Chronic Angina: Definition, Prevalence, and Implications for Quality of Life

Benjamin M. Scirica, MD, MPH

TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Chronic angina is a prevalent manifestation of cardiovascular disease and is most commonly due to insufficient oxygen supply from fixed epicardial lesions in the coronary arteries. In addition to increasing the risk of cardiovascular death and recurrent myocardial infarction, chronic angina has a significant impact on functional capacity and quality of life. All patients with cardiovascular disease should be closely questioned to determine the functional and symptomatic limitations attributable to ischemic symptoms. The Canadian Cardiovascular Society Classification of Angina is the easiest metric to use; however, more sensitive measures such as the Seattle Angina Questionnaire offer a better overall assessment of angina symptoms and quality of life and can be used to compare the efficacy of different treatments. Treatment strategies that begin with either immediate revascularization or optimal medical therapy with antianginal agents significantly improve angina frequency and quality of life. Initial revascularization, especially with coronary artery bypass grafting, appears to offer more rapid relief of angina compared with percutaneous coronary intervention or medical therapy in the first months after initial revascularization. After a year of follow-up, though, much of the treatment differences are lost and all strategies (surgical/percutaneous revascularization or medical therapy) result in a significant improvement of angina symptoms.

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Chronic stable angina is the most common manifestation of cardiac ischemia and is present in a large proportion of patients with established cardiovascular disease. With an aging population, a growing epidemic in diabetes, and reductions in overall cardiovascular mortality, the prevalence of chronic angina is likely to rise over the coming years. Understanding the magnitude of chronic stable angina, the underlying causes of ischemia, and in particular, the impact chronic angina has on quality of life (QoL) is important in the management of patients with symptomatic cardiovascular disease.

Definition and Pathophysiology

The diagnosis of chronic angina begins with a careful assessment of clinical symptoms. Although there is significant variability in the quality of angina symptoms, angina typically is a thoracic discomfort, often centered in the midsternum, that radiates to the neck, jaw, or arm. Some describe the discomfort as more epigastric than substernal. It is most commonly described as a pressure, squeezing, or tightness, rather than a sharp pain. Associated symptoms are common and include diaphoresis, dyspnea, nausea, or intense fatigue. In some patients, especially women and the elderly, dyspnea or diaphoresis alone without the "typical" symptoms of substernal pressure are present and are often ascribed to other causes, which causes delays in diagnosis.

The pattern of angina is critical to defining a chronic versus unstable ischemic syndrome.

The pattern of angina is critical to defining a chronic versus unstable ischemic syndrome. Patients with chronic angina experience symptoms that are predictable, repetitive, and inducible with exertion. Symptoms are typically stable over weeks and months. Although exertion—walking, climbing stairs, cleaning—is the most common precipitant, anxiety and stress can also elicit angina attacks. Angina is often worse in cold weather and after meals. Chronic angina always resolves with rest or with the use of sublingual nitroglycerin. Many patients report a slow onset of angina with exertion that requires them to diminish their level of exertion or even stop the activity. Often, after this initial episode subsides, patients can continue their activities without symptoms.

Careful questioning of a patient with suspected angina is necessary to determine how his or her QoL is affected. Many patients will begin to reduce their activities to prevent angina attacks and thus report a reduction in their pain. Any change in a chronic angina pattern with either onset at rest or angina with progressively less exertion requires a more urgent evaluation because it may indicate a conversion to an unstable ischemic syndrome.

Pathophysiology

Angina, the somatic manifestation of cardiac ischemia, results from a mismatch in oxygen supply and demand.[1,2] The exact noxious stimuli that provoke the poorly localized discomfort of ischemia are not clear, but are likely related to the local release of adenosine and bradykinin by ischemic myocytes. In most cases, chronic angina is the result of decreased supply due to fixed epicardial atherosclerotic lesions in the setting of increased oxygen demand during exertion. Typically, lesions do not become symptomatic until they effectively block 70% of the coronary flow. Due to eccentric remodeling, atherosclerotic lesions can become quite larger relative to the original artery diameter before they achieve a degree of occlusion that precipitates symptoms. Vasospasm likely plays an important role in all angina, even that caused by a typical atherosclerotic lesion, and may explain why cold air and stress exacerbate anginal symptoms.

In addition to fixed large-vessel coronary lesions, ischemia can develop in several other clinical settings that have a different underlying etiology. Microvascular disease, characterized by typical angina symptoms, often with objective evidence of ischemia despite an absence of significant epicardial disease, is likely due to either atherosclerotic or fibrotic blockages in the small intramyocardial arterial bed. This phenomenon, often termed *Syndrome X*, tends to be more common in women and patients with diabetes. Vasospastic anginal syndromes, such as Prinzmetal's angina, are less common, but they can be extremely symptomatic with dramatic episodes of vasoconstriction that produce complete and temporary coronary occlusion with typical anginal pains and significant ST-segment deviations.

Finally, angina from less severe lesions, or even in the absence of significant coronary disease, can provoke ischemia in other clinical situations with supra-physiologic oxygen demand, such as hypertensive emergencies and hyperthyroidism, or with diminished oxygen supply, such as anemia. Treatment of "secondary" angina should focus on treating the underlying comorbidity.

Grading of Angina

Quantifying the extent of anginal symptoms is important in the initial evaluation and follow-up of patients with chronic symptoms. Every patient should be classified according to the degree of exertion that precipitates angina as well as the number of angina episodes per week.[1,2] The most accepted schema is the Canadian Cardiovascular Society (CCS) Classification of Angina, which categorizes symptoms on a scale of 1 (angina only with strenuous or prolonged exercise) to 4 (inability to perform any activity without angina) (Table 1).[3] Other criteria such as the Seattle Angina Questionnaire (SAQ) or the Duke Activity Status Index are

Table 1
Canadian Cardiovascular Society Classification of Angina

Class I
Ordinary physical activity does not produce angina. Strenuous or prolonged exertion produces angina
Class II
Slight limitation of ordinary activity (eg, walking rapidly or climbing stairs). Angina may be worse after meals, in cold temperatures, or with emotional stress
Class III
Marked limitation of ordinary activity
Class IV
Inability to carry out any physical activity without angina. May occur at rest

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more detailed and complicated to use but may offer better risk discrimination and are useful in clinical trials to evaluate different therapies.[2,4]

Prevalence

Although it is difficult to determine with precision the number of people who suffer chronic ischemia, various organizations have attempted to estimate the worldwide prevalence. In 2006, the World Health Organization (WHO) estimated that almost 54 million people suffered chronic angina. Most cases were in Europe (~17 million), followed by South-East Asia (~16 million), and then the Western Pacific and the Americas.[5]

In the United States, it is estimated that more than 80 million people have at least 1 manifestation of cardiovascular disease, with nearly 17 million having coronary heart disease. Almost 10 million people are estimated to have angina pectoris.[6] There is significant geographical variation, even within the United States, with the highest prevalence in West Virginia (7.6% among adults) and the lowest in Utah (2.4%). More women than men suffer from chronic angina, and there appear to be race-related differences in prevalence, with blacks having a higher prevalence than nonblacks (Figure 1).[7]

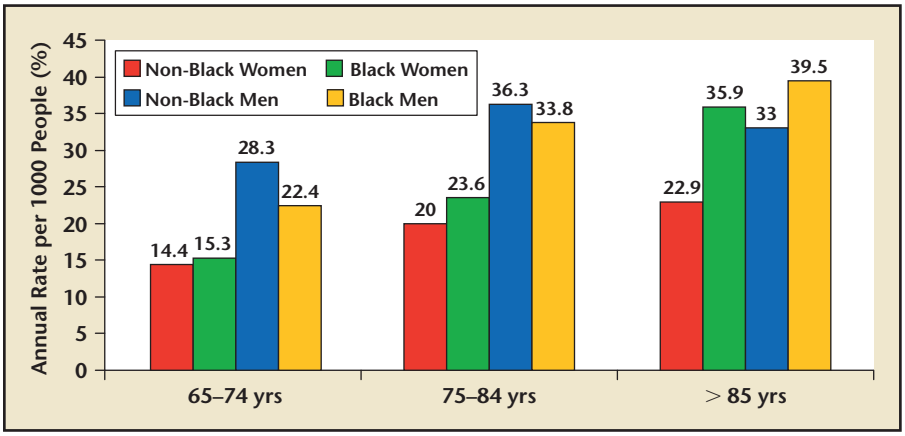
In Europe, the prevalence ranges from less than 1% in women aged 45 to 54 years to 10% to 15% in women older than 65 years. Prevalence is higher in men, with an estimated rate of 2% to 5% in men aged 45 to 54 years and 10% to 20% for men older than 65 years. Some of the highest rates of coronary heart disease are found in Eastern Europe and Russia.[1]

Several reports have now identified a subset of angina patients with "advanced angina," who have persistent unrelievable symptoms and who have no revascularization options due either to the presence of lesions that technically cannot be revascularized or to other comorbidities preventing revascularization. Different registries have estimated that this group of patients accounts for more than 10% of all patients with chronic angina.[1,7]

Economic Cost

In the United States, the estimated cost for treating coronary heart disease in 2009 will be $165.4 billion. Assessing the cost of chronic angina is extremely complicated; however, among patients with chronic angina, there is a direct relationship between the frequency of angina and healthcare cost. For example, in patients with a recent acute coronary syndrome but no chronic angina, the annual overall cost of treatment was $2928 versus $3909 in patients who experienced monthly angina (adjusted relative cost ratio, 1.29; 95% confidence interval [CI], 1.21-1.39), $4558 with weekly angina (adjusted

Figure 1. *Annual rate (per 1000) of chronic angina by race, sex, and age in the United States. Data from Lloyd-Jones D et al.[6]*



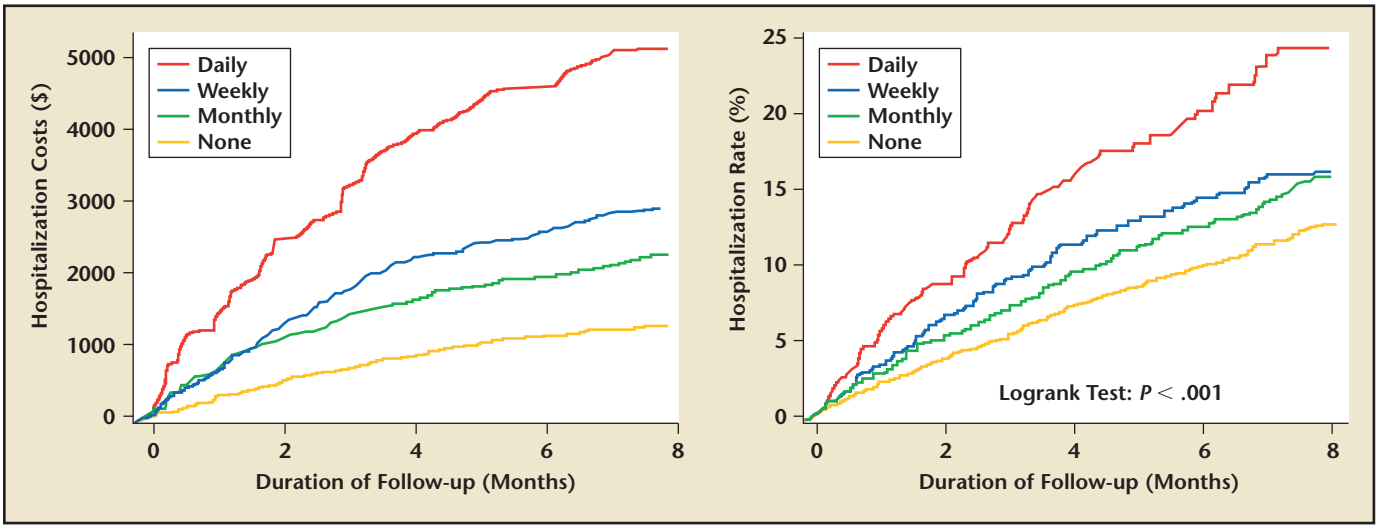


Figure 2. *Hospitalization rates and costs according to angina frequency in the 8 months following admission for non–ST-segment elevation acute coronary syndromes. Adapted with permission from Arnold SV et al. Economic impact of angina after an acute coronary syndrome: insights from the MERLIN-TIMI 36 trial.* Circ Cardiovasc Qual Outcomes. *2009;2:344-353.*[8]

relative cost ratio, 1.52; 95% CI, 1.48-1.67), and $6949 for daily angina (adjusted relative cost ratio, 2.32; 95% CI, 2.01-2.69; $P < .001$ for trend) (Figure 2).[8] The increased cost was mostly due to higher rates of hospitalizations and revascularizations in patients with a greater angina burden. In another cohort, the estimated lifetime cost for nonobstructive coronary artery disease (CAD) in women was nearly $770,000.[9]

Implications for QoL

Chronic angina has a significant impact on QoL and, as such, the dual goals of treating a patient with chronic angina are to prevent myocardial infarction (MI) and cardiovascular death and to improve QoL by reducing ischemic symptoms. Irrespective of other comorbidities, though, decreased QoL is associated with worse cardiovascular outcomes. It is therefore important to classify each patient's functional limitations due to his or her angina symptoms. The CCS's Angina Classification is the simplest method to assess the degree to which angina symptoms limit exertional capacity. According to several contemporary clinical trials of patients with chronic angina or CAD,[10-15] the majority of patients with chronic angina are in CCS Class I or II angina. Less than 20% of patients have class III angina. In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) trial, which enrolled 6560 patients with moderate-to-high-risk non–ST-segment elevation acute coronary syndrome, patients with a prior history of angina (54% of the population) included a greater proportion of patients (~30%) with Class III or IV angina 1 month prior to admission, likely due to the inclusion criteria requiring an ACS admission, which selected for a more unstable population.[14]

The CCS's classification is insensitive to the degree of functional limitation because it is primarily ascertained by the physician rather than by the patient. In addition, it is often insufficiently sensitive to use as a metric to evaluate different treatment effects. For example, in the Impact Of Nicorandil in Angina (IONA) trial that compared the novel antianginal agent nicorandil versus placebo, despite a reduction in cardiovascular death, MI, or unstable angina with nicorandil, there was no difference in the distribution of CCS class according to therapy, nor was there any difference in the rate of worsening angina class.[10]

There are several validated techniques to quantify QoL associated with chronic angina. The SAQ is a self-administered assessment that quantifies 5 angina domains: physical limitations, angina stability, angina frequency, satisfaction with therapy, and how the patient perceives that angina affects his or her QoL. Each of these measures is reported on a scale from 0 (severely limited) to 100 (minimal limitation).[4] There is a strong relationship between SAQ scores and cardiovascular outcomes (Figure 3).

Treatment Effects on QoL Metrics

As stated in current practice guidelines, "The goals of pharmacological treatment of stable angina pectoris are to improve quality-of-life by reducing the severity and/or frequency

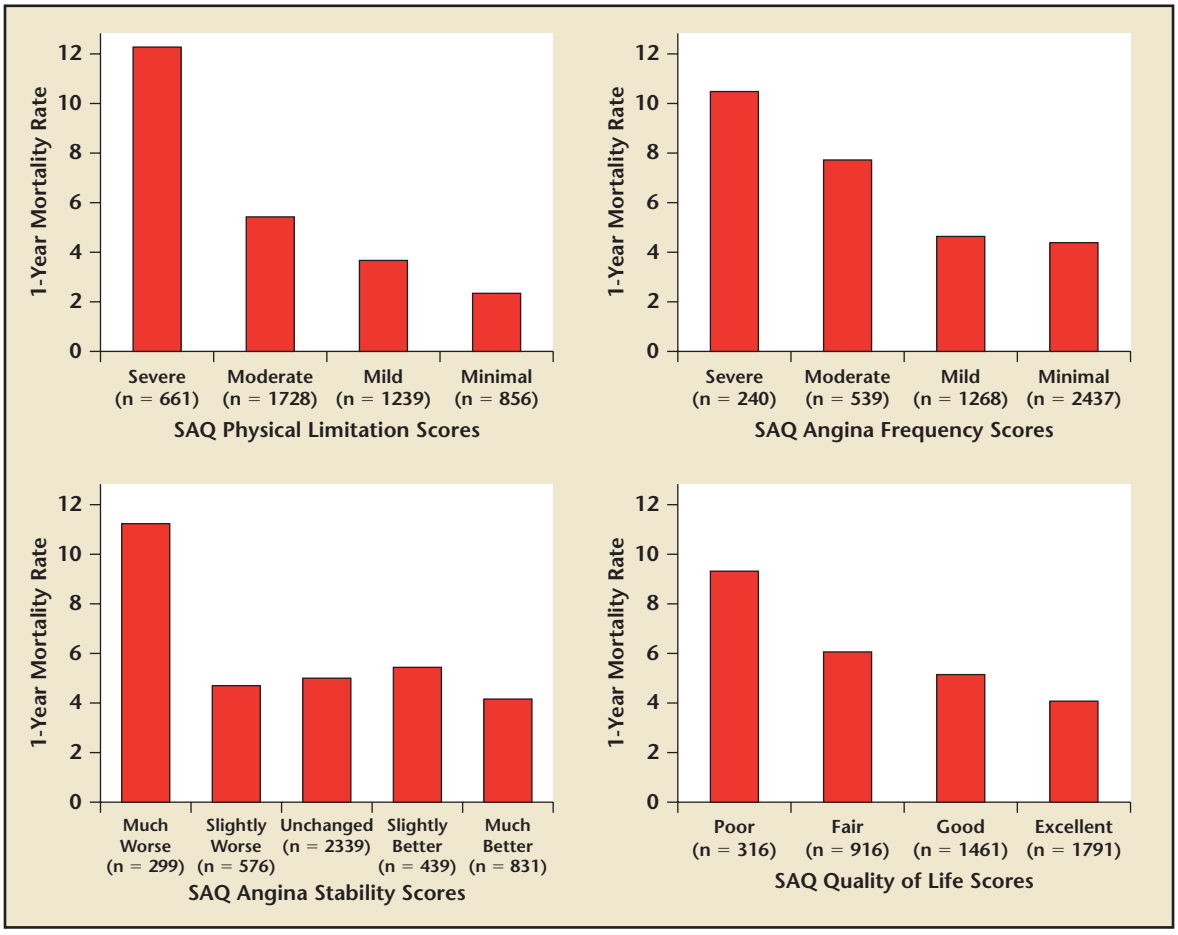


Figure 3. *Association between mortality and Seattle Angina Questionnaire (SAQ) scores. Adapted with permission from Spertus JA et al. Health status predicts long-term outcome in outpatients with coronary disease.* Circulation. *2002;106(1):43-49.*[4]

of symptoms, and to improve the prognosis of the patient."[1] Thus, it is important to evaluate antianginal therapy in terms of the effect on QoL measures. There are few data regarding the effect of traditional antianginal agents—β-blockers, calcium antagonists, and nitrates—compared with placebo on QoL measures, which is most likely due to the fact that most of the placebo-controlled studies of the traditional agents were completed before formal QoL measures had been validated and widely implemented.

There have been several randomized trials comparing the effect of either coronary artery bypass grafting (CABG) surgery versus percutaneous coronary intervention (PCI) or medical therapy versus PCI in terms of improvement in QoL measures. In the Stent or Surgery (SoS) trial, 988 patients with multivessel CAD were randomized to CABG versus PCI. Cardiac health status was assessed using the SAQ at baseline and then 6 and 12 months after randomization.[16] Both groups showed significant and dramatic improvements compared with baseline, indicating that both therapies offered important symptom relief. The improvement was greatest, though, in the patients assigned to CABG (83.8 vs 89.7; $P < .0001$ for angina frequency and 65.4 vs 69.1; $P = .04$ for QoL). The difference between revascularization strategies was greatest at 6 months and declined by 12 months, predominantly due to improved symptom relief in patients who underwent repeated PCI.[16]

The landmark Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomized 2287 patients with stable coronary disease to optimal medical therapy versus optimal medical therapy plus PCI.[17] Overall, there was no difference in the risk of death or myocardial infarction between both groups after a median of 5 years follow-up.[17] At baseline, 78% of all patients suffered angina. Similar to the SoS trial, both treatment groups experienced significant angina relief

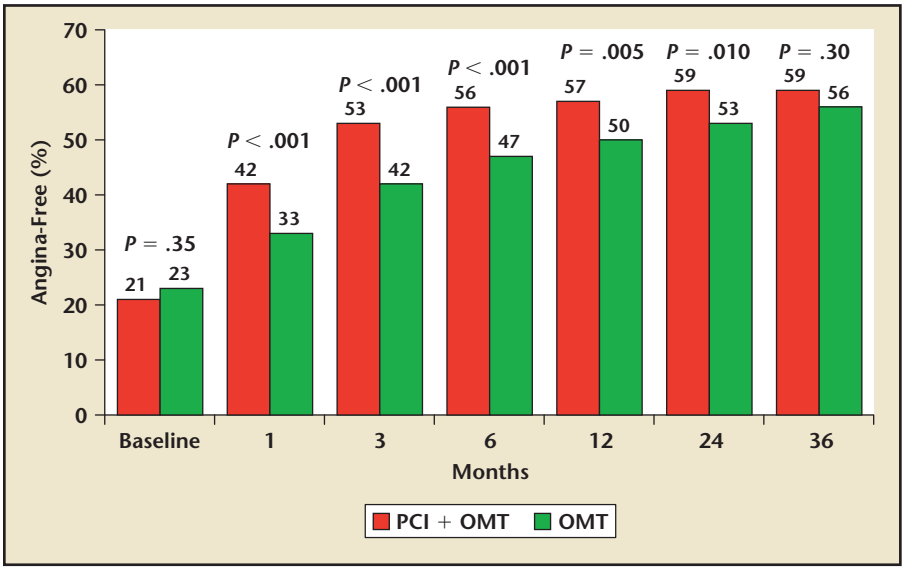


Figure 4. *Freedom from angina over time as assessed with the angina-frequency scale of the Seattle Angina Questionnaire, according to treatment group. OMT, optimal medical therapy; PCI, percutaneous coronary intervention. Adapted with permission from Weintraub WS et al. Effect of PCI on quality of life in patients with stable coronary disease.* N Engl J Med. *2008;359:677-687.*[18] *Copyright © 2008 Massachusetts Medical Society. All rights reserved.*

compared with baseline, although at 3 months patients assigned to PCI were more likely to be angina-free (53% in the PCI group vs 42% in the medical-therapy group; $P < .001$) (Figure 4). At 6 months, PCI was superior to medical therapy in terms of SAQ angina frequency (87 vs 83; $P < .001$) and QoL (75 vs 70; $P < .001$). QoL measures improved over time in both groups, although the difference between PCI and medical therapy diminished over time, likely because many patients assigned to initial medical therapy underwent revascularization.[18] In most patients with stable coronary disease, there does not appear to be a significant benefit in terms of a reduction in death or myocardial infarction between CABG, PCI, and medical treatment, although initial revascularization, especially with CABG, appears to offer more rapid relief of angina compared with PCI or medical therapy. After several years, the differences in initial treatment strategy are lost, likely due to improved medical therapy and greater use of revascularization.

QoL measures have been assessed in several of the trials comparing novel antianginal agents versus placebo. Fasudil, a rho-kinase inhibitor, was compared with placebo in 84 patients who had chronic angina despite treatment with traditional antianginal agents. Higher doses of fasudil significantly improved SAQ physical limitation and treatment satisfaction score, although it did not improve angina frequency or nitroglycerin use.[19]

The effect of ranolazine, a novel antianginal agent approved for treatment of chronic angina, on QoL measures has been assessed in 2 randomized trials. In the Efficacy of Ranolazine in Chronic Angina (ERICA) trial, 565 patients with persistent angina on maximum dose of calcium antagonists were randomized to ranolazine or placebo.[20] Treatment with ranolazine significantly improved the SAQ angina frequency score (22.5 vs 18.5; $P < .008$), although there was no improvement in the other SAQ domains. This improvement was predominantly due to a great improvement in angina frequency among patients with more than 4.5 angina episodes per week, whereas there was little difference between treatment groups in patients with fewer than 4.5 episodes per week.[20]

In the MERLIN-TIMI 36 trial, 6560 patients with moderate-to-high-risk non-ST segment acute coronary syndrome were randomized to ranolazine or placebo and followed for a median of 1 year.[21] Overall, treatment with ranolazine resulted in a lower rate of patients who moved to a worsening angina class compared with placebo (4.2 vs 5.9%; $P = .02$).[21] In the overall study population, there was also a minimal, though statistically significant, improvement in all the SAQ measures in patients treated with ranolazine versus placebo, with the greatest difference at 4 months after treatment. A larger effect of QoL measures, though, was observed in the 3565 patients (54%) with prior angina. At 12 months, ranolazine improved angina frequency score by 3.43 compared with placebo in patients with prior angina versus only 0.33 in patients without prior angina ($P = .003$ for interaction) (Figure 5). A similar pattern was seen in the other QoL dimensions. The use of nitrates and calcium antagonists was also lower over time in patients with chronic angina assigned to ranolazine.[22] The improvement at 12 months in SAQ angina frequency score in patients with prior angina assigned to ranolazine was similar to the benefit observed among patients assigned to the PCI arm in the COURAGE trial.

Conclusion

To reduce cardiovascular mortality and the risk of myocardial infarctions, all patients with chronic angina require aggressive risk factor modification to achieve optimal

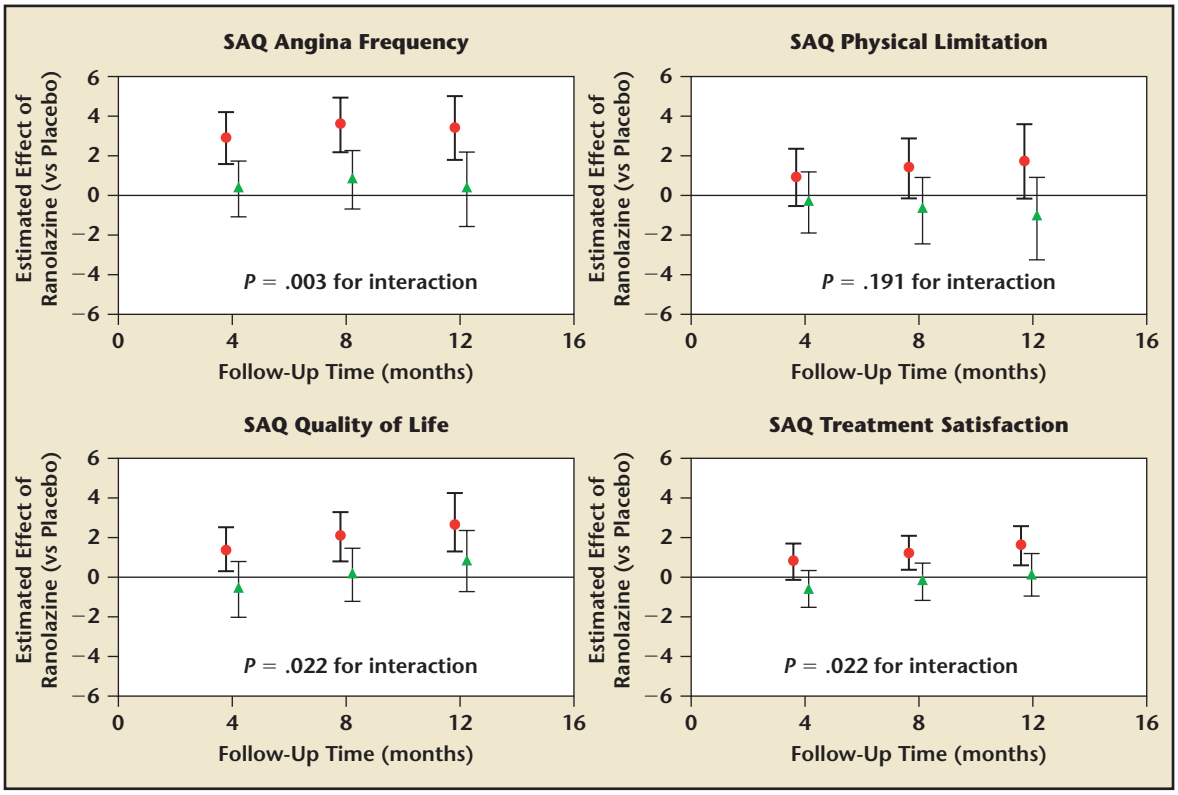


Figure 5. *Effect of ranolazine on Seattle Angina Questionnaire (SAQ) measures in patients with prior angina (circles) and patients without prior angina (triangles) randomized in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) trial. Adapted with permission from Arnold SV et al. Effects of ranolazine on disease-specific health status and quality of life among patients with acute coronary syndromes: results from the MERLIN-TIMI 36 randomized trial.* Circulation: Cardiovascular Quality and Outcomes. *2008;1:107-115.*[22]

Main Points

- Although there is significant variability in the quality of angina symptoms, angina typically is a thoracic discomfort, often centered in the midsternum, that radiates to the neck, jaw, or arm.
- Any change in a chronic angina pattern with either onset at rest or angina with progressively less exertion requires a more urgent evaluation because it may indicate a conversion to an unstable ischemic syndrome.
- In most cases, chronic angina is the result of decreased supply due to fixed epicardial atherosclerotic lesions in the setting of increased oxygen demand during exertion.
- Chronic angina has a significant impact on quality of life and, as such, the dual goals of treating a patient with chronic angina are to both prevent myocardial infarction and cardiovascular death and improve quality of life by reducing ischemic symptoms.
- In most patients with stable coronary disease, there does not appear to be a significant benefit in terms of a reduction in death or myocardial infarction between coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and medical treatment, although initial revascularization, especially with CABG, appears to offer more rapid relief of angina compared with PCI or medical therapy.
- In the Efficacy of Ranolazine in Chronic Angina (ERICA) trial, ranolazine, a novel antianginal agent approved for treatment of chronic angina, improved the Seattle Angina Questionnaire angina frequency score. In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36 (MERLIN-TIMI 36) trial, ranolazine resulted in a lower rate of patients who moved to a worsening angina class compared with placebo.

blood pressure, lipids, and glycemic control. Single or dual antiplatelet therapy is indicated for most patients with cardiovascular disease, and lifestyle modifications—smoking cessation and exercise—should be constantly emphasized. In addition, careful attention to limitations to exercise and QoL due to ischemic symptoms is required in all patients. Specific therapies, both procedural and medical, should be instituted to reduce angina symptoms and improve QoL. ■

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