Measurement of Clinical Efficacy in Studies of Heart Failure

To the Editor:

A recent clinical investigation reported by Packer et al. 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. These discrepancies 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. The NYHA classification has been shown to have poor reproducibility and validity when applied consistently at different times and by different investigators. 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.

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.

Thomas S. Rector, PhD
Senior Research Associate
Cardiovascular Division
University of Minnesota Medical School
Minneapolis, Minn


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**Depression After Myocardial Infarction**

*To the Editor:*

I recently reread the landmark paper by Frasure-Smith et al., 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 (Beck Depression Inventory) scores of 10 or more but did not meet the DIS (Diagnostic Interview Schedule) for major depression, i.e., suffered from minor or subsyndromal 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, i.e., 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,1–3 I believe a clarification of these important data by the authors of this seminal article is needed.

Raz Gross, MD
Division of Psychiatry
The Chaim Sheba Medical Center
Tel Hashomer, Israel


**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.

Nancy Frasure-Smith, PhD
François Lespérance, MD
Mario Talajic, MD
Montreal Heart Institute
Montreal, Quebec, Canada

**Intermediate Lipoproteins, Atherosclerosis, and Gofman**

*To the Editor:*

I was keenly disappointed that Dr Hodis and his coworkers (Circulation. 1997;95:2022–2026) failed to refer to Gofman and his work on the relationship between the intermediate lipoproteins (Sparticle 12 to 20) and atherosclerosis. This failure is especially egregious because Gofman’s work and Hodis and his coworkers’ work were both done at the same institution, the Donner Laboratory, Gofman’s work preceding Hodis by almost a half century.

Gofman’s work is also an excellent illustration of how a consensus report composed by many distinguished investigators at the time and chaired by the giant Ernest Page, who together with Braun-Menéndez simultaneously and independently described the “true nature” of renin and angiotensin,1 was wrong.2 The overwhelming denial of Gofman’s work probably discouraged him and other investigators from trying to determine the paths taken by the individual classes of lipoprotein cholesterol.

Gofman was also a vigorous and vocal opponent of the Vietnam War.

No history of the pathogenesis of atherosclerosis (or the Vietnam War) is complete without mentioning Gofman’s pioneering work on lipoproteins.

**Louis A. Soloff, MD**
Emeritus Chief of Cardiology
Temple University School of Medicine
Cardiology Section
Philadelphia, Pa


**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 al demonstrated in 1982 that brief occlusion of the septal artery with a balloon catheter causes transient reduction in the outflow pressure gradient. Knight et al 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:


Howard N. Hodis, MD
Associate Professor of Medicine and Preventive Medicine
Assistant Professor of Toxicology and Pharmacology
Director, Atherosclerosis Research Unit
University of Southern California, School of Medicine
Los Angeles, Calif

Ronald M. Krauss, MD
Senior Scientist
Head, Department of Molecular and Nuclear Medicine
Laurence Berkeley National Laboratory
University of California, Berkeley

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.8

As has been appreciated,5,7,9 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 (transcoronary ablation of septum hypertrophy, or TASH) has been performed by us in more than 1180 patients with favorable results.

Horst J. Kuhn, MD, FESC
Professor of Internal Medicine/Cardiology
Department of Internal Medicine/Cardiology
The Bielefeld Hospital
Bielefeld, Germany


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.

Peter A Brady, MD
Jassim Al-Suwaidi, MD
Stephen L Kopecky, MD
Andre Terzic, MD, PhD
Division of Cardiovascular Diseases
Mayo Clinic
Mayo Foundation
Rochester, Minn

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Thomas S. Rector

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