Measurement of Clinical Efficacy in Studies of Heart Failure

To the Editor:

A recent clinical investigation reported by Packer et al.1 used a multiplicity of end points to assess the efficacy of carvedilol for heart failure because the most appropriate measure(s) have not been firmly established. Statistically significant favorable effects of carvedilol compared with placebo were observed for measures commonly used in clinical practice, such as NYHA classification, physician’s assessment of changes in clinical status, and asking patients if they felt better compared with baseline. These congruent results do not represent independent assessments. Other measures, including a previously validated quality-of-life questionnaire, did not demonstrate significant differences.2–3 These discrepant results may have been due to differences in the content of measures, timing of assessments, and statistical methods. Nevertheless, the authors concluded that these results have important implications for future clinical trials, implying that simple symptom assessments were adequate to assess clinical efficacy because they correspond with clinical practice and demonstrated differences compared with placebo. Are the simple symptom assessments adequate measures of therapeutic efficacy?

Reliable clinical measurements result from methods that can be applied consistently at different times and by different investigators.4 The NYHA classification has been shown to have poor interobserver agreement in part because asking about “ordinary” physical activities is rather imprecise.5 When standard activities such as walking a specific distance or climbing a flight of stairs are used, it can enhance this measure’s reliability,6 but concerns about what investigators take into consideration persist. For example, 60% of the patients in the carvedilol study were classified as NYHA class III or IV. The protocol specified that class III patients should be symptomatic walking 200 yards or up a flight of stairs. However, the mean distance walked in a corridor was >345 m, and all patients had to walk at least 150 m. Perhaps these patients developed symptoms at much shorter distances and continued to walk. Another possibility is that protocol criteria for NYHA classification were not applied consistently.

Similarly, asking patients if they “feel better or worse” does not specify what the patient or investigator should focus on each time this measurement is made. Indeed, one doesn’t know what is actually being measured when patients say they feel better. Is the response based on changes in symptoms of heart failure or some other aspect of their care? The large placebo response seen in the carvedilol and other studies raises serious concerns about what was measured by these so-called “global” questions.7 Single questions are not global measures in the sense that patients do not consider many aspects of their heart failure when asked if they feel better. These potential measurement problems can be minimized by carefully designed written questionnaires that ask the same specific questions each time they are administered.

Measures of quality of life extend well beyond simple assessments of symptoms. Measures of quality of life focus on how well-being.7 Statistically significant changes in simple measurements of symptoms may be insufficient to alter lifestyle. Furthermore, quality of life can be affected by more than symptoms of heart failure. For example, side effects may adversely affect quality of life. The more frequent dizziness reported by patients receiving carvedilol compared with those receiving placebo may have reduced their quality of life even though the frequency of dyspnea, but not fatigue, was less in the carvedilol group. Clearly, commonly used symptom assessments cannot serve as adequate measures of quality of life.

Symptoms are certainly an important component of clinical efficacy. Selection of measurements of symptoms for clinical trials should not be unduly influenced by probability values in studies of investigational therapies. Rather, we should be explicit about what symptoms it is important to measure to determine if a treatment has value to patients. We should then develop unambiguous measures that comprehensively reflect what is judged to be important (ie, valid measures) and that provide for consistent applications (ie, reliable measures) in both clinical trials and practice. On the basis of these criteria, assessments such as the NYHA classification and so-called global questions are not the best possible measures of therapeutic efficacy. More recent attempts to develop comprehensive, reliable, and valid written questionnaires should not be discarded because they don’t demonstrate statistically significant effects in some clinical trials. Perhaps they are providing more meaningful data. We must continue to improve our measures of symptoms, adverse effects, and quality of life to understand the true value of treatments for heart failure.

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References


Depression After Myocardial Infarction

To the Editor:

I recently reread the landmark paper by Frasure-Smith et al.,1 in which the authors showed that depression while in the hospital after a myocardial infarction (MI) is a significant predictor of 18-month post-MI cardiac mortality. In the abstract, the authors wrote, “Thirty-five patients met the modified DIS criteria for major in-hospital depression after the MI. Sixty-eight had BDI scores >10, indicative of mild to moderate symptoms of depression.” There are no details in the article itself concerning the number of patients who had BDI (Beck Depression Inventory) scores of 10 or more but did not meet the DIS (Diagnostic Interview Schedule) for major depression, ie, suffered from minor or subsyndromal depression. Table 1 in the article suggests that among the 185 “nondepressed” patients, according to the DIS, only 6.4% have had BDI scores of 10 or more, which makes the number that appears in the abstract seem unlikely. Perhaps the figure 6.4% mistakenly “shifted” from the mortality rate for the nondepressed that appears in Table 2 in the article, which stands at 6.4%.

In view of the rapidly growing interest in the interrelations between depression and cardiovascular disease,2–4 I believe a clarification of these important data by the authors of this seminal article is needed.

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Response

Dr Gross is correct. There is a typographical error in Table 1 of our article. The percent of patients without major depression according to the DIS who had BDI scores ≥10, indicative of at least mild to moderate depression, should have been 22.2% (41 of 185 patients) instead of 6.4%. As Dr Gross suggests, the figure of 6.4% seems to have migrated from Table 2. We thank Dr Gross for his careful reading and taking the time to inform us and others of the error.

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Induced Septal Infarction/Nonsurgical Septal Reduction for Hypertrophic Obstructive Cardiomyopathy

To the Editor:

Eugene Braunwald1 calls the new catheter interventional therapy for hypertrophic obstructive cardiomyopathy (HOCM) an ingenious approach with quite favorable results.

Braunwald states that we have reproduced the results obtained by Knight et al2 both with transient ischemia and ethanol-induced infarction and that Sigwart et al3 demonstrated in 1982 that brief occlusion of the septal artery with a balloon catheter causes transient reduction in the outflow pressure gradient. Knight et al2 state that Sigwart’s findings4 were confirmed by us.5 However, checking the papers and/or abstracts published by Sigwart, the opposite proves to be the case.

1. In both articles,3,4 there is nothing written about HOCM or septal artery occlusion in HOCM. Both papers deal with the effect of transient therapeutic occlusion of the left anterior descending coronary artery (LAD) in patients with coronary artery disease.

2. Sigwart confirms that he has never published data regarding septal artery occlusion performed in 1982. He calls them unpublished “prior art.”

3. A study to develop a new catheter-based concept of treatment for patients with HOCM including the suggestion to inject 96% ethanol was first published by us in April 1994,7,9 ie, 15 months before the first paper by Sigwart.9

As has been appreciated,6,7,9 a catheter-induced septal necrosis by the injection of alcohol into a septal branch of the LAD was first performed by Brugada et al10 in patients with coronary artery disease for chemical ablation of ventricular tachycardia. This study stimulated us to begin development of the new catheter-based concept of treatment in 1991.9

It seems necessary to me to note that for historical reasons, to date the new approach (transcoryonary ablation of septum hypertrophy, or TASH) has been performed by us in more than 1180 patients with favorable results.

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**Sulfonylureas and Mortality in Diabetic Patients After Myocardial Infarction**

To the Editor:

A long-standing controversy that relates to the potentially harmful effects of sulfonylurea drugs within the ischemic myocardium was presented recently in *Circulation*.1 The controversy arises from the fact that sulfonylurea drugs inhibit ATP-sensitive potassium (KATP) channels.2 Although blockade of KATP channels in the pancreas promotes the release of insulin, conductance through KATP channels in the heart is thought to be critical to the protection afforded by ischemic preconditioning, which limits infarct size.2,3 Yet, despite experimental data that demonstrate that sulfonylurea drugs prevent ischemic preconditioning,4,5 increase infarct size,6 and may be associated with an increase in in-hospital mortality among patients undergoing direct angioplasty for myocardial infarction,7 clinical data on long-term outcome of patients treated with sulfonylurea drugs are sparse.

Therefore, in answer to the plea made by Engler and Yellon,1 we report findings from a population-based study involving 874 residents of Olmsted County, Minnesota, admitted to the Mayo Clinic Coronary Care Unit between January 1988 and October 1996 with acute myocardial infarction (WHO criteria) that compares long-term outcome of sulfonylurea and insulin-treated patients. In all, there were 102 diabetic patients receiving either insulin (n = 56) or a sulfonylurea (n = 46) at the time of admission to hospital. Mean age was 70±10 years in the sulfonylurea group versus 68±12 years in the insulin group. As determined by left ventricular ejection fraction, frequency of previous myocardial infarction, and severity of coronary artery disease, differences between the two groups were not significant (P = .28, P = .12, and P = .95, respectively). In addition, the prevalence of hypertension, hypercholesterolemia, and tobacco use was also similar between the two groups (P = .13, P = .15, and P = .54, respectively). During follow-up (mean 2.7±2.3 years, maximum 8.4 years), a total of 24 deaths occurred in the sulfonylurea group versus 20 in the insulin group. Of these, 12 deaths were attributable to cardiac causes in the sulfonylurea group versus 10 in the insulin-treated group.
(differences not significant; \( P = .79 \) for overall survival and \( P = .54 \) for survival to cardiac death [Kaplan-Meier estimates]).

Thus, our findings indicate that use of sulfonylurea drugs in diabetic patients at the time of myocardial infarction is not associated with increased long-term mortality. However, our data do not address several important issues, including the impact of sulfonylurea drugs on short-term mortality or cardiac morbidity, which may be increased secondary to impaired cardioprotection. These findings may be related to the known variable efficacy with which sulfonylurea drugs inhibit cardioprotective \( K_{\text{ATP}} \) channels. Indeed, the interaction between sulfonylurea drugs and \( K_{\text{ATP}} \) channels during metabolic stress is complex, with various factors governing sulfonylurea-inhibitory gating of the channel, leading to a nonuniform action of sulfonylurea drugs at the cellular level. Such complexity of regulation of cardiac \( K_{\text{ATP}} \) channels warrants further clinical and molecular studies to determine more fully the consequences of sulfonylurea drug use on the human heart.

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