

Prevalence of refractory angina in clinical practice

Luis Henrique Wolff Gowdak, MD, PhD, FESC
Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil

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

Abstract

According to the American Heart Association, an estimated 15.5 million Americans aged 20 years and over have coronary artery disease, and 8.2 million are living with angina pectoris. Despite enormous advances in medical therapy and myocardial revascularization procedures, a growing number of patients will present with disabling symptoms due to myocardial ischemia, in whom a combination of classic anti-anginal drugs and angioplasty or bypass surgery is ineffective in providing symptom relief. Those patients are usually referred to as having refractory angina. They usually suffer from poor self-perceived health status, have significant impairments in quality of life with a high incidence of depression, and represent a burden to the health care system due to significant resource utilization, including rehospitalization. Because of the variability in defining unsuitability for revascularization and the use of different medical strategies for symptom control, and with only limited clinical data available from small, observational studies, a precise estimate of the prevalence of refractory angina is not available. Nevertheless, its incidence has been estimated at between 5% and 15% of patients undergoing cardiac catheterization. Presently, the incidence of newly diagnosed patients with refractory angina in the United States is something between 50 000 to 100 000 per year. In Europe, the incidence is estimated to be at least 30 000 to 50 000 new cases per year. Because life expectancy is increasing worldwide, the number of patients who will fulfill the criteria for refractory angina is expected to increase as well. ■ *Heart Metab.* 2017;72:9-12

Keywords: optimal medical therapy; prevalence; refractory angina

According to the latest report from the American Heart Association¹ based on data from the National Health and Nutrition Examination Survey (NHANES), 2009 to 2012, an estimated 15.5 million Americans aged 20 years and over have coronary artery disease, translating to a prevalence of 7.6% for men and 5.0% for women. Based on the same document, in 2012, there were 8.2 million Americans living with angina pectoris with an estimated incidence of 565 000 newly diagnosed cases

each year. There is a strong association between aging and the prevalence of angina, as shown in *Figure 1*.¹

The exact prevalence of angina in different countries across the globe is challenging to determine because of the lack of large-scale epidemiological studies. In one of the few studies that examined this issue in 52 countries in all continents, comprising more than 210 000 participants, the prevalence of angina ranged from 2.44% in Tunisia to 23.89% in Chad.²

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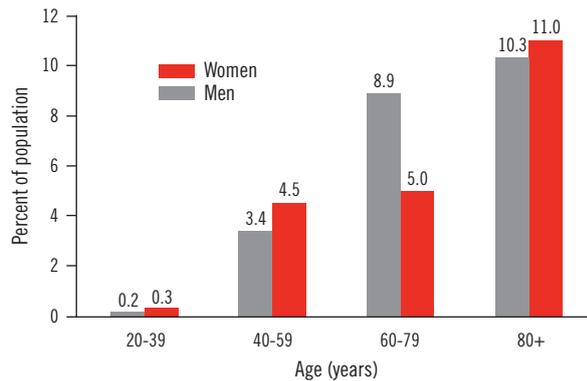


Fig. 1 Prevalence of angina pectoris by age and sex (National Health and Nutrition Examination Survey, 2009-2012; National Center for Health Statistics and National Heart, Lung, and Blood Institute).

Modified from reference 1: Mozaffarian et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2016;133:e38-e360. © 2016, American Heart Association, Inc.

Despite enormous advances in medical therapy and myocardial revascularization procedures, a growing number of patients among those with stable angina pectoris struggle to cope with disabling symptoms caused by myocardial ischemia, in whom a combination of classic antianginal drugs and angioplasty or bypass surgery is ineffective in providing symptom relief. Those patients are usually referred to as having refractory angina.

For those patients to be labeled as “no-option” patients, a careful assessment of the relationship between disabling symptoms, objective demonstrable myocardial ischemia, and unsuitability for revascularization must be performed (Figure 2).³ In a small study with 44 patients with refractory angina,⁴ the nursing diagnosis of activity intolerance was positively related to a higher Canadian Cardiovascular Society functional class and lower cardiac work during a treadmill test.

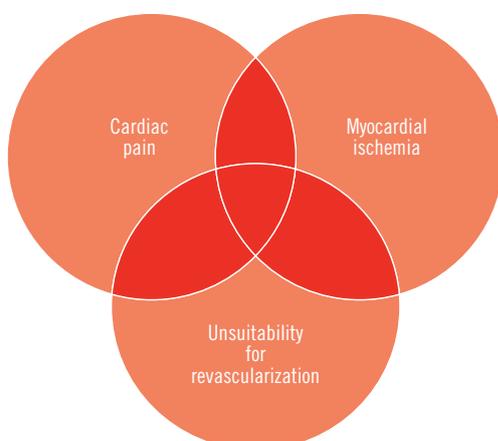


Fig. 2 Elements to be assessed in patients before they are diagnosed with refractory angina.

Modified from reference 3: Jolicoeur et al. *Can J Cardiol*. 2012; 28(2 suppl):S50-S59. © 2012, Elsevier.

The latter element to be considered in the diagnosis of refractory angina, the unsuitability for revascularization, is usually the most difficult one because it can reflect the extension of the disease, the risk profile of the patient, comorbidities, and the expertise of the health care providers in dealing with more complex, high-risk patients. For example, Atreya et al⁵ looked at predictors of medical management in patients undergoing elective coronary angiography for stable angina, and they found that the decision to proceed to percutaneous coronary intervention was largely dependent on patient and angiographic characteristics. Patients with advanced age and/or chronic kidney disease, or with distal and high-risk lesions, were more often referred for medical therapy.

Another aspect concerning the refractoriness to medical therapy is how aggressive antianginal agents are being used. Usually, antianginal therapies include a combination of hemodynamic agents like β -blockers, calcium-channel antagonists, and long-acting nitrates, agents that are widely available. Agents with different mechanisms of action can be found in some, but not all, countries; examples include trimetazidine, ivabradine, ranolazine, and nicorandil. In 136 patients who initially received a diagnosis of refractory angina, we have shown that intensive medical treatment with a combination of triple hemodynamic agents (β -blockers, calcium-channel antagonists, and long-acting nitrates) with trimetazidine and/or ivabradine was highly effective in providing angina relief: the number of angina attacks decreased from 7.8 ± 9.4 to 3.8 ± 5.1 and improvement in at least one Canadian Cardiovascular Society functional class occurred in half of those patients.⁶ So, a patient may be prematurely tagged as being refractory to medical therapy, even before all antianginal drugs have been used, leading to an overestimation of the number of patients with true refractory angina. One should keep in mind the concept that optimal medical therapy may be defined as the use of three or more antianginal drugs at maximally tolerated doses, including one heart rate-limiting agent and a coronary vasodilator.

Patients with refractory angina usually suffer from poor self-perceived health status,⁷ have significant impairments in quality of life⁸ with a high incidence of depression,⁹ and represent a burden to the health care system due to significant resource utilization,^{10,11} including rehospitalization.¹² They represent a very special subset in the spectrum of patients with angina

pectoris and, although chronic myocardial ischemia could impair left ventricle contractility, the long-term left ventricular function is usually preserved in patients with refractory angina.¹³

Because of the variability in defining unsuitability for revascularization, the use of different medical strategies for symptom control, and the limited clinical data available from small, observational studies, a precise estimate of the prevalence of refractory angina is not available.

Nevertheless, the incidence of refractory angina has been estimated at between 5% and 15% of patients undergoing cardiac catheterization.¹⁴ In a study conducted more than 20 years ago, the incidence of “no-option” patients was determined to be 11.8% on the basis of coronary anatomy, myocardial perfusion defects, and symptoms.¹⁵ Presently, the incidence of newly diagnosed refractory angina in patients in the United States is something between 50 000 to 100 000 per year.¹⁵ In Europe, the incidence is estimated to be at least 30 000 to 50 000 new cases per year.¹⁴

Although the true prevalence of refractory angina, as previously discussed, is difficult to ascertain, investigators agree that currently, up to 1.8 million individuals from the United States and more than 500 000 Canadians are estimated to have refractory angina.¹⁵ In a recent study from Brazil,¹⁶ the prevalence of moderate-to-severe angina was determined from a nationwide registry of more than 60 000 individuals. Participants were asked to answer the short version of the Rose/World Health Organization questionnaire,¹⁷ translated into Portuguese and validated in another study.¹⁸ Investigators found that the overall frequency of moderate-to-severe angina was 4.2%, more common in women (5.2%) than in men (3.0%).

Another difficult clinical scenario that may present itself as refractory angina relates to patients with angina in the absence of obstructive coronary artery disease at angiography and myocardial disease, now defined as type 1 coronary microvascular dysfunction. There is no specific therapy for this condition, so treatment approaches often remain empiric.¹⁹ Because there is no obstructive disease, revascularization procedures are not indicated, and patients should be treated medically. However, despite several different combined strategies for optimization of medical therapy, a substantial number of patients may remain symptomatic. In a study by Lamendola et al,²⁰ the resolution of symptoms was recorded dur-

ing a median follow-up of 11.5 years in 155 patients (mean age, 58.9±10 years; 40 men) with type 1 coronary microvascular dysfunction. Although obstructive coronary artery disease was excluded at baseline, 89 patients (57.8%) had to be readmitted to hospital because of recurrent angina, and coronary angiography had to be repeated at least once in 33 patients (21.3%). Symptom control was far from ideal; angina was considered to have improved over time in only 82 patients (52%), remained unchanged in 51 patients (33%), and got worse in 21 patients (14%), meaning that roughly half of patients with type 1 coronary microvascular dysfunction remained symptomatic despite treatment.

Because life expectancy is increasing worldwide, cardiologists should prepare to deal with an even larger number of patients who will fulfill the criteria for refractory angina. This is only the beginning. ■

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