Beyond the P Value
The Quest for Improving Health Status in Patients With Ischemic Heart Disease

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Ischemic heart disease is highly prevalent in the United States, affecting 17.6 million patients (~7.9% of the adult population), and is associated with increased mortality, hospitalizations, and an estimated annual cost of $177 billion.1 Diabetes mellitus is a coexistent complication for many of the patients living with ischemic heart disease with similar short-term outcomes whether it predates or is diagnosed at the time of the initial acute coronary syndrome.2 Targets of therapy for these ischemic heart disease patients are focused on improved mortality and reduced major adverse nonfatal cardiovascular events, including myocardial infarction, unstable angina, stroke, and need for repeat revascularization. As a result in part of research advances in the management of acute coronary syndromes and implementation of primary and secondary prevention efforts, overall mortality rates attributable to ischemic heart disease in the United States have decreased dramatically since 1970 with an additional 36% decrement between 1996 and 2006.1,3 Because more patients are living with ischemic heart disease, improving quality of life or health status has emerged as an important additional target of therapy.

Valid health status instruments in ischemic heart disease can be quantified with tools that have established psychometric properties and can be used to measure the socioeconomic impact of the disease, to ascertain the efficacy of an intervention, to provide prognostic information for future events, and to identify populations who may benefit from novel interventions because of persistent excess disease burden. Key health status factors that influence quality of life in patients with ischemic heart disease include angina, functional capacity, fatigue/energy, depression, social functioning, self efficacy/motivation, side effects of medicines, anxiety, and perceived illness. Despite well-characterized observational data regarding factors influencing quality of life in ischemic heart disease, the high rate of missing quality-of-life data in randomized clinical trials has been a key limitation of interpreting the impact of therapy on these important outcomes.

Patients with ischemic heart disease have markedly impaired quality of life compared with the general population. A recent study of >37 000 Americans demonstrated worse quality of life among patients with compared with patients without ischemic heart disease regardless of age, sex, race/ethnicity, risk factors, and comorbidities.4 Among the ischemic heart disease population, quality of life is even more impaired among those who are younger, female sex, black race, or Hispanic ethnicity.5 A variety of factors have been implicated in this worse quality of life among ischemic heart disease patients, including the persistence of angina, depressive symptoms, chronic obstructive pulmonary disease, heart failure, stroke, arthritis/severe functional impairment,6 unfavorable comparison to perceived status of their age-matched peers, and illness perceptions.7 Diabetes mellitus further complicates health status, especially among those taking insulin therapy.8 Pharmacological interventions have variable influences on quality of life, including nitrates, β-blockers, calcium channel blockers, and Ranolazine.9,10 As expected, these effects are typically seen in those patients with more severe angina. Percutaneous coronary intervention marginally improved health status in patients with stable ischemic heart disease11 and those presenting with an occluded artery late after the myocardial infarction.12 Coronary artery bypass graft surgery (CABG) further improves quality of life.13

In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D),14 the authors expand our understanding of the impact of common treatment modalities for ischemic heart disease patients with type 2 diabetes mellitus on health status using a 2×2 factorial design: (1) prompt revascularization (stratified at randomization by CABG or percutaneous coronary intervention) with intensive medical therapy or intensive medical therapy alone and (2) insulin-sensitization or insulin-provision therapy to achieve glycohemoglobin (HbA1c) <7%. Health status was measured with

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the Duke Activity Status Index and modified RAND instruments Energy/Fatigue, Health Distress, and Self-Rated Health, all well-validated instruments with prior use in this population. Depression was captured during the trial conduction with the Center for Epidemiological Studies Depression Scale. The overall health status scores were improved in all groups after randomization, a common occurrence in clinical trials, possibly resulting from the increased attention and disease management associated with study follow-up; however, the persistence of improved health status through 3 years is somewhat atypical given the stability of the patients at trial enrollment. Statistically significant improvement in the Duke Activity Status Index was noted among patients randomized to early revascularization compared with medical therapy alone by year 1, and this difference persisted through year 4. However, effect modification between revascularization strategies was noted with the Duke Activity Status Index in that the difference between early revascularization and medical therapy was driven by the nonrandomized decision to use CABG as the revascularization strategy, which may be a reflection of selection bias at baseline. Additionally, survivor bias may be greater in the CABG group because the frailer people may have died with surgery (ie, people with heart failure, worse left ventricular function, poorer targets) and thus a healthier cohort may have emerged for paired analysis among the CABG group not seen in the percutaneous coronary intervention arm. Nominal improvements in energy and self-rated health in patients randomized to early revascularization were noted, and this difference persisted in the multivariate models.

Several factors were associated with deterioration of health status over time, including baseline history of heart failure, insulin use at baseline, female gender, older age, duration of diabetes mellitus, neuropathy, and current smoking. Interestingly, less severe angina at baseline was associated with greater decrement in health status than in the patients with more severe angina using the angina-free patients as the reference group. Nevertheless, anginal symptoms during follow-up attenuated the associations between revascularization and health status but did not fully explain the variability, consistent with other studies. Although the mean HbA1c achieved in the insulin-sensitization arm was lower than in the insulin-provision arm (7.0% versus 7.5%; \( P<0.001 \)) and there was less hypoglycemia, health status and depressive symptoms were not different between the 2 groups. This study, along with other randomized trials detailed by the authors, suggests that the association between insulin therapy and impaired quality of life may be due to the underlying severity of disease.

Although the statistical significance of the BARI 2D results is evident, the clinical meaningfulness of the findings is a bit more difficult to interpret. This concept represents the smallest change in a scale that a patient recognizes as important. The authors report a “clinically meaningful” difference of 3 points for Duke Activity Status Index and 5 points for the RAND scales, a threshold not met within the prespecified between-group comparisons of the randomization arms. The magnitude of the change in health status within the entire population was clinically meaningful and greater than the magnitude of any of the between-group differences. Moreover, the effect size of many patient factors such as heart failure and smoking status exceeded the effect size of the randomization to revascularization or medical therapy, suggesting that these instruments are potentially responsive to change. Although the decision of revascularization or medical management alone was randomized, patients were unblinded to the actual revascularization; therefore, the effect size of health status may have been influenced by the patient’s perceived benefit of the intervention but counterbalanced with the crossover of CABG/percutaneous coronary intervention that occurred during follow-up among the medically managed patients. Given the marginal health status improvements coupled with no significant differences in death, myocardial infarction, and stroke, clinicians should individualize the management approach of patients with ischemic heart disease and concomitant diabetes mellitus on the basis of the patient’s baseline symptom burden and clinical needs. Moreover, the coordinated, multidisciplinary care of ischemic heart disease and diabetes mellitus performed in BARI 2D may be a useful model for improving the quality of life of this vulnerable population.

Future research efforts should develop strategies to measure health status routinely in clinical practice to identify the population who may benefit from more aggressive interventions. Well-designed clinical trials such as BARI 2D should test the efficacy of an intervention, and quality of life or other health status measures should be key end points of interest. In addition, nonpharmacological approaches to improve health status and disease management strategies should be further developed.

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References

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