20%, resulting in a reduction of more than 80% in the number of angina attacks per week (–1.8±1.92) and in weekly nitrate use (–1.8±2.76), similar to the total metoprolol group (Figure 2).

**Ivabradine in combination with metoprolol improves health-related quality of life**

The symptomatic management of angina is expected to improve HRQoL, primarily by reducing the severity and frequency of angina symptoms. With respect to improvement of HRQoL, primarily by reducing the severity and frequency of angina symptoms, information is really scarce. For β-blockers, we know at least that they are neutral with respect to HRQoL in patients with peripheral arterial disease and COPD. From a methodological point of view, the best information is available for ivabradine and comes from the randomized SIGNIFY trial: 4187 SCAD patients (2084 in the ivabradine group and 2103 in the placebo group) were evaluated using the Seattle Angina Questionnaire and a generic visual analogue scale (VAS) on health status. Though a significant early positive effect of ivabradine on the physical limitation dimension was seen after 6 months (P=0.046), there was no significant difference in the physical limitation score at 12 months (4.56 points for ivabradine vs 3.40 points for placebo; P=0.085). Notably, ivabradine was associated with a significant maintained improvement in angina frequency and stability, disease perception, treatment satisfaction, and health status. As 83% of the SIGNIFY patients were under treatment with β-blockers, these findings can be interpreted as an improvement in important aspects of HRQoL by ivabradine in SCAD patients even on β-blocker treatment.

HRQoL can also be measured in daily practice, as was done in a subgroup of the ADDITIONS study with 877 SCAD patients treated for four months with ivabradine (mean dose 12.6 mg/day) in addition to concomitant metoprolol treatment (mean dose 107.9±50.3 mg/day). HRQoL measurement with the EQ-5D index score significantly (P<0.0001) increased from 0.68±0.27 at baseline to 0.76±0.23 at one month, and to 0.84±0.20 after 4 months, and the VAS score rose from 58.1±18.4 to 65.5±16.1 and 72.2±15.5, respectively. It is worth mentioning that the EQ-5D index of patients in this trial on metoprolol alone (0.68±0.27) is similar to the value of patients with stable angina in the Swedish population (0.70±

![Figure 2](image-url)
0.018) as well as in Chinese patients (0.75±0.19)42, while the EQ-5D index, while adding ivabradine to metoprolol (0.84±0.20) in this trial is comparable to that of the general population in Sweden (0.84±0.005)42 and in Chinese patients (0.90±0.20).42 Improvements in HRQoL with ivabradine comparable to those described for the subgroup concomitantly treated with metoprolol were also found for patients concomitantly treated with beta blockers (bisoprolol, carvedilol, nebivolol) in the pooled analysis.42

Data from the SIGNIFY trial39 and prospective observational studies63,39 therefore demonstrate an improvement in HRQoL by additional ivabradine treatment concomitant with -blocker therapy in SCAD patients.

The benefit of a fixed-dose combination like Implicor for the treatment of angina

Since drug approval 10 years ago, the role of ivabradine in the treatment of stable angina has changed from a rare alternative to -blockers in the case of contraindications or intolerance to a partner drug with a proven net increase in therapeutical effects. Therefore a fixed-dose combination of -blocker with ivabradine can help to optimize antianginal treatment, as fixed-dose combinations in general improve drug adherence.36 Implicor®, the first fixed-dose combination of metoprolol tartrate and ivabradine, which is available in 4 dosages (25 mg/5 mg, 50 mg/5 mg, 25 mg/7.5 mg, 50 mg/7.5 mg), will afford more relief of angina and more quality of life improvement for more patients with SCAD than is achievable with -blocker monotherapy at suboptimal dose or suboptimal effect.

Treating patients with a fixed combination of two heart rate-reducing drugs warrants a thorough review on the occurrence of side effects. The safety profile of Implicor® is assumed to be in the same range as the safety profile of the reported metoprolol-ivabradine–treated subgroup of the ADDITIONS trial36: only 7 out of 989 patients in the safety set (<1%) reported 14 adverse drug reactions, most frequently phosphates and visual impairment (4 patients) as well as dizziness and headache (3 patients). Bradycardia was reported in only 1 patient. No serious drug reaction occurred. The tolerability of the metoprolol and ivabradine combination was rated as “very good” or “good” by >99% of physicians. Of course, observational studies without a control group may overestimate treatment effects and underestimate adverse effects, as they were spontaneously reported and not specifically sought.

Therefore, we should bear in mind the respective data from the BEAUTIFUL20 and SIGNIFY39 RCTs: in the BEAUTIFUL study with 84% of concomitant -blocker therapy, reversible visual symptoms (phosphates, blurred vision, visual disturbance; 0.5% in the ivabradine group and 0.2% in the placebo group) were the only reported adverse events besides bradycardia20; in the SIGNIFY trial, besides bradycardia, again phosphates and blurred vision occurred more frequently in the ivabradine group (6.6% vs 0.9%); in addition, atrial fibrillation (5.3% vs 3.8%) and QT interval prolongation (1.8% vs 0.7%) were significantly more frequent in the ivabradine group.39

Conclusion

In symptomatic patients with SCAD and sinus rhythm ≥70 bpm, the combination of metoprolol and ivabradine reduces heart rate with a high safety profile, thereby lowering the rate of angina attacks and nitrate use and improving HRQoL in patients with stable angina. Implicor®, the fixed-dose combination of ivabradine and the -blocker metoprolol, can therefore help those SCAD patients already taking metoprolol and ivabradine separately to simplify their medication regimen.

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**Keywords:** angina pectoris; -blocker; Implicor; health-related quality of life; ivabradine; stable coronary artery disease

Implicor: a new therapeutic solution for patients with angina – Werdan
Self Portrait, from L’Ile Saint-Louis. Henri Rousseau (1844-1910); 1890; oil on canvas; 146x113 cm. Narodni Galerie, Prague, Czech Republic. © Bridgeman Images.
Je ne sais pas si vous êtes comme moi, mais quand je pénètre dans ces serres et que je vois ces plantes étranges des pays exotiques, il me semble que je rentre dans un rêve.

“I don’t know if you are like me, but when I walk into these hot-houses and I see these strange plants from exotic lands, it seems to me that I’m entering a dream.”

Henri Rousseau

Untutored in the fine arts yet steadfast in his artless, childlike approach to painting, Henri Rousseau (1844-1910) intrigued his contemporaries. Poet Guillaume Apollinaire praised the sunny disposition of “this poor old angel.” What Rousseau sees, said surrealist poet Paul Éluard, “will always fill our eyes with wonder.” Avant-garde painter Robert Delaunay believed that Rousseau represented “the popular genius of the French people,” while Russian artist Wassily Kandinsky and German expressionist painter Franz Marc considered him to be one of the fathers of abstract art. And Pablo Picasso was bewitched by Rousseau’s Portrait of a Woman (circa 1895): “one of the truest of French psychological portraits.” Who then was this most puzzling figure of the art world in late nineteenth and early twentieth century France? Undaunted by lack of experience and ignorance, Rousseau, who had long painted in his spare time, turned seriously to painting at forty-one years of age, sustained by boundless self-confidence. Public and critics laughed at his misshapen likenesses, ghostly industrial landscapes, and fanciful jungles with fierce animals locked in combat. Were they not so mysterious and inanimate, his views of the River Seine could be likened to folk art. If his portraits were more lifelike, they would be less compelling. And were the flora and fauna of his ‘jungles’ more realistic, his protean natural world would inspire less fear. But it was precisely because of these peculiarities, this whimsy, his self-made pictorial rules and aplomb that Rousseau proudly declared to Picasso: “We are the greatest painters of the age, I in the modern style and you in the Egyptian!” Doubtless he was right.

Portrait of a woman

Pictured full-length, in a long black dress, the pale blue of her lace collar and belt mirroring the sky above, the woman stands almost life-size on a balcony backed by a hillscape in the same watery hues. Her hand rests on the cut end of a branch, its twigs touching the floor, as if it were a cane or a pedestal table. In her right hand, a drooping flower. Pansies and marguerites in earthenware pots grow under the guardrail. To the woman’s right hangs a heavy fringed drape, its orange, white, and red motifs enlivening the grays of the ensemble. Incongruous, a small bird flies from right to left across the top of the canvas, just beneath the frame.

In this Portrait of a Woman (1895), with its frontal pose, extreme simplification of shapes, clear outlines, primary colors, clumsy execution, Henri Rousseau (1844-1910) depicts Clémence, his late first wife. Midway between a child’s drawing and
Naïve painter, innocent or archaic, amateur or genius? What terms have not been used to pigeonhole Rousseau, one of the most singular artists in the history of French painting in the late nineteenth and early twentieth centuries? By turns praised to the skies and derided by peers and critics alike, this self-taught artist, born 1844 in Laval, northwest France, the son of an ironmonger, struggled for recognition throughout his life, dying almost alone and in debt in 1910.

Playfully nicknamed by his friend the writer Alfred Jarry Le Douanier, the French for customs officer, his job, Rousseau took up painting seriously only at the age of forty-one, before when it had been a pastime. Lacking instruction, but fearless, Rousseau seemingly was guided by a sort of mystical grace, almost as if he were under a spell. A strange man who painted scenes of daily life, riverside views, factories and their smoking chimneys, as well as detailed portraits of himself or his friends Jarry and the poet Guillaume Apollinaire, and above all amazing ‘jungles’ where wild beasts, sometimes human-like, fight to the death. All of this without training, without con-

the realistic manifesto of the Italian primitives, who sought to humanize religious figures by bringing them down from their ethereal abode to earthly scenes among manmade structures, Rousseau’s strange Portrait of a Woman runs counter to the Impressionist revolution that convulsed the world of painting in the second half of the nineteenth century. The Impressionists distanced themselves from the classical masters by taking easels and paints out of their studios and into the daylight, whose protean nature blurs contours, lending their canvasses an out-of-focus quality. Rousseau, meanwhile, was limning as if it were obvious, even when implausible.

Keen on African masks and tribal art, Pablo Picasso, who had just completed Les Demoiselles d’Avignon (1907), was enthralled by Rousseau’s work. He stumbled across the portrait of Clémence in 1908 in a junk shop near his Montmartre studio and bought it for a song. This was the first of several of the artist’s paintings that Picasso acquired during Rousseau’s lifetime and after his death, and he never parted with it.
tacts in the art world, without ever having ventured beyond the suburbs of Paris or seen a world more exotic than that within the greenhouses of the Jardin des Plantes in the capital’s 5th arrondissement.

“Long live, long live Rousseau!”

Soon after having acquired the astonishing portrait of Clémence, Picasso organized a banquet in Rousseau’s honor, to lionize the ingenuous, almost comical Rousseau who, with his ill-proportioned figures and fun fair imagery, seems to walk alone towards a new art.

The banquet was held one November evening in 1908, in the seedy Bateau-Lavoir on the heights of Montmartre. In all the years that the artists, intellectuals, alcoholics, and eccentrics who frequented the maze of studios around Picasso’s had shared the same privations, they had never seen its like. With the exception of a large trestle table, a few African masks collected by Picasso, and Rousseau’s Portrait of a Woman acquired by Picasso a few days before, the room was empty. Fernande Olivier, Picasso’s partner at the time, prepared a huge dish of Catalan rice on a portable stove pending delivery by the grocery store Félix Potin of the meal, for which the guests had clubbed together.

The neighboring studio, where the painter Juan Gris worked, had been transformed into a cloakroom. Garlands and Chinese lanterns were hung throughout the room and a banner proclaimed “Hail Rousseau!” The lauded painter took his place on a throne improvised by perching a chair atop a packing case. Given the eminent guests—who included Apollinaire, the artist Marie Laurencin, the critic André Salmon, the painter Georges Braque, art collector and critic Leo Stein, his...
sister the writer Gertrude Stein and her lifelong partner Alice Toklas—their heavy drinking, and the unusual personality of the guest of honor, this was an evening destined to go down in history.

Rousseau charmed and amused in equal measure. Anomalous, quaint, a simple, gruff, big-hearted man unmatched in naivety, married and widowed twice, father of nine children with his first wife, all but one of whom died young, Rousseau turned seriously to painting at the age of forty-one, when his work situation finally left him time to devote to art. It was 1885, the year which, he wrote in his autobiography, marked his “beginnings in art, after a good many setbacks, alone, with no teacher other than nature.”

“I am my own student,” he declared to the academic painter Jean-Léon Gérôme from whom he sought advice, as he did from Félix-Auguste Clément, a winner of the Grand Prix de Rome. Both encouraged Rousseau and smoothed his access to the Louvre to allow him to copy its masterpieces. His memory of Equality before Death (1848) by William Bouguereau inspired Rousseau in 1894 to paint War, also called The Ride of Discord, one of his most astonishing paintings in which a frenzied gorgon, hair disheveled, rides a horse across a battlefield strewn with naked corpses redolent of the drowned of Géricault’s Raft of the Medusa, also in the Louvre collection.

**Solitude in the modern world**

From 1872, Rousseau was appointed to oversee inspections of boat-borne merchandise, including wines and spirits, along the banks of the River Seine at the gates of Paris, and it became his custom to sketch the surroundings in idle moments and rework the result later. All his life Rousseau painted these naïve scenes of daily life along the banks of the Seine or its main tributary the River Oise. A strange atmosphere emanates from these images of the modern world.
Nature is omnipresent because the painter was almost enamored of trees and flowers: “Would you believe that when I go to the country and see the sun, this greenery, these flowers, I sometimes say to myself: it’s mine.” But the skies of his paintings are often stormy, crossed by an airship or plane, as in Landscape and Four Fishermen. Factory chimneys spew black smoke in Footbridge at Passy (1890-91), telegraph poles line roads that lead nowhere in View of Malakoff (1908). The Suburban House (1905) seems deserted. Rousseau’s universes are ghostly, the rare figures reduced to silhouettes glimpsed from afar. Each painting is a reflection of solitude. In The Chair Factory at Alfortville (1897), where is the minuscule lady with parasol going? Rousseau used urban life and the inventions of the modern world to chronicle his century and claimed to have coined the term “portrait-landscape,” in which figures depicted are as important as their surroundings.

Behind the mustached man wearing a fez in Portrait of Monsieur X (around 1910)—without doubt painted from a photograph of Pierre Loti, poet, writer, and Member of the French Academy—Rousseau depicts four factory chimneys, one belching black wreaths. And for his full-length self-portrait, Myself, Portrait-Landscape (1889–1890), veritable manifesto intended to assert himself in the eyes of the art world as a painter with the attributes of his profession—palette, brush, black suit, beret—Rousseau depicts himself in the middle of Paris near the Pont du Carrousel, the Eiffel Tower in the background. Along with Georges Seurat, Rousseau was one of the first artists to take an interest in the Eiffel Tower, the flagship of French know-how, a steeped iron structure erected for the Exposition Universelle (world’s fair) of 1889 in Paris.

Reversals of fortune
Few artists have experienced such rapid reversals of fortune as Rousseau. Hardly fifteen years separate his heavy-handed artistic efforts, which prompted mockery and gibes, and his championing as one of the great avant-garde artists. Picasso, Robert Delaunay, and Wassily Kandinsky considered him as one of the fathers of modernity, and the surrealists identified with his dreamlike universe. Having failed in his request for admission to the prestigious Salon, the official art exhibition of the
Academy of Fine Arts, Rousseau first tried his luck in 1885 by presenting two canvases—Italian Dance and Sunset—to the Salon des Refusés (exhibition of rejects), along with the dissidents of the ‘group of independents.’ His unclassifiable work was received with jokes, insults even. One contemporary press report asserted that “Mr Henri Rousseau’s ghastly work is laughable.” The next year, armed with his unshakeable self-confidence, he submitted Carnival Evening, which depicts a couple dressed in carnival costumes standing at the edge of a forest of barren trees, beneath a bright moon. Criticized for his amateurism, lack of technique, oversimplified shapes, and naivety, Rousseau was the butt of an unsympathetic public’s jokes.

Yet his work, which seemed to emerge from nowhere, fascinated his peers, interested as they were in art brut (raw art, meaning art created outside official culture) and the advent of primitive forms. Not given to bestowing praise on others, Paul Gauguin admired Rousseau’s “inimitable black.” Seurat said: ‘Monsieur Rousseau, in general I don’t like the garish coloring we see at the Salon des Indépendants, but I greatly like yours because it is true.” Swiss/French painter Félix Vallotton, astonished by the originality of Tiger in a Tropical Storm (Surprised!) (1891), declared of Rousseau: “His tiger surprising its prey ought not to be missed; it’s the alpha and omega of painting.” This tiger, teeth bared, prowling among plants and trees lashed by a violent storm, is the first of a long series of jungle paintings, to which Rousseau returned time and again until his death, painting exotic and increasingly extraordinary and exuberant vegetation. With these wild and cruel ‘jungles,’ this mysterious imagery, the painter at last succeeded in attracting the attention of the public. “Where are the Rousseaus?” clamored the crowds at each new Salon.

Rousseau soaked up everything he saw: masterpieces by great painters, children’s picture books, photographs of wild animals in magazines, the catalogs of department stores, and, of course, the greenhouses in the Jardin des Plantes.

Gigantic lotuses, bunches of white bananas hanging from naked stems, oranges suspended like Christmas tree baubles, yellow-eyed monkeys lurking behind curtains of palms, ele-
phants merging into bracken: Rousseau’s universe is phantasmagorical. The poisonous allure of The Snake Charmer (1907), the exotic fruit of Eve (1906-1907) struggling with temptation, the terrible Fight between a Tiger and a Buffalo (1908), the ape-like pranks, the red ball of the sun setting behind the tufted curtain of grasses in The Hungry Lion throws itself on the Antelope (1898-1905) bear witness to the power of invention of an artist who frenetically recreated the plant and animal world as if on a mission.

Robert Delaunay compared Rousseau’s technique to that of “old craftsmen who covered the walls of palaces, convents, and churches with their paintings.” He linked Rousseau’s craftsmanship, which is less empirical than it appears, with that of the “illuminators who left no detail to chance, lines above to indicate the masses, other lines for the foreground.” But he detected too the premises of a new art in this painting of “thousands of green hues” in which everything “is thought through, premeditated.”

The ingenuous Rousseau seemed overwhelmed by this luxuriance looming from his canvasses as if a mysterious force was guiding his hand. “One day I was painting a fantastic subject,” he once confided to a friend, “and I had to open the window because fear was upon me.”

The Dream
An outsider who, despite eventual critical success, lived throughout his life from hand to mouth, Rousseau was at times not above a small embezzlement or two, for which he served time. On occasions he disconcerted his most ardent supporters as a maverick of painting who obeyed no one but
The Dream. 1910; oil on canvas; 298.5 x 204.5 cm. Museum of Modern Art, New York, New York, USA. © VCG Wilson/Corbis via Getty Images.
himself. Alfred Jarry destroyed a canvas he didn’t like; Apollinaire wondered sometimes whether perhaps Rousseau’s general culture was too meager, yet commissioned from him a portrait for which he posed for hours in the Luxembourg Gardens. The result, The Muse inspiring the Poet (1908), shows Apollinaire alongside his mistress, the sylph-like Marie Laurencin, here depicted with the generous curves Rousseau clearly associated with a muse. Another recurring incongruity in Rousseau’s work is that because he was unable to draw feet he solved the problem by hiding them. Apollinaire and Marie Laurencin’s feet are lost in the grass behind a row of sweet williams.

But it was with The Dream (1910), his last painting, that Rousseau reached full maturity. After Rousseau appealed to him—“You will unfold your literary talent and avenge me for all the insults and abuse I have experienced”—Apollinaire wrote: “Beauty radiates from this painting, there’s no doubt about it. I believe that this time, no one will dare laugh. Ask the painters, they are unanimous: they admire everything, I tell you, and are right to do so.” Rousseau’s mysterious odalisque, naked and reclining on a Louis-Philippe-style (1830-1848) sofa in the middle of a threatening jungle, epitomizes the painter’s fantasies. It was also his swansong, as he was dying. But in the twilight of life he had fallen for Léonie, a widow of fifty-nine who ran a warehouse for milk on the Boulevard des Batignolles in Paris. She readily accepted his gifts, but refused to marry him because he was only a ‘dauber.’

Rousseau reacted to this slight by asking Apollinaire and the art dealer Ambroise Vollard to testify to his talent, and he even wrote a draft of a plan to make a settlement on Léonie after his death. All to no avail. Léonie still rebuffed him and never did become part of his life, but lives on in his artistic legacy, as it is she the fantasized odalisque in The Dream.

A few months later, on his hospital bed, his leg eaten away by gangrene, abandoned by all but a faithful few, did Rousseau remember the banquet at the Bateau-Lavoir, the gathering in his honor at Picasso’s studio? Was his mind peopled by images of those present that evening, everyone who was anyone in the arts and culture in Paris? Did Apollinaire’s toast—“Long live, Long live Rousseau!”—ring joyously in his memory one last time before the final curtain fell?
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