

Prognostic implications of refractory angina

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Abstract

In the current era of widespread use of myocardial revascularization, angina has not disappeared. It is a common symptom among patients with stable coronary artery disease (affecting approximately 20% of patients) and has ominous prognostic implications in terms of subsequent risk of death and myocardial infarction. It is also associated with an increased risk of hospitalization for cardiovascular reasons and, as such, with increased costs. Refractory angina, (ie, chronic angina that cannot be controlled by a combination of medical therapy, angioplasty, and bypass surgery, where the presence of reversible myocardial ischemia has been clinically established to be the cause of the symptoms) is a more limited subgroup, given the spontaneous tendency for anginal symptoms to improve over time and the existing pharmacologic armamentarium to treat symptoms. However, refractory angina remains associated with a sizeable long-term mortality, estimated at 20% over 5 years, and has an important impact on patients' quality of life.

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Angina pectoris is a common symptom of coronary artery disease (CAD) and, in the past, angina relief was the main goal of treatment, as most antianginal agents did not affect long-term outcomes. However, over the past 40 years, the advent of myocardial revascularization dramatically changed the epidemiology of angina, both in terms of prevalence and prognostic implications; whereas angina was previously considered to be an “acceptable symptom” and treated with antianginal agents, in more recent years, the mere existence of angina despite medical therapy (and sometimes without a course of optimal antianginal therapy) has become a trigger for coronary angiography with a view to

revascularization. At the same time, due to accumulating evidence regarding the prognostic benefit of pharmacological therapy for stable CAD, the goals of therapy have moved toward prevention of cardiovascular death and acute myocardial infarction (MI).¹

Given the expanding scope of percutaneous coronary intervention, today, the only patients who have persistent angina are typically those for whom revascularization is considered unsuitable either because they have undergone previous—often multiple—revascularization procedures or because they have severe comorbidities, left ventricular dysfunction, or very extensive and complex anatomical features of CAD.

Abbreviations

BARI-2D: Bypass Angioplasty Revascularization Investigation 2 Diabetes; **CAD:** coronary artery disease; **CLARIFY:** prospective observational Longitudinal Registry of patients with stable coronary artery disease; **MI:** myocardial infarction; **OPTIMIST:** OPTions In Myocardial Ischemia Syndrome Therapy

Prognosis of patients with refractory angina

There is only limited contemporary data regarding the current prognosis of patients with stable angina and even less for those patients with refractory angina. Most studies are small or relatively old with a very large range (3% to 21%) of annual mortality reported for patients with refractory angina.² In addition, there are several methodological issues that make it difficult to accurately and consistently assess the prognosis of patients with angina.³ First, there may be a discrepancy between outcomes assessed in population series (such as the Framingham study) versus those

obtained from clinical trials with highly selected participants. Furthermore, there are several definitions of angina, and though the expression “stable angina” is sometimes used to define a group of symptomatic patients with angina, it is also sometimes used to refer to patients with established CAD, distancing it from an acute coronary syndrome, regardless of symptoms. Finally, given the marked predominance of men among patients with angina, the information regarding the prognosis of angina in women is limited.

In historical series, mortality was very high; in the Framingham study, in the 1960s, 10-year mortality rates in patients with angina were approximately 40% for men aged over 50 years and women aged over 60,⁴ quite like that of patients with a previous MI. In 1988, Swedish investigators from the Multifactor Primary Prevention Trial⁵ reported that men with angina but no previous MI had a 14.1% incidence of fatal and nonfatal coronary events during 7.3 years of follow-up; the incidence was 29.4% in men with angina and previous MI. More recently, in a series of 59 patients from the Cleveland Clinic, 1-year mortality was 17%.⁶ In a series of patients undergoing

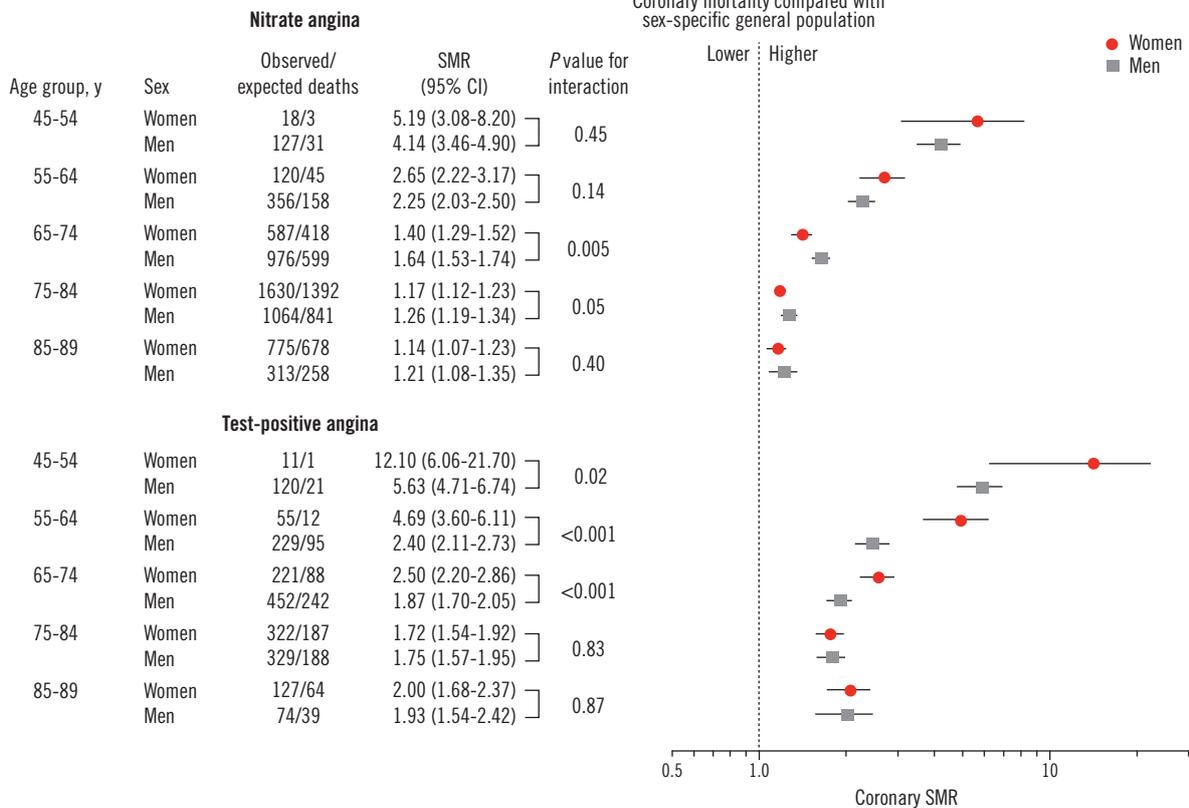


Fig. 1 Prognosis of nitrate and test-positive angina: standardized mortality ratios for coronary heart disease, by sex, within age groups. **Abbreviations:** CI, confidence interval; SMR, standardized mortality ratios. **After reference 9:** Hemingway et al. JAMA. 2006;295:1404-1411. © 2006, American Medical Association.

coronary angiography at the Duke University, mortality was 38% at an average follow-up of 2.2 years in 487 patients who did not undergo revascularization.⁷ These figures suggest that mortality of this group may be very high and certainly higher than that of patients subjected to elective revascularization. Indeed, in another series from the Minneapolis Heart Institute, the mortality rate at 3 years for patients who underwent complete revascularization was lower than for those who underwent suboptimal revascularization or who were not amenable to revascularization (14.8% vs 6.6%, $P=0.004$, respectively).⁸

A large Finnish, prospective, population-based study examined coronary mortality in ambulatory patients with angina, defined either by the prescription of nitrates or by abnormal noninvasive or invasive test results.⁹ The age-standardized annual incidence per 100 population of all cases of angina was 2.03 in men and 1.89 in women, with a sex ratio of 1.07 (95% confidence interval, 1.06-1.09). Coronary mortality was highly correlated with age (*Figure 1*),⁹ but in each age group, the relative increase in mortality between patients with versus those without angina was similar for men and women. In another study, angina

was present in approximately half of the patients after acute coronary syndrome, and it was associated with a marked increase in the risk of hospital admission.¹⁰

The prognostic importance of angina versus myocardial ischemia has been examined in several studies.^{11,12} In the CLARIFY registry of stable CAD patients (prospective observational Longitudinal Registry of patients with stable coronary artery disease), among more than 20 000 patients who had undergone a noninvasive test for myocardial ischemia, 65% of the patients had neither angina nor evidence of myocardial ischemia, 15% had evidence of myocardial ischemia but no angina, 9% had angina alone, and 11% had angina and ischemia. Angina, with or without ischemia, was clearly associated with higher rates of cardiovascular death or MI at follow-up, whereas silent ischemia was not (*Figure 2*).¹¹ Interestingly, most outcome events occurred in patients with neither.¹¹ These findings are consistent with the literature indicating that angina is associated with worse outcome.^{13,14} However, in the Heart and Soul study¹² and in the BARI-2D trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes),¹⁵ myocardial ischemia, rather than angina, appeared to be the key driver of prognosis.¹⁶

Finally, with respect to the outcome of patients with refractory angina, one of the most rigorous recent studies was a single-center study (the OPTIMIST program [OPTions In Myocardial Ischemia Syndrome Therapy])

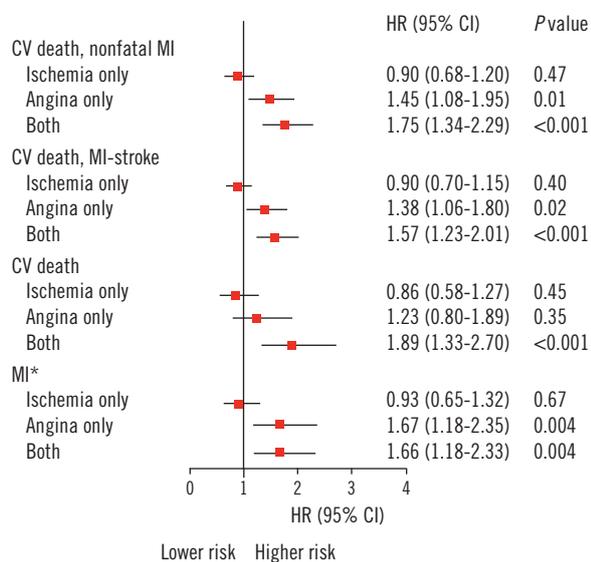


Fig. 2 Anginal symptoms during a noninvasive test are more prognostic than presence or absence of myocardial ischemia. Adjusted hazard ratios for the primary and various composite outcomes for patients with ischemia, angina, and both, relative to patients with neither angina nor ischemia. Outcomes are adjusted for age, sex, geographical region, smoking status, hypertension, dyslipidemia, and diabetes. *Indicates fatal and nonfatal.

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

After reference 11: Steg et al. JAMA Intern Med. 2014;174:1651-1659. © 2014, American Medical Association.

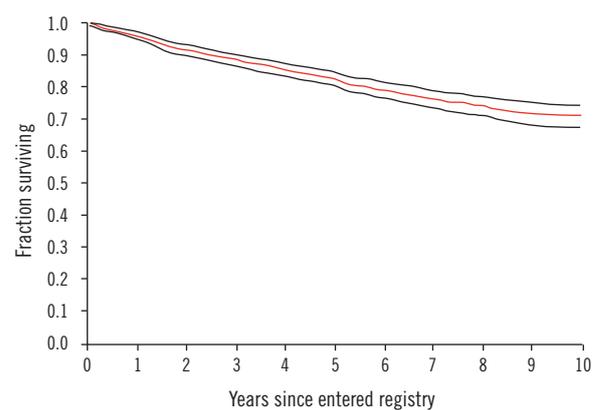


Fig. 3 Mortality estimation in patients with refractory angina. Kaplan-Meier survival curve in 1200 patients with refractory angina from the OPTIMIST study. The upper and lower lines represent 95% confidence intervals.

Abbreviations: OPTIMIST, OPTions In Myocardial Ischemia Syndrome Therapy.

After reference 2: Henry et al. Eur Heart J. 2013;34(34):2683-2688. © 2013, The Author. Published on behalf of the European Society of Cardiology.

conducted at the Minneapolis Heart Institute, which enrolled 1200 consecutive patients referred from 1996 to 2001 for refractory angina or myocardial ischemia. Most of these patients had undergone previous percutaneous coronary intervention (74.4%), previous coronary artery bypass grafting (72.4%), and had had a previous MI (72.6%). Overall, during a median follow-up of 5.1 years, 20.1% of the patients died, largely (71.8%) of cardiovascular causes. Kaplan-Meier analysis yielded a mortality of 3.9% at 1 year and 28.4% at 9 years (Figure 3).² The main independent predictors of all-cause mortality were age, diabetes, angina class, chronic kidney disease, left ventricular dysfunction, and congestive heart failure.² These results suggest that, in the contemporary era, the actual outcome of patients with refractory angina may not be as severe as previously thought. The improvement in survival may reflect much broader use of secondary prevention and adherence to evidence-based medications (antiplatelet agents, β -blockers, statins, and renin-angiotensin antagonists), as well as aggressive risk factor modification.

Prognosis of patients with angina due to nonobstructive CAD

In most cases, angina stems from flow-limiting stenoses in the coronary arteries. However, there may be other mechanisms for angina, with different outcomes. Patients with anginal symptoms and non-invasive evidence of myocardial ischemia in the absence of obstructive epicardial CAD are referred to as having microvascular angina. Their prognosis was traditionally considered to be good,¹⁷ with long-term outcomes like those of the general population.¹⁸ However, recent studies, done largely in women, have highlighted that long-term outcomes may not be as favorable as previously thought.¹⁹⁻²¹

Another group of interest is the patient with variant angina, typically corresponding to coronary artery spasm in angiographically normal coronary arteries. Whereas the acute episodes of spasm can be potentially lethal, the long-term outcome of these patients, once identified and treated with appropriate medical therapy, appears good, with a low long-term mortality.²²

Conclusion

Despite today's widespread use of myocardial revascularization, angina has not disappeared. It is a com-

mon symptom among patients with stable CAD and has ominous prognostic implications. Despite anginal symptoms' tendency to spontaneously improve over time and the existence of a number of pharmacologic treatments for anginal symptoms, refractory angina, a more limited subgroup, is associated with substantial long-term mortality—estimated at 20% over 5 years—and has an important impact on patients' quality of life. ■

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