A PROMISE Fulfilled That Quality-of-Life Assessments Afford Incremental Value to Coronary Artery Disease Management

Joshua Schulman-Marcus, MD; William E. Boden, MD

Current American College of Cardiology/American Heart Association Clinical Practice Guidelines for patients with coronary artery disease (CAD) advocate dual goals of management: (1) to reduce incident rates of death or myocardial infarction, and (2) to improve angina and enhance the patient’s functional capacity, or quality of life.1 For certain subsets of patients, notably those with acute coronary syndromes, studies have shown that both goals can be achieved when optimal medical therapy is combined with myocardial revascularization. For subjects with chronic angina and stable CAD, however, revascularization has not been shown to reduce either short-term or long-term rates of death or myocardial infarction in comparison with optimal medical therapy alone.2,3 In such instances, therefore, treatment is primarily directed toward symptom control and improving quality of life.

Most patients seek medical care out of a desire to address or ameliorate worrisome symptoms or improve functional status. In turn, clinicians derive great personal satisfaction and professional fulfillment in relieving patients of the burden associated with persistent or worsening symptoms, whether it is through meticulous diagnosis, intensive treatment, or psychological reassurance. And yet, despite these important patient-centered benefits, improvements in quality of life are often relegated to a secondary outcome in many clinical trials that address treatment efficacy. Perhaps, in part, this is a consequence of the highly individual and subjective aspects that make quality of life challenging to standardize and quantify in populations of treated subjects. Therefore, even though making patients feel better is a major objective of why we practice medicine and is a continuing source of physician gratification (and patient satisfaction), there is an almost inherent dismissiveness in how many professionals view quality-of-life measures. Although only ≈60% of PROMISE patients were included in the present analysis (because of budgetary constraints), the surveyed cohort was numerically large with excellent representation of both women and minorities, and with relatively minimal loss to follow-up. Cardiac risk factors were highly prevalent, with almost one-quarter of subjects having a CAD risk equivalent, whereas baseline statin and aspirin use was observed in nearly half of subjects. Thus, these findings are likely to be generalizable to more unselected populations. Second, the diagnosis of obstructive CAD by either strategy was infrequent (12%–13%), reflecting an intention to recruit lower-risk patients. However, the low prevalence of CAD, when combined with the pragmatic study design for posttest treatment, likely attenuated the power to observe changes in quality of life over time between 2 noninvasive diagnostic strategies for symptomatic patients with suspected CAD in the recently reported Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. In PROMISE, subjects at low to intermediate risk were randomly assigned to an anatomic strategy using upfront cardiac computed tomographic angiography or a functional strategy using stress testing, most often myocardial perfusion imaging. The hypothesis of the trial was that an anatomic strategy would lead to a more accurate diagnosis or exclusion of CAD than functional testing which, in turn, would lead to more targeted downstream treatment and reduced events.5 However, no significant difference was observed in a composite of hard end points (a composite of death, myocardial infarction, unstable angina, or procedural complication) at a median 2 years of follow-up.6 Likewise, the authors observed no significant difference between the 2 strategies for improvement in quality of life.4 This strategic equivalence was robustly observed across numerous validated scales measuring different aspects of quality of life and in all reported subgroups.

Several aspects of this important work deserve comment. First, the trial was impressively conducted by experienced subject matter experts who used several well-validated quality-of-life scales. Although only ≈60% of PROMISE patients were included in the present analysis (because of budgetary constraints), the surveyed cohort was numerically large with excellent representation of both women and minorities, and with relatively minimal loss to follow-up. Cardiac risk factors were highly prevalent, with almost one-quarter of subjects having a CAD risk equivalent, whereas baseline statin and aspirin use was observed in nearly half of subjects. Thus, these findings are likely to be generalizable to more unselected populations. Second, the diagnosis of obstructive CAD by either strategy was infrequent (12%–13%), reflecting an intention to recruit lower-risk patients. However, the low prevalence of CAD, when combined with the pragmatic study design for posttest treatment, likely attenuated the power to observe...
between-group differences. The authors noted that, although patients with a cardiac computed tomographic angiography study positive for obstructive CAD had significantly greater initiation of aspirin, statin, and β-blockers than patients with a positive functional test, the differences in secondary prevention usage were small. Conversely, negative studies were associated with lower rates of medication discontinuation in both arms. Similarly, the total number of revascularization procedures was likely too small to measurably affect between-group differences in quality of life, a point the authors readily acknowledge.

However, there was meaningful and sustained within-group improvement in quality of life over the duration of the study for patients treated with both diagnostic strategies. The observed changes were broad in scope, reflecting clinically important improvements in functional status, angina frequency, physical limitation, and treatment satisfaction as measured by the Duke Activity Status Index and Seattle Angina Questionnaire. Changes in more generic quality-of-life scales were less impressive but also demonstrated improvement. Interestingly, these findings echo the trajectory of within-group quality-of-life improvement over time in patients randomly assigned to either a strategy of optimal medical therapy or optimal medical therapy with percutaneous revascularization in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. It would appear that 1 lesson from both trials is that quality of life in patients with suspected or stable CAD appears to improve over time regardless of the initial diagnostic or therapeutic strategy used.

The within-group improvements in quality of life in PROMISE are especially striking in light of the modest post-test treatment changes and the overall low prevalence of positive noninvasive diagnostic studies. It is likely that much of improvement occurred in patients with normal noninvasive diagnostic tests, although a subgroup analysis by initial diagnostic test result was unfortunately not described in the present report. There are several possible factors that could have contributed to improvements in quality of life in such patients. Many cardiologists would intuit that reassurance could play a major role. However, a clinician’s reassurance after a normal test result does not inevitably ensure symptomatic relief. Rather, it is far more likely that it is the physician who will be reassured by a normal diagnostic study. Another possibility is that patients with normal (or nondiagnostic) studies may proceed to an alternative diagnostic pathway to identify a noncardiac cause of chest pain. This may be a plausible explanation for the findings in the present study, where the overwhelming predominance of subjects had baseline concerns of atypical chest pain or dyspnea on exertion. Patients with such concerns are often referred for cardiac diagnostic testing out of an understandable desire to exclude obstructive CAD, even when it is unlikely on the basis of history and physical examination.

It must be remembered that cardiac disease is an uncommon cause of chest pain in ambulatory settings, particularly among subjects with atypical symptoms, and that many of the more common noncardiac causes (eg, musculoskeletal or gastrointestinal etiologies) may be effectively treated or self-resolved with a subsequent improvement in quality of life.

For this reason, these PROMISE trial findings likewise highlight the need for better diagnostic tools to more accurately diagnose low- to intermediate-risk patients with suspected CAD. For example, a novel, commercially available whole blood test incorporating an age- and sex-matched gene expression score, scaled from 1 to 40, has been developed to help clinicians rule out suspected obstructive CAD. The Corus CAD test (CardioDx) examines the actual messenger RNA expression of 23 genes shown to be closely associated with angiographically significant CAD. A gene expression score <15 has a 96% negative predictive value for obstructive CAD, thereby efficiently excluding low-risk, principally noncardiac, patients from needing to undergo more formal cardiovascular diagnostic investigation. But, even beyond better and more cost-effective screening tools for CAD detection in low- to intermediate-risk patients, we need a recognition that symptom relief and improvement in functional status are important treatment goals for clinicians.

Last, changes in reported rates of depression observed in the present study may have played a role in the improved within-group quality-of-life measures. Nearly 20% of study patients had depression at baseline, which is higher than the general population average, but likely reflects the real world of such patients who are frequently evaluated for suspected CAD. Of note, the prevalence of moderate to severe depression as assessed by the Patient Health Questionnaire-9 decreased by ≥50% over the 2-year follow-up in both diagnostic strategies. Depression is known to be associated with worsened pain symptoms regardless of etiology, and the association is bidirectional. However, it is unclear to what degree the observed decrease in depression resulted from physician reassurance, treatment of chest pain symptoms, or increased treatment of depression itself. Clarifying these uncertainties is critically important and deserves greater attention in future prospective studies of similar patients.

In summary, assessments of quality of life in patients with suspected CAD matter to practicing physicians—and to our patients. Although the findings of the present study are exacting and thorough, they also demonstrate some of the shortcomings of our current measurement tools. Indeed, both the Duke Activity Status Index and Seattle Angina Questionnaire were derived predominantly from patients with established CAD rather than atypical symptoms, whereas the more generic, nondisease-specific quality-of-life scales may lack the granularity to identify what drives changes over time in this common clinical situation. Hopefully, the increasing importance of patient-related outcome measures will result in an expanded toolkit for measuring and understanding quality-of-life changes in future trials. Until then, it is abundantly clear that we need to fully embrace these outcome measures as both worthy of our attention and actionable in our daily clinical practice.

Disclosures

None.

References

1. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB III,


Key words: Editorials ■ angina pectoris ■ clinical trials as topic ■ diagnosis
A PROMISE Fulfilled That Quality-of-Life Assessments Afford Incremental Value to Coronary Artery Disease Management
Joshua Schulman-Marcus and William E. Boden

_Circulation_. 2016;133:1989-1991; originally published online April 27, 2016;
doi: 10.1161/CIRCULATIONAHA.116.022732
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/133/21/1989

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/